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Chemoselective Rearrangement Reactions of Sulfur Ylide Derived from Diazoquinones and Allyl/Propargyl Sulfides

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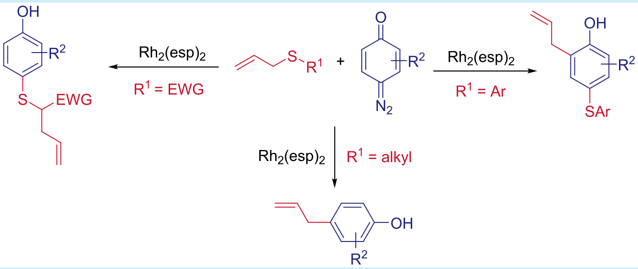
ABSTRACT: Here, we describe three types of rearrangement reactions of sulfur ylide derived from diazoquinones and allyl/propargyl sulfides. With $Rh_2(esp)_2$ as the catalyst, diazoquinones react with allyl/propargyl sulfides to form a sulfur ylide, which undergoes a chemoselective tautomerization/[2,3]-sigmatropic rearrangement reaction, a Doyle−Kirmse rearrangement/Cope rearrangement cascade reaction, or a Doyle−Kirmse rearrangement/elimination reaction, depending on the substituent of the sulfides. The protocol provides alkenyl and allenyl sulfides and multisubstituted phenols with moderate and high yields.



Whereas transition-metal-catalyzed carbene transfer reactions of diazo compounds have been well-established as powerful tools for C−C and C−heteroatom bond formation,[1] examples of the use of cyclic diazo compounds as the carbene source are scarce. Diazoquinones are a class of planar six-membered ring compounds with carbonyl, alkene, and diazo groups in conjugation.[2] The unique structure endows the quinoid carbene some distinctive reactivity profiles such as the tendency for aromatization,[3−6] high electrophilicity,[3a,e,4e] and quinone-like hydrogen atom transfer (HAT) reactivity.[3h,6c] In recent years, diazoquinones have attracted increasing attention as unusual carbocyclic carbene sources and phenol synthons.[3−6] They have been demonstrated to be reactive for a variety of carbene transfer reactions, including C−H insertion,[3] cyclopropanation,[4] and O−H insertion.[5] However, compared to that of traditional acyclic diazo compounds, such as ethyl diazoacetate and methyl phenyldiazoacetate, there is currently a rather limited knowledge of diazoquinones in catalytic carbene transformations.

Transition-metal-catalyzed [2,3]-sigmatropic rearrangement reactions of diazo compounds and allylic sulfides, namely, the Doyle−Kirmse reaction, represent a powerful method for the reorganization of molecular skeletons and C−C bond formation (Scheme 1a), which has found many applications in the synthesis of bioactive natural products and pharmaceuticals.[7] α-Diazoacetates have been demonstrated to be effective carbene precursors for such reactions. To our knowledge, there has been no report on rearrangement reactions of sulfur ylide derived from diazoquinones with allylic sulfides. In view of the unusual structural and electronic properties of diazoquinones, new reaction patterns for diazoquinones and allylic sulfides would be expected. Herein, we report three types of rearrangement reactions of sulfur ylide derived from diazoquinones and allyl/propargyl sulfides, which give alkenyl and allenyl sulfides and multisubstituted phenols, respectively, depending on the sulfide substituents (Scheme 1b). The relative structures of the products have been found in many bioactive molecules (Scheme 1c).[8]

At the outset, we investigated the reaction between diazoquinone **1a** and allylic sulfide **2a** (Table 1). With $Rh_2(esp)_2$ as the catalyst, the reaction proceeded smoothly at 40 °C to give a rearrangement product **3a** with a 98% yield (entry 1), and no Doyle−Kirmse reaction product was observed. Other dirhodium catalysts, including $Rh_2(OAc)_4$, $Rh_2(oct)_4$, $Rh_2(tpa)_4$, and $Rh_2(tfa)_4$, are less efficient than $Rh_2(esp)_2$, giving **3a** in 5−65% yield. Copper complexes, $Cu(acac)_2$, $Cu(MeCN)_4BF_4$, and $Cu(hfac)_2$, which have been reported to be effective for sulfur ylide transformations with α-diazoacetates as the carbene source,[9] failed to catalyze the rearrangement reaction under the same conditions. Solvent screening showed that toluene or CH_3CN gave **3a** in a yield comparable to that of $ClCH_2CH_2Cl$ (DCE), but the use of tetrahydrofuran (THF) had a detrimental effect on the reaction, giving **3a** in low yield. The rearrangement reaction was performed in a one-pot fashion without the need for the slow addition of diazoquinones.

With the optimized condition, the substrate scope of the reactions was examined. As shown in Scheme 2, a range of allylic sulfides underwent the rearrangement reaction with diazoquinone **1a** with moderate to high yields. We first

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Scheme 1. Rearrangement Reactions of Sulfur Ylide

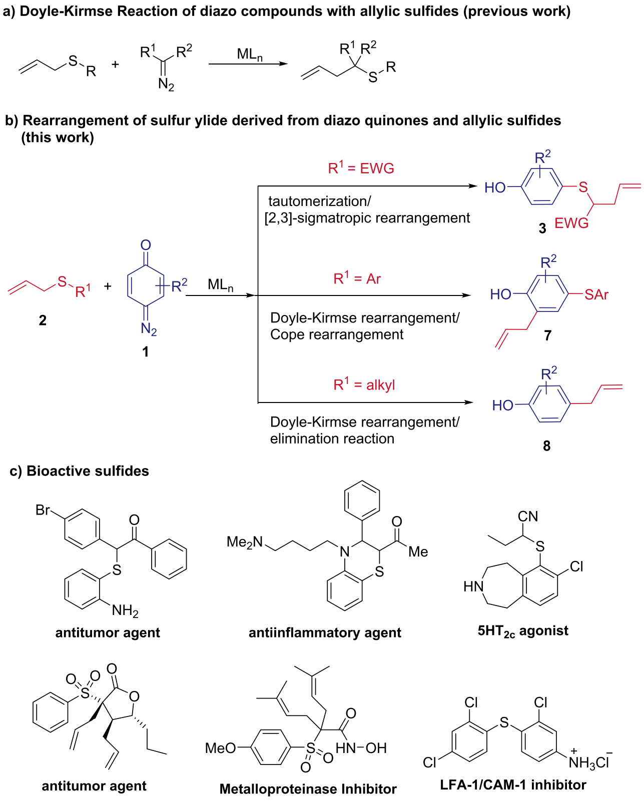
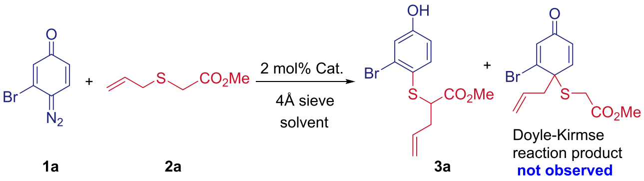


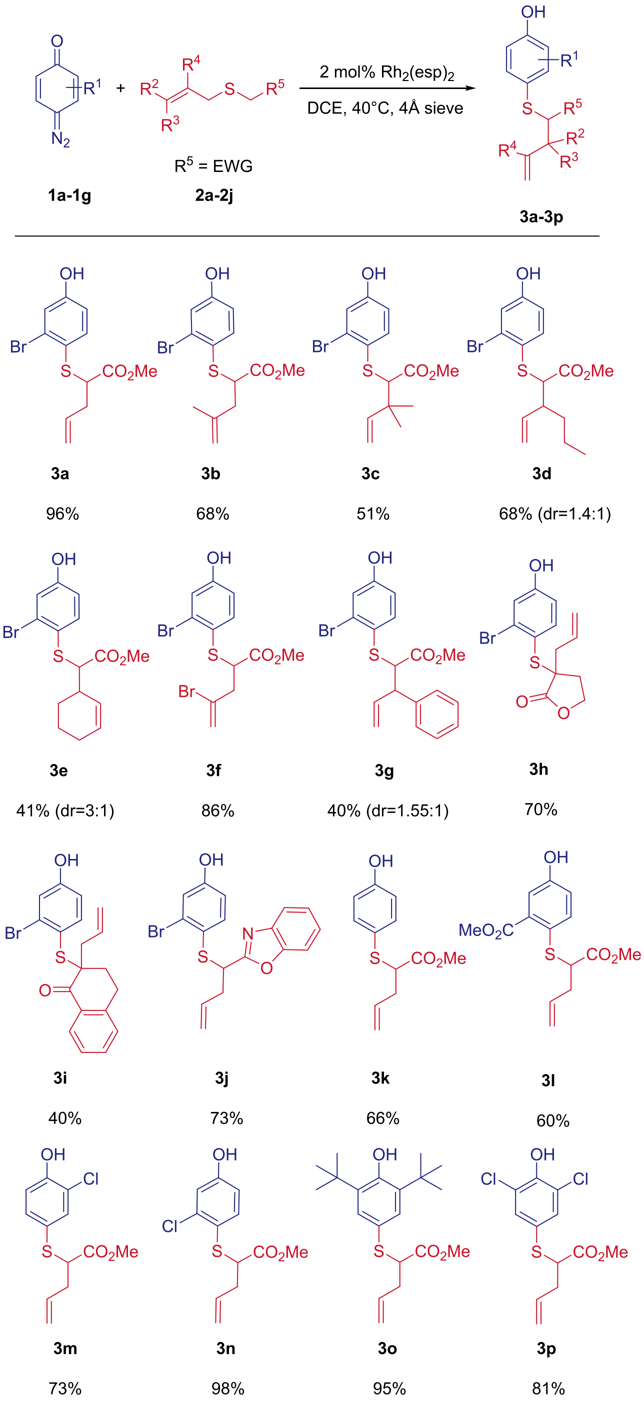
Table 1. Optimization of Reaction Conditions[a−c]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)
1	**$Rh_2(esp)_2$**	**DCE**	**40**	**20**	**98**
2	$Rh_2(OAc)_4$	DCE	40	20	46
3	$Rh_2(oct)_4$	DCE	40	20	41
4	$Rh_2(tpa)_4$	DCE	40	20	65
5	$Rh_2(tfa)_4$	DCE	40	20	5
6	$Cu(acac)_2$	DCE	40	20	trace
7	$Cu(hfac)_2$	DCE	40	20	0
8	$Cu(MeCN)_4BF_4$	DCE	40	20	trace
9	$Rh_2(esp)_2$	DCE	30	24	73
10	$Rh_2(esp)_2$	DCE	50	13	97
11	$Rh_2(esp)_2$	DCE	60	6	81
12	$Rh_2(esp)_2$	THF	40	20	7
13	$Rh_2(esp)_2$	toluene	40	20	90
14	$Rh_2(esp)_2$	CH_3CN	40	20	81
15[c]	$Rh_2(esp)_2$	DCE	40	20	83

[a]The reaction was performed with 0.3 mmol **1a** and 0.9 mmol **2a** in 2.0 mL of solvent under argon. [b]Determined by ^{1}H NMR analysis of the reaction mixture using 1,3,5-trimethylbenzene as an internal standard. [c]0.45 mmol **2a** (1.5 equiv) was used.

Scheme 2. Reaction of Diazoquinones with Allyl Sulfides[a−c]



[a]The reaction was conducted with 0.3 mmol **1** and 0.9 mmol **2** in 2.0 mL of DCE. [b]Isolated yield. [c]The dr ratios were determined by ^{1}H NMR of the reaction mixture.

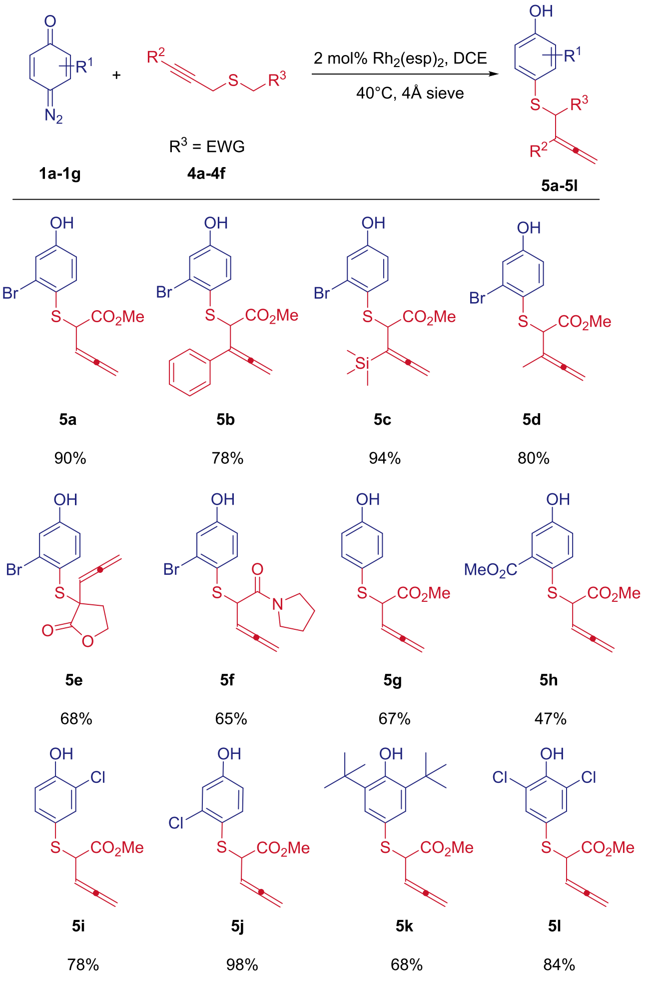
investigated the substitution effect of the allyl moiety on the reaction. Various substitution patterns including *β* and *γ* substitutions, mono- and disubstitutions, and cyclic substitutions are compatible with the reaction, giving corresponding rearrangement products with 41−96% yields (**3a**−**3e**). Bromo and phenyl substituents were found to be tolerant to the reaction, giving the desired product **3f** and **3g** in 86 and 40% yields, respectively.

In addition to linear allylic sulfides, lactone- and cyclic-ketone-derived allylic sulfides are also reactive in the rearrangement reaction, giving corresponding products bearing a quaternary center with good yields (**3h**, **3i**). Benzoxazole is a common moiety in pharmaceutical compounds and bioactive natural products.[10] The benzoxazole-derived allyl sulfide can undergo the rearrangement reaction to give a benzoxazole-containing sulfide with a good yield (**3j**).

The scope of diazoquinones was also examined with sulfide **2a** as the substrate. As depicted in Scheme 2, various diazoquinones, including *meta-*, *ortho-*, and disubstituted diazoquinones, are effective carbene precursors for the Rh(II)-catalyzed rearrangement reaction, affording good to high product yield (60−98%, **3k**−**3p**). In the case of **3k**, the moderate product yield might be attributed to the poor solubility of unsubstituted diazoquinone **1b** in 1,2-dichloroethane. Compared to diazoquinone **1a**, the reaction with ester-substituted diazoquinone **1c** was slower; this observation is consistent with the electron-withdrawing group often make diazo compounds less susceptible toward metal-catalyzed decomposition.[11]

We next investigated the reaction of propargyl sulfides with diazoquinones, which provides efficient access to allenyl sulfides. As shown in Scheme 3, a variety of propargyl sulfides reacted with diazoquinone **1a** to give the corresponding allenyl sulfides **5a**−**5d** in high yields. Internal alkynes are well-tolerated for the reaction, leading to the formation of 1,1-disubstituted allenyl sulfides (**5b**−**5d**). It is worth noting that silane-substituted propargyl sulfide is reactive, giving allenylsilane **5c** in a 94% yield. Allenylsilanes have been demonstrated to be key intermediates in the synthesis of many complex natural products.[12] In addition to the ester group, the R^3 group, such as lactone and amide, is also compatible with the rearrangement reaction, giving corresponding allenyl sulfides with good yields (**5e**, **5f**).

Scheme 3. Reaction of Diazoquinones with Propargyl Sulfides[a,b]



[a]The reaction was conducted with 0.3 mmol **1** and 0.9 mmol **4** in 2.0 mL of DCE. [b]Isolated yield.

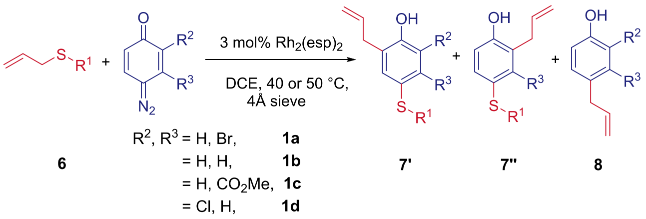
The scope of diazoquinones was also examined in the rearrangement. As shown in Scheme 3, various substituted diazoquinones are reactive and give desired allenyl sulfides with moderate to high yields (**5g**−**5l**).

We next investigated the substitution (R^1) effect of allylic sulfides on the reaction (Table 2). Interestingly, it is found that varying substituent R^1 could dramatically change the reaction pathway of the reaction with diazoquinones. When phenyl allyl sulfide was used, the reaction with diazoquinone **1a** gave a phenylthio-substituted phenol **7a** as a major product with a 64% yield and a regioisomeric ratio of 2.6:1, along with phenol **8a** as a minor product (entry 1). The toluene substituent led to a similar result (entry 2). When electron-deficient aryl substituents were used, the reaction required longer reaction time and higher temperature to be completed (entries 3−5). The ratio of **7**/**8** was around 1:1−3.5 when diazoquinones **1b**, **1c**, and **1d** were used as the carbene precursors (entries 6−8). However, when R^1 is an alkyl group, the reaction of allylic sulfides with diazoquinone **1a** or **1d** led to the formation of only **8a** or **8d** with good yield, and no product **7** was observed (entries 9−12).

Product **7** presumably stems from the cascade reaction of Doyle−Kirmse rearrangement and Cope rearrangement of sulfur ylide. This hypothesis is supported by the control experiments in Scheme 4. Treatment of 4-chlorophenyl allyl sulfide **6c** with diazoquinone **1a** or **1b** at 40 °C for 20 h gave Doyle−Kirmse reaction products **9** and **10** in 69 and 60% yields, respectively (Scheme 4a). The structure of **10** was unambiguously confirmed by X-ray crystallography. The electron-withdrawing groups on the aryl moiety were found to stabilize the Doyle−Kirmse reaction product and vice versa (Table 2, entries 1 and 2 vs entries 3−5). This observation is reminiscent of the rate acceleration of the anionic oxy-Cope reaction, where an anionic alkoxy group substantially weakens the adjacent C(3)−C(4) bond presumably due to anionic hyperconjugation.[13] Compound **9** was observed to convert to compound **7** with a regioisomeric ratio of 3:1 at 60 °C via Cope rearrangement (Scheme 4b). It is worth noting that $Rh_2(esp)_2$ could facilitate the Cope rearrangement, as the conversion of the reaction is low in the absence of $Rh_2(esp)_2$ under the same conditions. This result is consistent with the previous reports that Bronsted and Lewis acids are capable of promoting Cope rearrangement presumably by delocalization of the charge and the six electrons of the Cope transition state.[14] Along with **7**, phenol **8a** and disulfide **11** were also observed in the control experiment, indicating that the formation of **8** arose from the elimination of the thio group from the Doyle−Kirmse reaction product.

A tentative reaction mechanism is proposed in Scheme 5. Dirhodium carboxylate decomposes diazoquinone to generate a metallo-quinone carbenoid species which is trapped by the allylic sulfide to form a free sulfur ylide or metal-associated sulfur ylide.[15] Depending on the R^2 substituent of the sulfides, the sulfur ylide can proceed via three possible pathways. In path A (R^2 = ester), the sulfur ylide undergoes a rapid tautomerization to give intermediate **II** due to the acidity of

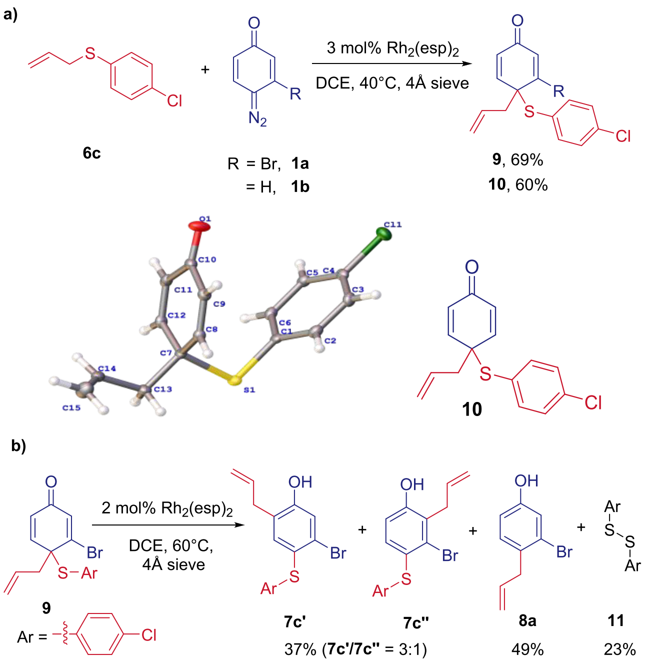
Table 2. Reaction of Diazoquinones with Aryl Allyl Sulfides or Alkyl Allyl Sulfides[a–c]



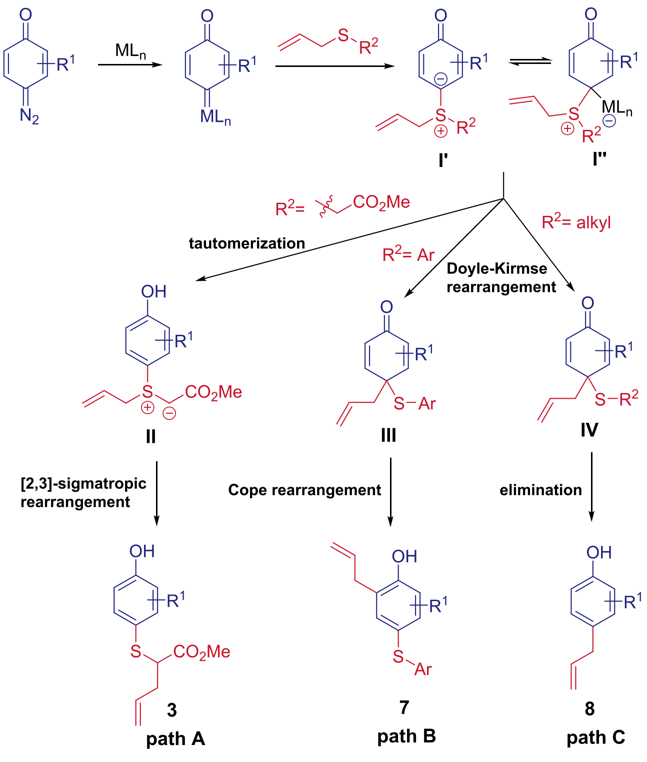
entry	R^1	R^2	R^3	yield	
				7	8
1	Ph	H	Br	64% (7a′/7a″ = 2.6:1)	23%, **8a**
2	4-Me-Ph	H	Br	74% (7b′/7b″ = 3:1)	4%, **8a**
3[c]	4-Cl-Ph	H	Br	33% (7c′/7c″= 2:1)	64%, **8a**
4[c]	4-F-Ph	H	Br	52% (7d′/7d″ = 4.1:1)	40%, **8a**
5[c]	4-CF_3-Ph	H	Br	50% (7e′/7e″ = 1.9:1)	48%, **8a**
6	4-Me-Ph	H	H	32%, **7f**	41%, **8b**
7	Ph	H	CO_2Me	25% (7g′/7g″ = 8:1)	21%, **8c**
8	Ph	Cl	H	21%, **7h**	75%, **8d**
9	Me	H	Br	0	53%, **8a**
10	$CH_2CH{=}CH_2$	H	Br	0	55%, **8a**
11	CH_2Ph	H	Br	0	60%, **8a**
12	$CH_2CH{=}CH_2$	Cl	H	0	42%, **8d**

[a]The reaction was performed with 0.3 mmol **1** and 0.9 mmol **6** in 1.2 mL of DCE under argon. [b]Isolated yield (rr ratios were determined by ^1H NMR). [c]Temperature = 50 °C, reaction time = 96 h.

Scheme 4. Control Experiments



Scheme 5. Proposed Reaction Mechanism



the α-C−H proton of thioacetate and the propensity of aromatization of cyclohexadienone. The intermediate undergoes [2,3]-sigmatropic rearrangement to give product **3**. In path B (R = aryl), sulfur ylide undergoes the cascade reaction of Doyle−Kirmse rearrangement and Cope rearrangement to furnish multisubstituted phenol **7**. However, in the case of R = alkyl (path C), the sulfur ylide tends to undergo Doyle−

Kirmse rearrangement and elimination of the thio moiety, giving product **8**. The actual reason why intermediate **IV** undergoes elimination in preference to Cope rearrangement is not clear at this stage.

In conclusion, three types of rearrangement reactions of sulfur ylide derived from diazoquinone and allyl/propargyl sulfides were developed. Dependent on the sulfide substituent, diazoquinones undergo a chemoselective tautomerization/[2,3]-sigmatropic rearrangement reaction, a Doyle−Kirmse rearrangement/Cope rearrangement cascade reaction, or a Doyle−Kirmse rearrangement/elimination reaction, providing alkenyl and allenyl sulfides and multisubstituted phenols in moderate and high yields.

■ ASSOCIATED CONTENT

SI Supporting Information

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Experimental procedures, characterization of new compounds, and spectral data (PDF)

Accession Codes

CCDC 2021262 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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