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Mechanistic Studies on Garratt–Braverman Cyclization: The Diradical–Cycloaddition Puzzle

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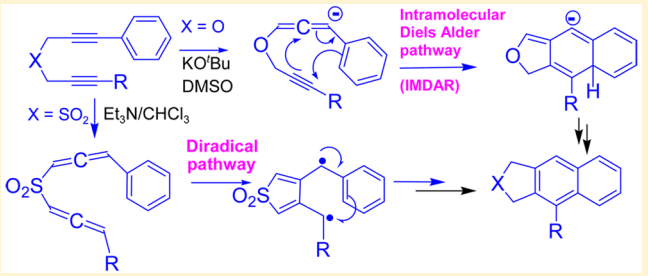
Supporting Information

ABSTRACT: In this work, we present the results of extensive multiprong studies involving the fate of deuterium-labeled substrates, EPR, trapping experiments, and LA-LDI mass spectrometry to sort out the controversies relating to the mechanism of Garratt–Braverman cyclization in two systems, namely bis-propargyl sulfones and ethers. The results are in conformity with a diradical mechamism for the sulfone, while for the ether, the anionic [4 + 2] appears to be the preferred pathway. This shows that the mechanistic pathway toward GB cyclization is dependent upon the nature of heteroatom (O or S in sulfone) bridging the propargyl arms.



INTRODUCTION

Cycloaromatization reactions[1] have become an important research area because of their interesting mechanistic possibilities[2] which control the reactivity of molecules undergoing such reactions and the extent of their interactions with biomolecules.[3] Several cycloaromatization reactions are known starting from the famous Bergman cyclization reported first in 1971.[4,5] A few years after Bergman's paper, Garratt and Braverman[6,7] independently reported the reactivity of the bis-propargyl systems (sulfide, sulfone, ether, amine) under base-mediated conditions. The final outcome of the reaction, now popularly known as the Garratt–Braverman (GB) cyclization, was dependent upon the nature of the substituent in the propargyl arm as well as the reaction conditions. For example, in the case of an unsubstituted thioether, a dimeric product was obtained in virtually quantitative yield via the bis-allene (path A).[8a] The reaction was carried out in two stages: an initial treatment with KO^{t}Bu at −65 °C to get the bis-allene followed by warming the latter in $CHCl_3$ to 50 °C. For di-*tert*-butyl propargyl thioether, the product was mainly the cyclobutane-fused thiophene.[8a] Later on, Garratt et al. reported the isolation of similar products in low yields from all of the systems (thioether, ether, and amine) using KOH/MeOH.[8b] For alkyl-substituted substrates, 3,4-disubstitued 5-membered heterocycles were formed (path B).[9] On the other hand, aryl- or vinyl-substituted starting materials provide a new aromatic system via the participation of the aryl or vinyl double bond, ultimately leading to the formation of a naphthalene- or benzene-fused heterocyclic system (path C).[10] All of these possibilities are shown in Scheme 1

The generally accepted mechanism for the process as depicted in pathways **A**–**C** of Scheme 1 involves the formation of a diradical from a bis-alleneic intermediate[8] (Scheme 2A). Support for this mechanism came from various experiments like successful trapping of the diradical with $^3O_2$ to form the *endo* peroxide[11] (in case of sulfide), the nonperturbation of the rate upon varying solvent polarity,[12] as well as the isolation of **XIII** as an intermediate (Scheme 2A). In recent years, through a combination of experiment and computations on the selectivity of aryl-substituted bis-propargyl sulfones, the diradical mechanism was shown to be the preferred pathway.[13] Moreover, the complete GB selectivity of substrates capable of undergoing multiple reactions could be successfully explained on the basis of the diradical mechanism.[14]

Some ambiguities still remain regarding the diradical mechanism for the GB process, especially for reactions going through path C in view of the fact that the bis-allene, the progenitor of the diradical, is generated only after double isomerization and also has multiple mechanistic options. In some of the earlier experiments with sulfones by Braverman,[7a] the bis-allene was directly generated, and hence, not much ambiguity existed for those cases. However, in the classical GB reaction, where bis-propargyl systems are the starting materials, bis-allene formation is an important issue which should be a sequential event. If the mono- to the bis-allene formation is slow,[15] by the time it undergoes isomerization, it may give rise to the same products via an alternate route. For example, one can draw a [4 + 2] cycloaddition (intramolecular Diels–Alder reaction (IMDAR) mechanism) to arrive at the products from aryl-substituted systems. Such a mechanism was originally proposed by Iwai and Ide[10a] and later on reinforced by Kudoh et al.[16] for rearrangement of bispropargyl ethers in the presence of strong bases like NaH or Triton B in DMSO involving a

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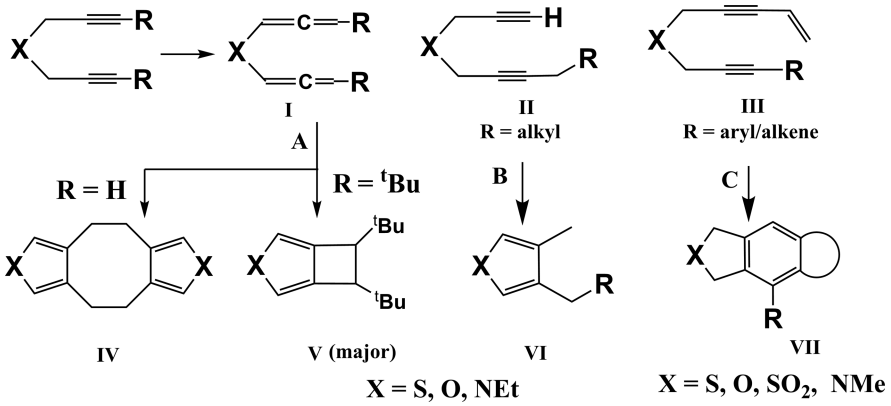
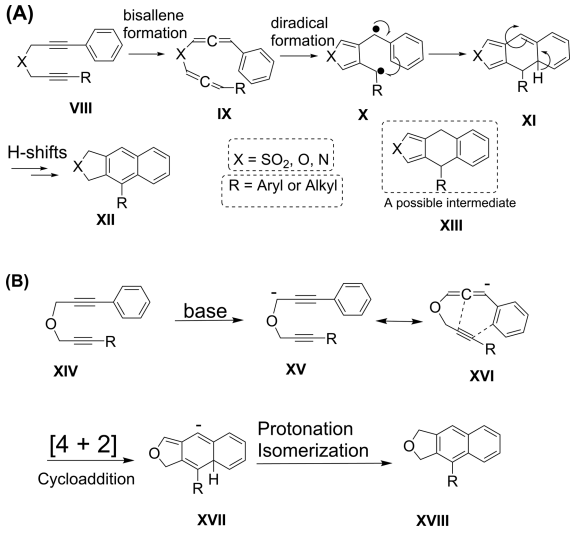
Scheme 1. Garratt–Braverman Cyclization



Scheme 2. (A) Diradical Mechanism. (B) Anionic IMDAR Mechanism



monoallenic anion followed by an intramolecular Diels–Alder reaction and subsequent quenching of the resulting anion by DMSO (Scheme 2B). The final product was obtained via a 1,5-migration of the anion generated at ring fusion carbon and subsequent quenching. The mechanism was supported by labeling experiments with deuterated solvents and computations. Recently, Balci et al.[17] have reported the synthesis of chromenopyridines exploiting the IMDAR mechanism from an in situ generated azadiene and an alkyne system. Although Kudoh et al.[16] synthesized several arylnaphthalenes using their protocol, for their mechanistic study involving deuterium incorporation, the group used a system which can only isomerize to a monoallene as the other arm was disubstituted at the propargyl position, thus limiting the generality of such a pathway in systems capable of undergoing isomerization to the bis-allene.

RESULTS AND DISCUSSION

With this backdrop, we undertook a detailed study to address these mechanistic issues. Specifically we have the following questions in mind: (i) Do all these bis-propargyl systems (S, SO_2, O, N) follow the same mechanism or are mechanisms a different for different systems considering the variations in the reaction conditions employed for different propargyl systems? (ii) If that be the case (different mechanisms), will the selectivity pattern from unsymmetrical systems follow different trend? (iii) Will it be possible to use appropriately deuterated substrates to discriminate between the monoallene vs bis-allene mechanism? (iv) Finally, will it be possible to capture any EPR signal during the course of the reaction? The present work was aimed to address these issues, and we have been able to provide evidence for the reaction pathways for the ether and the sulfone which are presented in this paper.

Table 1. Results of Base-Mediated Reaction of Sulfones and Ethers

SM	X	A	yield (%)	product ratio
1a	O	2-naphthyl	97	**3a**:**4a** (2:1)
1b	O	6-methoxynaphthyl	94	**3b**:**4b** (1:2)
1c	O	4-methoxyphenyl	95	**3c**:**4c** (1:8)
1d	O	2,4-dimethoxyphenyl	94	**3d**:**4d** (1:10)
2a	SO_2	2-naphthyl	95	**5a**:**6a** (3.16:1)
2b	SO_2	6-methoxynaphthyl	90	**5b**:**6b** (5.16:1)
2c	SO_2	4-methoxyphenyl	85	**5c**:**6c** (2:1)
2d	SO_2	2,4-dimethoxyphenyl	87	**5d**:**6d** (5.16:1)

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The selectivity issue was taken up first. Toward that end, we prepared several unsymmetrically substituted bis-propargyl ethers/sulfones and treated them with a suitable base depending upon the nature of substrate (KO^{t}Bu in DMSO for ethers and Et_3N in $CHCl_3$ for sulfones) to gain insight into the outcome of GB reaction, and the reaction was carried out at room temperature. The product ratio was determined from the integrations for characteristic signals of the two isomers in the ^{1}H NMR spectrum of the crude reaction mixture. The results of the GB reaction which showed opposite selectivity for the ethers vis-à-vis sulfones are compiled in Table 1. Previously,[18] we reported the product ratio for the ether systems using different reaction conditions (DBU/toluene/reflux). The trend of selectivity followed similar pattern. The structures of the products were confirmed mainly on the basis of ^{1}H NMR, ^{13}C NMR, DEPT-135, and correlation spectroscopy in some cases. For the sulfones, the major product arises from the preferential participation of the more electron-rich aryl ring, while for the ether, the less electron-rich aryl ring predominantly participates. Prima facie, this contrast in selectivity for the sulfone vis-à-vis ether, indicated different mechanisms for the two reactions. The results fit well with the anionic cycloaddition mechanism for the ether but not for the sulfone. However, we must keep in mind the different electronic nature of sulfone (−R, −I effects) vis-à-vis the ether (+R, −I), which might explain the different selectivity for the both of the reactions even if they involve a common diradical pathway (Figure 1). In the case of sulfone, the radical benzylic to the electron donor aryl ring will be captodatively stabilized. while in the case of ether it will be the opposite with an electron-withdrawing aryl group stabilizing the benzylic radical.[13,18]

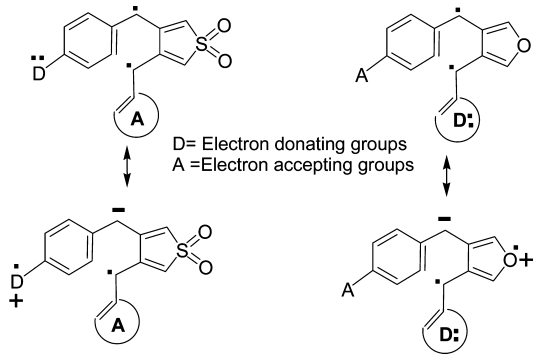
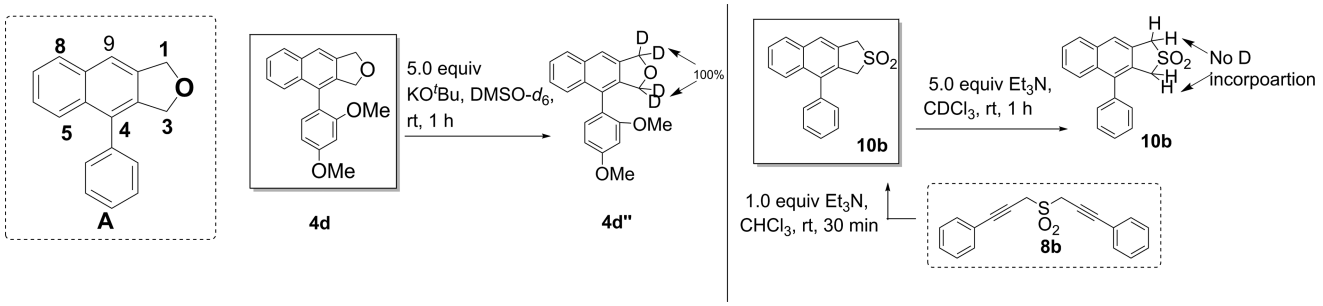


Figure 1. Differential electronic nature of sulfone and ether.

We next turned our attention to a more assertive experiment based on the outcome by carrying out the reaction in deuterated solvents. Before carrying out these experiments, we wanted to check the exchangeability of the heterocyclic methylenes in the GB products under basic conditions. Thus, the GB products derived from both the sulfone and the ether were subjected to the respective reaction conditions in the presence of deuterated solvents. The phthalans derived from the ether were stirred in DMSO-d_6 in the presence of KO^{t}Bu, whereas the counterpart dihydrothiophene 1,1-dioxide was treated with Et_3N in the presence of $CDCl_3$ (Scheme 3) to find out the level of deuterium incorporation, if any, at C-1 and C-3. The temperature was maintained at the room temperature of 30 °C in both the cases, which is also the GB reaction temperature. Interestingly, but not unexpectedly, varying degrees of deuterium were found at these positions in the phthalans, and the extent of deuteration depends upon the amount of base. With excess of KO^{t}Bu in DMSO-d_6, 100% deuteration was observed at both the methylene positions. Although lesser extent of deuterium incorporation occurs with 1.0 equiv of base, any mechanistic study based on deuterium incorporation at the methylene positions may not be reliable. For the dihydrothiophene 1,1-dioxide, although no such exchange at the methylenes was observed, there was a possibility of incorporation of D during propargylallene isomerization. Experimental results showed that no deuterium was incorporated at any position of the product from the reaction of sulfone with Et_3N and $CDCl_3$, thus ruling out any D exchange during propargylallene isomerization. This observation is important as anionic [4 + 2] cyclization (IMDAR) suggests deuterium incorporation, especially at C-9. This single observation rules out the anionic IMDAR mechanism for the rearrangement of sulfone, a conclusion also supported by the results obtained from deuterated substrates (as discussed below). A general structure showing the numbering is included in Scheme 3 (structure **A**).

For the rearrangement of labeled substrates having deuterium at both of the *ortho* positions of the phenyl ring, the possible outcomes of the deuterium retention, loss or migration, are shown in Scheme 4. In the case of diradical mechanism, the intermediate XXII has all of the D intact. This will be followed by a series of migrations involving H (D). If these migrations are concerted, then the highest level of deuterium is expected to be observed at the migrating position. If such migrations are nonconcerted and follow in a stepwise manner, a lower percentage of D incorporation is then expected. For the intermediate sulfone (X = SO_2), because of the nonaromatic character of heterocycle, 1,5-D-shift (from C-11 to C1) along with a 1,3-H shift from C-4 to C-3 are expected to lead to the creation of the new aromatic ring. The stability of the anion α to the sulfone may also aid the 1,5 shift.

Scheme 3. Results of Exchange Reactions



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Scheme 4. Possible Fate of Deuterated Substrate

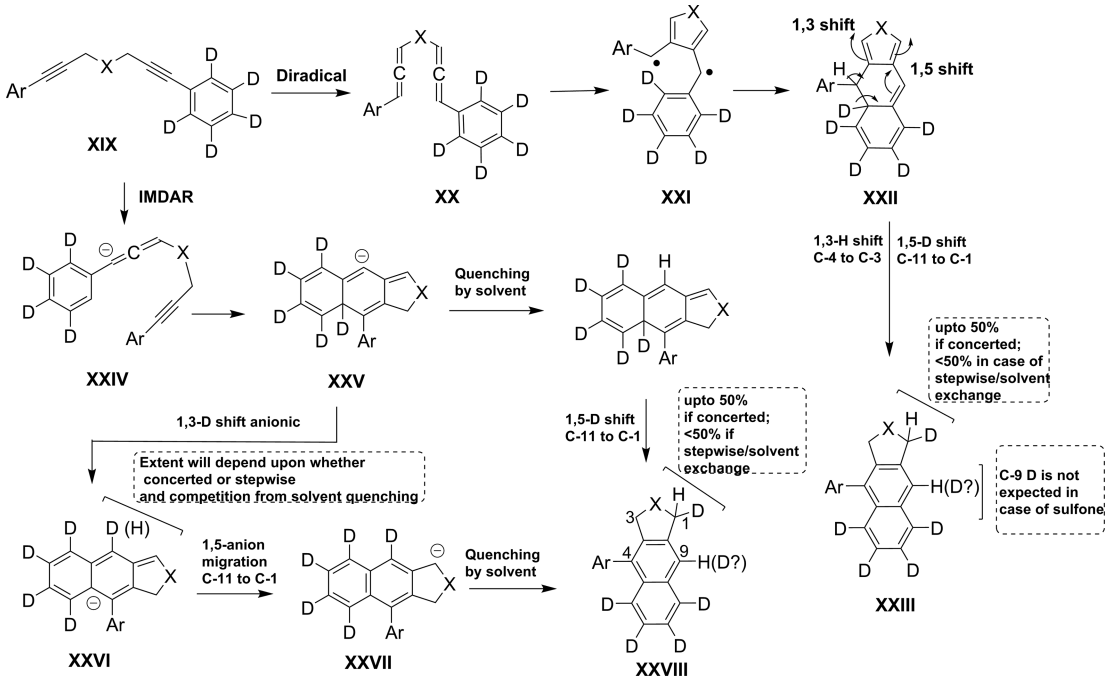
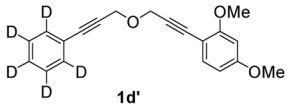
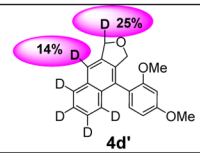
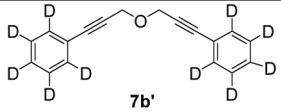
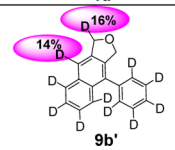
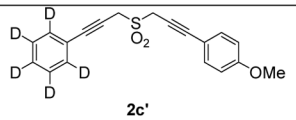
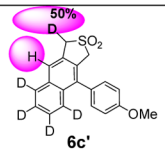
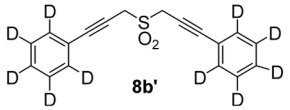
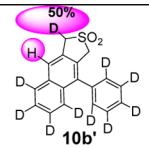
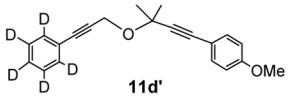
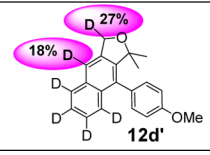


Table 2. Experimental Results on Deuterated Substrates

Substrate	Condition	Product*
 1d'	KO^{t}Bu (1 eq)/DMSO/rt/1h	 4d'
 7b'	KO^{t}Bu (1 eq)/DMSO/rt/1h	 9b'
 2c'	Et_3N (1 eq), $CHCl_3$, rt, 30 min	 6c'
 8b'	Et_3N (1 eq), $CHCl_3$, rt, 30 min	 10b'
 11d'	KO^{t}Bu (1 eq)/DMSO/rt/1h	 12d'

[a]The percent incorporations of deuterium are approximate values within the limits of integration.

1,3-D migration from C-11 to C-9 was ruled out because that still retains the nonaromatic thiophene dioxide ring. If these processes are concerted, D incorporation at C-1 was expected to the extent of 50% in the final product. However, prima facie, the transoid geometry of the diene framework should prohibit a concerted 1,5-sigmatropic shift, thus raising doubts about the expected level of deuteration. No deuterium is expected at C-9 for sulfone; however, for the ether, because of the aromaticity of furan, a 1,3 shift from C-11 to C-9 can take place. Another 1,3 shift from C-9 to C-1 will lead to the final product. The

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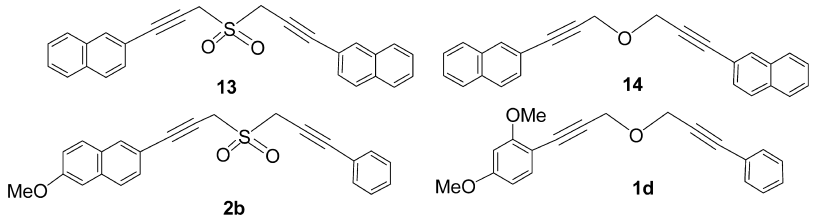

Figure 2. Compounds used in EPR study.

extent of deuterium at these positions (C-1 and C-9) depends upon the concertedness of migration and possible exchange with the nondeuterated solvent. For anionic IMDAR mechanism, if a concerted 1,3-H shift from C-11 to C-9 occurs, one can expect high level of deuterium at C-9. Kudoh et al.[16] mentioned in their paper such a possibility of a concerted H migration via an anionic 1,3- sigmatropic shift from C-11 to C-9, although no evidence to support this was proposed. The incorporation of deuterium at C-1 was explained on the basis of migration of the ring junction anion to C-1 through the π-network followed by quenching (DMSO-d_6). These possibilities are shown in Scheme 4 (numbering has been shown in structure **XXVIII**).

With this information in hand, the pentadeuterated phenyl based bis-propargyl ethers (**1d′**, **7b′**, and **11d′**) and sulfones (**2c′** and **8b′**) were prepared and subjected to the GB conditions in nondeuterated solvents as mentioned previously. The results for both ethers and sulfones are shown in Table 2. In these cases, although there exists the possibility of exchange of deuterium at C-1 and C-3 positions, the presence of any extent of deuterium at these positions can only arise through migration and not through exchange considering the fact that the reaction is carried out in nondeuteriated solvent, which is used in large excess.

Determination of the Extent of Deuterium. The extent of deuterium incorporation was determined from the integration of various proton signals in the ^{1}H NMR spectra (SI). Comparison of intensities of the signals in the corresponding ^{13}C NMR spectra (SI) of deuterated product against the fully protiated compound also provided qualitative information about deuterium incorporation. The ^{2}H NMR spectrum of ether **4d′** (SI) showed the presence of deuterium at C-1 via the appearance of a broad singlet at δ 5.43. The signal for D at C-9 was masked by the broad signals of D present in the other aromatic rings. However, in the corresponding lactone **15d′**, deshielding by the lactone carbonyl made it to appear at δ 8.67 (SI). For the sulfone, we could clearly observe the signal at δ 4.59 due to the D at C-1 (SI). The assignments of various signals were done from ^{1}H−^{1}H COSY NMR experiments.

Inspection of the results of D-incorporation leads to some key differences between the reactions of ether vis-à-vis sulfone. The levels of deuterium incorporation at C-1 and C-9 are different in the case of ethers and sulfones, thus pointing out different mechanisms for their pathways. In case of ethers, C-9 showed a low but distinct presence of D (∼14%). A similar observation was made for the dimethyl propargyl ether **11d′**, which can react only via the monoallene. The presence of deuterium at C-9 in the case of deuterated substrates confirms an intramolecular 1,3-shift which is, however, a minor pathway as indicated by the low level of D incorporation, the major pathway being the quenching of the anion by DMSO. Base-mediated intramolecular 1,3-H shifts have been reported by Mulzer et al.[19] For the ethers, varying degrees of D (16−27%) incorporation were observed at C-1, indicating possible exchange under the reaction conditions. However, the presence of D certainly proves the intramolecular nature of the 1,5-migration. All these findings are in agreement with the anionic [4 + 2] mechanism involving the monoallenide anion as proposed by Kudoh et al.[16] The presence of deuterium at C-1 and C-9 can also be explained on the basis of 1,3-prototropic shift for ethers. Deuteration at these positions can be achieved after diradical cycloaromatization followed by 1,3-prototropic shift leading to rearomatization of the phenyl. It may be noted that in the case of ether the intermediate has a furan ring which is aromatic. In the case of sulfone, due to the lack of aromaticity of the heterocyclic ring[20] and relative stability of the anion at C-1-position α to the sulfone, base-catalyzed 1,5-H shift can occur immediately. A definitive support for this mechanism was obtained when the monoallenic intermediate was successfully trapped as evidenced from the formation of mono methoxy enol ether **16** [peak at m/z 417 (M + K$^+$) in the LA-LDI MS[21]] by carrying out the reaction of naphthyl propargyl ether with KO^{t}Bu in a mixture of DMSO and MeOH. No double adduct of methanol (m/z at 449) could be detected (SI).[22] In the case of labeled sulfones **2c′** and **8b′**, ∼50% deuterium incorporation at C-1 was observed, while C-9 had no deuterium. The observed results ruled out the involvement of a 1,3-H(D) migration from C-11 to C-9 from the intermediate **XXII** (Scheme 4) formed during the GB process; only intramolecular 1,5-H(D) migration occurred from C-11 to C-1 as confirmed by the occurrence of ∼50% D at C-1. The concerted nature of 1,5-migration most likely involves deprotonation and reprotonation strictly through an intramolecular fashion as sigmatropic shift may be ruled out because of geometric constraints pointed earlier. This observation ruled out the involvement of intermediate **XIII** (Scheme 2), which is also in line with the observation by Feldman[23] after their unsuccessful attempt to trap the intermediate in a [4 + 2] fashion. No deuterium incorporation at C-9 from deuterated substrates as well as from the reaction of unlabeled precursors in $CDCl_3$ and Et_3N ruled out the normal or anionic [4 + 2] cyclization route for the sulfone and supported the diradical mechanism via the involvement of a bis-allene. The involvement of the latter (bis-allene) as an intermediate was also proven by the isolation of bis-enol ether along with the GB product by carrying out the reaction in the presence of methanol, confirmed by ^{1}H NMR and LA-LDI MS [peak for dimethanol adduct **19** at m/z 497 (M + K$^+$), no peak at m/z 465 for the mono methanol adduct and peak for GB product at m/z 433 (M + K$^+$)] (SI). It may be mentioned that Braverman et al.[12] through a combination of ^{1}H NMR and kinetic studies have reported the involvement of bis-allene during rearrangement of sulfones. This is in line with the previously reported involvement of bis-allene proven. Finally, EPR studies, as discussed below, confirmed the diradical nature

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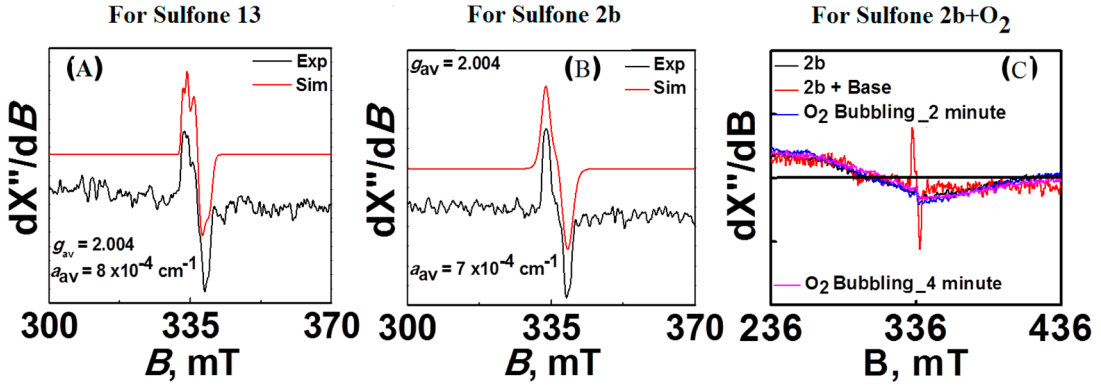

Figure 3. X band (9.44 GHz) EPR spectra of a mixture of sulfone and Et_3N in CH_2Cl_2 at room temperature. Conditions: X-band microwave frequency (GHz), 9.44; modulation frequency (kHz), 100; modulation amplitude (G), 140.0; and microwave power, 0.998 [μW]. Spectra (**A**) is for bis-naphthyl-substituted bispropargyl sulfone **13**; (**B**) is for sulfone **2b** and (**C**) is for a solution of sulfone **2b** purging with O_2 gas at room temperature. All of the solutions of samples in dry CH_2Cl_2 contained Et_3N as base. EXP and SIM represent experimental and simulation spectra, respectively.

of the intermediate only in the case of rearrangement of sulfones and not for the ethers.

EPR Studies. The EPR spectra were then recorded by carrying out the reactions of sulfones **13** and **2b** as well as ethers **14** and **1d** (Figure 2) under appropriate conditions after initially purging the solutions with Ar gas for 5 min to remove the dissolved oxygen. Suitable bases or TEMPO or both were added as per the requirement of the reaction. For the sulfones **13** and **2b**, we did observe nice stable EPR signals at room temperature (spectrum shown in parts A and B, respectively, of Figure 3) with an isotropic g value of 2.004. The g value was found to be close to that for TEMPO (g = 2.00036) and is thus surely an indication for the generation and presence of organic free radical in cases involving sulfones.[24−26] This was also tested by a quenching experiment with molecular O_2 in the triplet ground state. Thus, the EPR signal disappeared when the spectrum was recorded while the reaction mixture was being purged with O_2 gas for 2−4 min (Figure 3C).

It is to be noted that a hyperfine splitting of the EPR signal is expected, which is also clearly observed in the experimental spectra of compound **13**. However, the spectral broadness did not allow us to calculate the hyperfine splitting constant (A value) due to the strong spin delocalization within the aromatic core and the benzylic proton[24a−c] as well as strong spin−spin exchange.[24d,e] The same is true for compound **2b** for which a broad signal was observed. The strong nucleophilic/electrophilic nature of the radical under the influence of electron-donor/acceptor substituent in the aromatic core may also be a probable reason for weak hyperfine coupling of compound **2b**.[24b] However, the hyperfine splitting is resolved in the simulated spectra. Thus, the best fit to the experimental data provided the parameters g_{av} = 2.004 and hyperfine coupling constant, A_{av} = 8 × 10^{-4} cm^{-1} for compound **13**, and compound **2b** shows the same g value with a slightly weaker hyperfine coupling constant A_{av} = 7 × 10^{-4} cm^{-1}. Both the experimental and simulated spectra of compound **13** showed the average triplet EPR signal for the two radicals under the coupling influence of two separate hydrogens attached to the radical bearing carbons. However, at this stage, it is difficult to clearly explain the splitting pattern or the exact interactions with our available experimental setup.[24a]

To check whether the observed signal has any interaction with a stable organic radical like TEMPO, we monitored the signal intensity of a fixed concentration of TEMPO in the presence of the reaction mixture of compound **13**. It is well-known that TEMPO gives a triplet EPR signal with an isotropic hyperfine splitting a_N = 15.5 G and g_0 = 2.0055 as was reported by Talsi et al.[24d,26] However, under our experimental conditions at room temperature, TEMPO exhibited a single line EPR spectrum with a center g value of 2.013, which possibly due to high concentration of the TEMPO. We observed a reduction of EPR signal intensity by 17% of a solution containing the compound **13** (1.7 mM), Et_3N, and TEMPO (0.5/1.0 equiv) in CH_2Cl_2. This is in comparison to the signal intensity of a 0.5/1.0 mM of TEMPO in CH_2Cl_2. The effect is more pronounced in the case of compound **2b** under similar conditions. In this case, the signal intensity of TEMPO was reduced by 41% (Figure 4A,B). (All of these

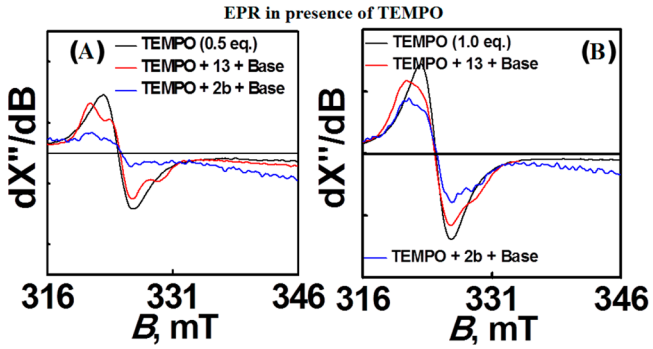

Figure 4. (A) and (B): X band (9.44 GHz) EPR spectra of a mixture of TEMPO and sulfones **13** and **2b** and Et_3N in CH_2Cl_2, Conditions: X-band microwave frequency (GHz), 9.44; modulation frequency (kHz), 100; modulation amplitude (G), 140.0; and microwave power, 0.998 (μW).

observations are shown in a tabulated form in Table 3.) The results indicate that there is an antiferromagnetic interaction between TEMPO and our GB diradical in solution.[27] It should be mentioned that at this stage we are unable to quantify the spin.

However, a correlation could be made by examining the area of absorbance (Integration of the first-derivative EPR and integration again) of sample and that of TEMPO. This gave the relative spin concentration, which is mentioned in a tabular

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Table 3. Effect of Sample Spin on the Spin of TEMPO

	EPR absorbance area	$\Delta_{\text{EPR absorbance area}}$	% decrease in spin conc of TEMPO
TEMPO (1 mM)	938		
TEMPO + **13** (1:1)	738	155	17
TEMPO + **2b** (1:1)	563	375	41
TEMPO (2 mM)	1983		
TEMPO + **13** (1:1)	1635	348	18
TEMPO + **2b** (1:1)	1178	805	41

form in the SI. As the sample would generate diradical, understanding the exact spin state is not conclusive at this stage and needs further study. In the case of bispropargyl ethers **1d** and **14**, no EPR signals were observed during the reaction under the standard conditions (KO^tBu/DMSO), indicating that the GB pathway mainly follows a nonradical pathway.

CONCLUSION

In summary, definitive evidence have been provided to confirm the mechanistic pathways followed by bis-propargyl ethers and sulfones during their GB rearrangement to arylnaphthalene systems. A multiprong strategy involving fate of deuterium-labeled substrates, trapping of possible intermediates (mono or bis-allenes) with an external nucleophile (MeOH), and EPR experiments supported the anionic [4 + 2] cycloaddition of the monoallenide species for rearrangement of ethers, while the corresponding cyclization of sulfones implicated a pathway involving the diradical generated from the bis-allene. All of the present studies are new, and for the first time that EPR signals could be detected for reactions of sulfones, the intermediates could be trapped by methanol as indicated by LA-LDI MS and deuterium NMR recorded to determine the fate of rearrangement of deuterium-labeled substrates. Although issues like intramolecular 1,5-H shift remain to be resolved, this study hopefully dispels some of the confusion regarding the mechanism of GB cyclization, which is definitely proven to be system (ether or sulfone) dependent.

EXPERIMENTAL SECTION

All reactions were monitored by TLC using Polygram SILG/UV254 precoated (0.25 mm) silica gel TLC plates. Column chomatography was performed with silica gel (60−120 or 230−400 mesh). NMR data were recorded on 200, 400, and 600 MHz NMR instruments in $CDCl_3$ unless mentioned otherwise. For ^2H NMR, the compounds were dissolved in distilled $CHCl_3$ with 1 drop of CD_3CN (δ 2.1) as internal standard. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparently, and b = broad signal. All coupling constants (J) are given in hertz (Hz). Mass spectra were recorded in ESI+ mode (ion trap). The LA-LDI experiments were carried out using a MALDI-TOF mass spectrometer. UV laser: smart beam II laser, 355 nm wavelength; laser rep rate 2000 Hz, reflector mode. The mass spectra were recorded in positive-ion mode.

All dry solvents used for reactions were purified according to the standard protocols. Dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and triethylamine (Et_3N) were distilled from calcium hydride, and chloroform ($CHCl_3$) was distilled over anhydrous $CaCl_2$. All of the solvents for column chomatography were distilled prior to use. In most of the column chomatographic purifications, ethyl acetate (EA/EtOAc) and petroleum ether (PE) of boiling range 60−80 °C were used as eluents.

General Procedure for the Synthesis of Sulfones (2b−d,c′, 8b,b′, and 13). To an ice-cold solution of sulfide[28] (0.1 mmol) in a mixture of THF (10 mL) and methanol (2 mL) were added Oxone (4.0 equiv) and a few drops of water, and the reaction was allowed to stir at room temperature overnight. The reaction was then quenched with water (20 mL) and extracted with ethyl acetate. The organic layer was then dried over Na_2SO_4, evaporated, and subjected to column chromatography [Si gel, petroleum ether−ethyl acetate (5:1) mixture as eluent]. For sulfone **2a**, see ref 29.

General Procedure for the O-Propargylation: Synthesis of Bis-propargyl Ethers (1a−d,d′, 7b,b′, 11d′, and 14). To an ice-cold solution of alcohol derivatives (0.1 mmol) in dry DMF (10 mL) was added NaH (2 eq, 60% suspension in mineral oil), and the mixture was stirred for 30 min at ice-cold temperature under N_2 atmosphere. After the alkoxide was generated, the respective propargyl bromide (1.0 equiv) diluted in dry DMF (10 mL) was added dropwise to the reaction mixture by maintaining the ice-cold temperature. The reaction was then allowed to stir at room temperature for 1 h. It was quenched with a saturated solution of NH_4Cl and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate, evaporated, and subjected to column chromatography [Si gel, petroleum ether−ethyl acetate (10:1) mixture as eluent].

General Procedure for the Garratt−Braverman Cyclization: Synthesis of Arylnaphthalenes. *Ethers **3/4a−d, 4d′, 9b′, and 12d′**.* To a solution of ether (0.05 mmol) in dry DMSO (1 mL) was added 1.0 equiv of KO^tBu, and the solution was allowed to stir at room temperature for 1 h. It was then quenched with NH_4Cl and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to obtain the crude product that was purified by column chromatography with hexane−ethyl acetate (10:1) mixture as eluent.

*For sulfones **5/6a−d, 5c′, 6c′, 10b,b′**.* To a solution of sulfone (0.05 mmol) in dry $CHCl_3$ (1 mL) was added Et_3N (1 equiv) and the solution was allowed to stir at room temperature for 30 min. It was then quenched with NH_4Cl and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and evaporated to get the crude product that was purified by column chromatography with hexane−ethyl acetate mixture (5:1) as eluent.

Oxidation to the Lactone: Synthesis of Compound 15d′. A DMSO (1 mL) solution of phthalan (10 mg, 0.025 mmol) was mixed with freshly prepared IBX (4.0 equiv) and stirred at 90 °C overnight under nitrogen. The solution was then filtered through Celite and rinsed thoroughly with ethyl acetate several times. The organic layer was then washed with water, dried over Na_2SO_4, and concentrated in vacuo, and the crude product was purified by column chromatography with hexane−ethyl acetate mixture (4:1) as eluent.

EPR Measurement. The sample solutions were prepared in dry dichloromethane and purged with Ar gas for 5 min to remove any dissolved oxygen. Then base, TEMPO, or both was added as per the requirement of the reaction and prior to recording the EPR spectra. The radical-quenching experiment was performed via purging O_2 gas to a sample solution containing Et_3N as base for 2 and 4 min. Continuous-wave EPR experiments at the X band (9.44 GHz) were carried out using an ESR spectrometer at center field 330 mT with a sweep width 30 mT and a modulation frequency (kHz), 100; modulation amplitude (G), 140.0; and microwave power, 0.998 (μW) at temperature, 22 °C.

Spectral Data of New Compounds. *2,4-Dimethoxy-1-(3-((3-(1,2,3,4,5-$^2H_5$)phenylprop-2-yn-1-yl)oxy)prop-1-yn-1-yl)benzene (**1d′**):* yellow liquid; yield 21 mg, 67%; ^1H NMR (400 MHz, chloroform-*d*) δ 7.36 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 6.43 (s, 1H), 4.58 (s, 2H), 4.56 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (50 MHz, chloroform-*d*) δ 161.6, 161.5, 134.7, 131.5 (t, J = 24.5 Hz) 127.9 (2C, s merged with t, J = 24.4 Hz), 122.5, 104.9, 104.3, 98.5, 87.1, 86.7, 84.8, 83.4, 57.9, 57.4, 55.9, 55.5; HRMS calcd for $C_{20}H_{13}D_5O_3$ + H^+ 312.1643, found 312.1640.

*4-(2,4-Dimethoxyphenyl)-1,3-dihydro(5,6,7,8-$^2H_5$)naphtho[2,3-c]furan (**4d′**):* sticky mass; yield 11 mg, 74%; ^1H NMR (600 MHz,

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chloroform-*d*) δ 7.70 (s, 0.86H, 0.14D), 7.15 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.64 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 5.32−5.31 (m, 1.5H, 0.5D), 5.04−4.96 (m, 2H), 3.92 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (150 MHz, chloroform-*d*) δ 161.0, 158.2, 139.5, 138.1, 137.6, 137.5, 133.7, 132.5, 132.0, 129.0, 119.2, 118.8, 118.7, 114.3, 104.7, 99.2, 73.6, 73.3 (t, *J* = 25.8 Hz), 55.7, 55.6; HRMS calcd for $C_{20}H_{13}D_5O_3$ + H^+ 312.1643, found 312.1628; calcd for $C_{20}H_{14}D_4O_3$ + H^+ 311.1580, found 311.1568.

*1-Methoxy-4-[3-(3-(1,2,3,4,5-$^2H_5$)phenylprop-2-yn-1-sulfonyl)-prop-1-ynyl]benzene (**2c′**):* white solid; mp 119−120 °C; yield 23 mg, 70%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 4.32 (s, 2H), 4.31 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 160.6, 133.8, 131.9 (t, *J* = 24.0 Hz), 129.0 (t, *J* = 25.0 Hz), 128.1 (t, *J* = 25.0 Hz), 121.5, 114.3, 113.6, 88.3, 88.1, 76.2, 74.7, 55.6, 44.9, 44.7; HRMS calcd for $C_{19}H_{11}D_5O_3S$ + H^+ 330.1207, found 330.1194.

*6-Methoxy-4-(1,2,3,4,5-$^2H_5$)phenyl-1,3-dihydronaphtho[2,3-c]-thiophene 2,2-dioxide (major) (**5c′**) + 4-(4-methoxyphenyl)-1,3-dihydro(5,6,7,8-$^2H_5$)naphtho[2,3-c]thiophene 2,2-dioxide (minor) (**6c′**) (2:1):* yellow sticky solid; yield 14 mg, 85%; ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.81 (s, 1H, minor), 7.77 (d, *J* = 9.0 Hz, 1H, major), 7.74 (s, 1H, major), 7.22 (d, *J* = 8.4 Hz, 2H, minor), 7.19 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H, major), 7.06 (d, *J* = 8.4 Hz, 2H, minor), 6.84 (d, *J* = 2.4 Hz, 1H, major), 4.56 (app s, 2H, major, 1H, minor, 1D, minor), 4.26 (s, 2H, minor), 4.20 (s, 2H, major), 3.91 (s, 3H, minor), 3.70 (s, 3H, major); ^{13}C NMR (150 MHz, chloroform-*d*) δ 159.7, 158.6, 138.0, 137.7, 136.8, 133.6, 133.4, 132.5, 130.9, 129.7, 129.6, 129.0, 128.6, 128.4, 126.2, 124.8, 124.7, 119.6, 114.6, 104.9, 57.3, 57.1 (t, *J* = 21.6 Hz), 56.8, 56.7, 55.6, 55.4; HRMS calcd for $C_{19}H_{11}D_5O_3S$ + H^+ 330.1207, found 330.1213.

*6-Methoxy-4-phenyl-1,3-dihydronaphtho[2,3-c]thiophene 2,2-dioxide (major) (**5c**) + 4-(4-Methoxyphenyl)-1,3-dihydronaphtho[2,3-c]thiophene 2,2-dioxide (minor) (**6c**) (2:1):* yellow sticky solid; yield 14 mg, 85%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.86 (d, *J* = 8.0 Hz, 1H, minor), 7.80 (s, 1H, minor), 7.76 (d, *J* = 8.8 Hz, 1H, major), 7.74 (s, 1H, major), 7.61 (d, *J* = 8.8 Hz, 1H, minor), 7.55−7.41 (m, 3H, major, 2H, minor), 7.30 (d, *J* = 6.8 Hz, 2H, major), 7.21 (app t, *J* = 8.8 Hz, 1H, major, 2H, minor), 7.06 (d, *J* = 8.8 Hz, 2H, minor), 6.83 (d, *J* = 2 Hz, 1H, major), 4.58 (s, 2H, minor), 4.56 (s, 2H, major), 4.25 (s, 2H, minor), 4.20 (s, 2H, major), 3.90 (s, 3H, minor), 3.70 (s, 3H, major); ^{13}C NMR (100 MHz, chloroform-*d*) δ 159.7, 158.5, 138.0, 137.9, 136.8, 133.6, 133.4, 132.6, 129.7, 129.6, 129.5, 129.2, 129.0, 128.7, 128.6, 128.4, 128.3, 128.1, 127.0, 126.9, 124.8, 124.7, 119.5, 114.5, 104.9, 57.4, 57.3, 56.8, 56.7, 55.6, 55.3; HRMS calcd for $C_{19}H_{16}O_3S$ + H^+ 325.0893, found 325.0912.

*(Sulfonylbis(prop-1-yne-3,1-diyl))(2,3,4,5,6-$^2H_5$)dibenzene (**8b′**):* pale yellow crystalline solid; mp 108−109 °C; yield 26 mg, 85%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.33 (s, 4H); ^{13}C NMR (50 MHz, chloroform-*d*) δ 131.8 (t, *J* = 24.5 Hz), 129.0 (t, *J* = 24.5 Hz), 128.1 (t, *J* = 24.5 Hz), 121.4, 88.2, 76.1, 44.8; HRMS calcd for $C_{18}H_4D_{10}O_2S$ + H^+, 305.1415, found 305.1423.

*4-(2,3,4,5,6-$^2H_5$)Phenyl-1,3-dihydro-(5,6,7,8-$^2H_5$)naphtho[2,3-c]-thiophene 2,2-dioxide (**10b′**):* white solid; mp 177−178 °C; yield 14 mg, 90%; ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.85 (s, 1H), 4.6 (app s, 1H, 1D), 4.26 (s, 2H); ^{13}C NMR (150 MHz, chloroform-*d*) δ 138.2, 137.5, 133.3, 132.2, 129.2 (t, *J* = 25.0 Hz), 128.6 (t, *J* = 26.8 Hz), 128.6, 128.1, 127.8 (t, *J* = 24.1 Hz), 127.7 (t, *J* = 25.2 Hz), 126.6 (t, *J* = 24.6 Hz), 126.5 (t, *J* = 24.0 Hz), 126.1 (t, *J* = 24.3 Hz), 125.0, 57.0 (t, *J* = 21.75 Hz), 56.7; HRMS calcd for $C_{18}H_4D_{10}O_2S$ + H^+ 305.1415, found 305.1402.

*(Oxybis(prop-1-yne-3,1-diyl))(2,3,4,5,6-$^2H_5$)dibenzene (**7b′**):* yellow liquid; yield 17 mg, 65%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.57 (s, 4H); ^{13}C NMR (50 MHz, chloroform-*d*) δ 131.6 (t, *J* = 28.5 Hz), 128.1 (2 × merged t, *J* = 24.0 Hz), 122.5, 86.9, 84.6, 57.6; HRMS calcd for $C_{18}H_4D_{10}O$ + H^+ 257.1745, found 257.1740.

*4-Phenyl-1,3-dihydro-(5,6,7,8-$^2H_5$)naphtho[2,3-c]furan (**9b′**):* gummy mass; yield 9 mg, 70%; ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.72 (s, 0.86H, 0.14D), 5.32 (s, 1.65H, 0.35D), 5.04 (s, 2H); ^{13}C NMR (150 MHz, chloroform-*d*) δ 138.1, 137.8, 137.0, 133.8, 132.7, 131.9, 129.2 (t, *J* = 24.1 Hz), 128.3 (t, *J* = 24.0 Hz), 125.6−125.1 (m), 118.9, 73.6, 73.1; HRMS calcd for $C_{18}H_4D_{10}O$ + H^+, 257.1745, found 257.1731; calcd for $C_{18}H_5D_9O$ + H^+ 256.1683, found 256.1675.

*4-(2,4-Dimethoxyphenyl)-(5,6,7,8-$^2H_5$)naphtho[2,3-c]furan-1(3H)-one (**15d′**):* sticky solid; yield 4 mg, 50%; ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.52 (s, 0.86H, 0.14D), 7.17 (d, *J* = 8.4 Hz, 1H), 6.69−6.67 (m, 2H), 5.24 (ABq, *J* = 15 Hz, 2H), 3.94 (s, 3H), 3.7 (s, 3H); ^{13}C NMR (150 MHz, chloroform-*d*) δ 171.8, 161.6, 158.1, 139.9, 135.7, 133.8, 132.1, 130.8, 126.3, 123.1, 116.7, 105.1, 99.3, 70.2, 55.8, 55.7; HRMS calcd for $C_{20}H_{12}D_4O_4$ + H^+ 325.1374, found 325.1358; calcd for $C_{20}H_{11}D_5O_4$ + H^+ 326.1436, found 326.1419.

*1-Methoxy-4-[3-methyl-3-(3-(2,3,4,5,6-$^2H_5$)phenylprop-2-ynyloxy)but-1-ynyl]benzene (**11d′**):* yellow liquid; yield 21 mg, 67%; ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.40 (d, *J* = 9 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.60 (s, 2H), 3.83 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (150 MHz, chloroform-*d*) δ 159.8, 133.4, 114.9, 114.3, 114.1, 89.2, 86.6, 85.5, 85.2, 72.0, 55.5, 53.5, 29.3; HRMS calcd for $C_{21}H_{15}D_5O_2$ + H^+ 310.1850, found 310.1851.

*9-(4-Methoxy-phenyl)-1,1-dimethyl-1,3-dihydro(5,6,7,8-$^2H_5$)-naphtho[2,3-c]furan (**12d′**):* sticky mass; yield 9 mg, 60%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.66 (s, 0.82H, 0.18D), 7.20 (d, *J* = 12.6 Hz, 2H), 7.02 (d, *J* = 12.6 Hz, 2H), 5.18 (app s, 1.73H, 0.27D), 3.90 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 159.2, 143.3, 139.5, 138.4, 133.8, 133.2, 133.0, 132.0, 129.5, 119.0, 114.3, 113.5, 86.4, 69.3, 55.5, 53.6, 31.1, 29.9; HRMS calcd for $C_{21}H_{15}D_5O_2$ + H^+ 310.1850, found 310.1833; calcd for $C_{21}H_{16}D_4O_2$ + H^+ 309.1789, found 309.1804.

*1-Methoxy-4-[3-(3-phenylprop-2-yne-1-sulfonyl)prop-1-ynyl]-benzene (**2c**):* white solid; mp 110−111 °C; yield 23 mg, 72%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.50 (d, *J* = 6.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.38−7.32 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.31 (s, 2H), 4.30 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (50 MHz, chloroform-*d*) δ 160.5, 133.8, 132.2, 129.4, 128.6, 121.6, 114.2, 113.6, 88.3, 88.1, 76.2, 74.7, 55.5, 44.9, 44.6; HRMS calcd for $C_{19}H_{16}O_3S$ + H^+ 325.0898, found 325.0912.

*2,4-Dimethoxy-1-[3-(3-phenylprop-2-yne-1-sulfonyl)prop-1-ynyl]benzene (**2d**):* pale yellow solid; mp 127−128 °C; yield 25 mg, 71%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.49 (d, *J* = 7.6 Hz, 2H), 7.36−7.31 (m, 4H), 6.46−6.43 (bm, 2H), 4.40 (s, 2H), 4.33 (s, 2H), 3.82 (merged s, 6H); ^{13}C NMR (100 MHz, chloroform-*d*) δ 162.2, 162.1, 134.7, 132.3, 129.4, 128.6, 111.3, 105.1, 100.2, 98.6, 87.9, 85.1, 78.7, 76.4, 56.0, 55.7, 45.3, 44.2; HRMS calcd for $C_{20}H_{18}O_4S$ + H^+ 355.1004, found 355.1003.

*2-Methoxy-6-[3-(3-phenylprop-2-yne-1-sulfonyl)prop-1-ynyl]-naphthalene (**2b**):* yellow solid; mp 109−110 °C; yield 28 mg, 76%; ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.96 (s, 1H), 7.70 (d, *J* = 1.2 Hz, 2H), 7.53−7.49 (m, 3H), 7.40−7.34 (m, 3H), 7.19 (d, *J* = 11.4 Hz, 1H), 7.13 (s, 1H), 4.39−4.38 (merged s, 4H), 3.95 (s, 3H); ^{13}C NMR (150 MHz, chloroform-*d*) δ 158.9, 134.8, 132.4, 132.3, 129.6, 129.5, 129.0, 128.6, 128.4, 127.2, 121.6, 119.9, 116.4, 106.0, 88.8, 88.2, 76.2, 75.6, 55.6, 44.9, 44.8; HRMS calcd for $C_{23}H_{18}O_3S$ + Na^+ 397.0874, found 397.0874.

*3-Methoxy-11-phenyl-8,10-dihydrophenanthro[2,3-c]thiophene 9,9-dioxide (major) (**5b**) + 4-(6-Methoxynaphthalen-2-yl)-1,3-dihydronaphtho[2,3-c]thiophene 2,2-dioxide (minor) (**6b**) (5.16:1):* yellow sticky solid; yield 17 mg, 90%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.82 (s, 1H, major), 7.70 (s, 2H, major), 7.58−7.52 (m, 3H, major), 7.42 (d, *J* = 9.6 Hz, 1H), 7.28 (app d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 2.8 Hz, 1H), 6.73 (dd, *J* = 9.6 Hz, 2.8 Hz, 1H), 4.62 (s, 2H, major, 2H, minor), 4.28 (dd, *J* = 16.8 Hz, 26.2 Hz, 2H, minor), 4.15 (s, 2H, major), 3.99 (s, 3H, minor), 3.88 (s, 3H, major); ^{13}C NMR (100 MHz, chloroform-*d*) δ 158.0, 142.3, 137.6, 135.6, 132.8, 130.9, 130.3, 129.3, 129.2, 128.7, 128.6, 128.4, 128.0, 127.6, 126.0, 124.6, 115.8, 109.3, 57.8, 57.7, 55.5; HRMS calcd for $C_{23}H_{18}O_3S$ + H^+ 375.1055, found 375.1079.

*6,8-Dimethoxy-4-phenyl-1,3-dihydronaphtho[2,3-c]thiophene 2,2-dioxide (major) (**5d**) + 4-(2,4-dimethoxyphenyl)-1,3-dihydronaphtho[2,3-c]thiophene 2,2-dioxide (minor) (**6d**) (5.16:1).* sticky solid; yield 16 mg, 93%; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.15 (s, 1H, major),7.54−7.46 (m, 3H, major), 7.29 (app d, *J* = 5.6 Hz, 2H, major), 6.53 (s, 1H, major), 6.39 (s, 1H, major), 4.56 (s, 2H major, 2H minor), 4.18 (s, 2H major, 2H minor), 3.99 (s, 3H, major),

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3.91 (s, 3H, minor), 3.71 (s, 3H, minor), 3.67 (s, 3H, major); ^{13}C NMR (100 MHz, chloroform-*d*) δ 159.0, 156.6, 138.3, 136.4, 134.1, 129.6, 129.2, 128.3, 125.4, 122.0, 119.4, 98.4, 96.9, 57.6, 56.9, 56.0, 55.4; HRMS calcd for $C_{20}H_{18}O_4S + H^+$ 355.1004, found 355.0987.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00490.

^{1}H, ^{13}C, and ^{2}H NMR, HRMS, LA-LDI MS, and EPR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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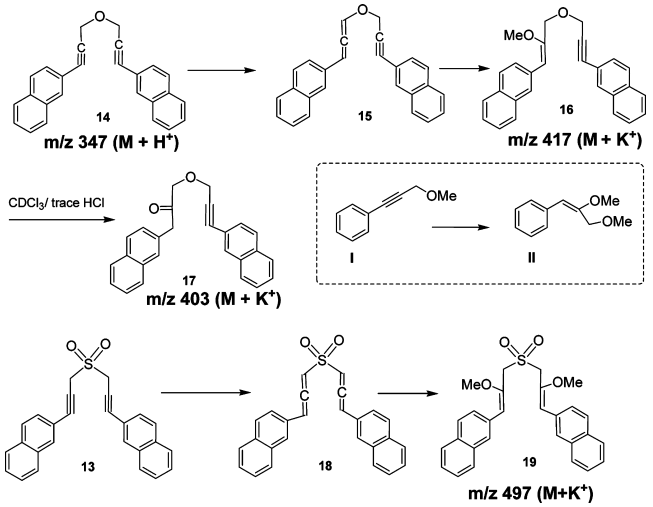

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