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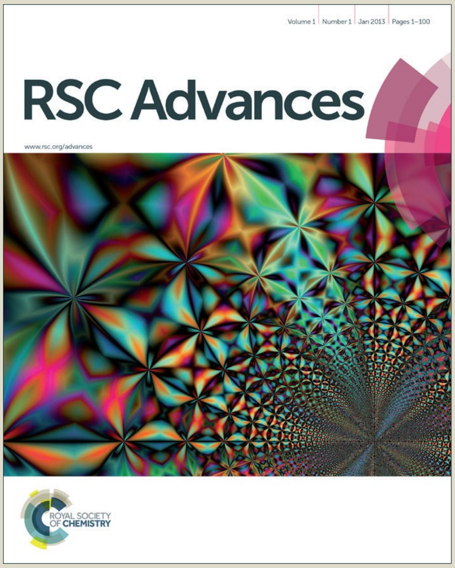

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Stereoselective *Z*-halosulfonylation of terminal alkynes using sulfonohydrazides and CuX (X = Cl, Br, I)

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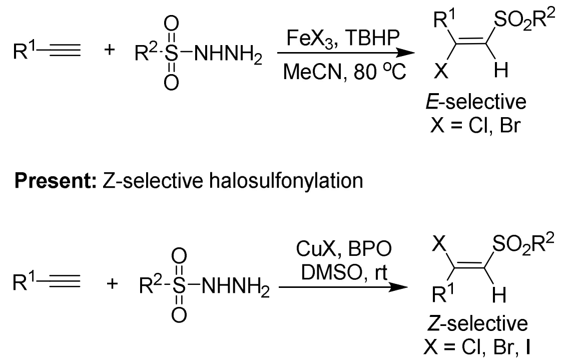
The *Z*-selective halosulfonylation of terminal alkynes has been achieved via the halosulfonylation of terminal alkynes by using sulfonohydrazides and copper (I) halides (CuI, CuBr and CuCl), which enables the generally applicable synthesis of halogenated vinyl sulfones with satisfactory efficiency.

The difunctionalization of alkynes is a crucial strategy in modern organic synthesis by providing straightforward and flexible accesses to poly functionalized alkene derivatives.[1] Among the various known patterns of alkyne difunctionalization, the halosulfonylation which provides halogenated vinyl sulfones has received extensive attention in recent years because of the prevalent presence of sulfonylated vinyl substructure in biologically functional molecules as well as their valuable application in organic synthesis.[2] There have been longstanding efforts made by chemists for the synthesis of these halogenated vinyl sulfones during the past decades, the survey on related literature shows that these halogenated vinyl sulfones can be synthesized by the electrophilic halogenation of sulfonylated vinyl zirconium,[3] the oxidation of β-halogenated vinyl sulfides,[4] and more universally, the difunctionalization of alkynes using various sulfonyl reagents. Generally, the halosulfonylation using sulfonyl halides,[5] sodium sulfinates/halogen source,[6] sulfinic acid/iodine[7] and sulfonohydrazides have all been known as practical routes to halogenated vinyl sulfones.[8] While these known protocols provide enriched options in the synthesis of these functionalized compounds, an amazing fact was that almost all these known methods give vinyl sulfone products with *E*-selectivity, and the only known example of *Z*-selective alkyne difunctionalization toward the β-halo vinyl sulfone synthesis has been reported by Liang and co-workers wherein sulfonyl chloride is used as the difunctionalizing reagents in the presence of copper catalyst, stoichiometical Me_2S ligand with 110 °C heating.[5d] On the other hand, the reactions employing stable sulfonohydrazides as partners are known to provide selectively *E*-configurated products (Scheme 1).[8] Additionally, another challenge in the difunctionalization-based synthesis of halogenated vinyl sulfones is that almost no method showing general applicability to the synthesis of chloro-, bromo- and iodo-vinyl sulfones is present available because of either the limited tolerance of the catalytic conditions or the unavailability of related halogen sources. In this regard, developing alkyne halosulfonylation reactions of *Z*-selectivity and/or general application to the synthesis of Cl, Br and I functionalized vinyl sulfones is presently an issue of urgent significance. Upon our recent research interest in the sulfonohydrazide-based synthesis[9] and related reactions



Scheme 1 Stereoselective halosulfonylation of alkynes

involving efficient C-S bond formation,[10] we report herein an unprecedented and generally applicable *Z*-selective halosulfonylation reactions of alkynes using CuX (X = Cl, Br, I) as halogen sources as well as the switchable alkyne hydrosulfonylation reactions (Scheme 1).

Originally, the reaction between phenylacetylene **1a** and tosyl hydrazine **2a** was conducted in the presence of CuI, BPO (benzoyl peroxide), and CuI/BPO, respectively. The results indicated that the presence of both CuI and BPO enabled the

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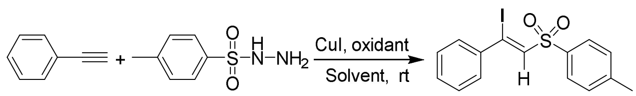
Electronic Supplementary Information (ESI) available: [general experimental information, procedure for the synthesis of **3** and **4**, ^1H and ^{13}C NMR spectra of all products and the crystallographic data of **3i**]. See DOI: 10.1039/x0xx00000x production of (*Z*)-iodosulfonylated styrene **3a** with moderate yield (entries 1-3, Table 1). While CuI was a mandatory component acting as both the catalyst and iodine source in the reaction, we then examined the effect of peroxide to the reaction. It was found that peroxides such as hydrogen peroxide and TBHP (*t*-butyl hydrogen peroxide) was not practical for the target transformation. Interestingly, the variation on the reaction medium with various organic solvents, including DMF, ethyl lactate (EL), EtOH, water, dichloromethane and toluene suggested that none of these solvent could mediate the reaction, implying the specific function of DMSO for this reaction probably by acting as a ligand to stabilize the copper catalyst (entries 6-11, Table 1). While the entry increasing the amount of CuI did not improve the yield of **3a** (entry 12, Table 1), increasing the loading of **2a** to 1.5 eq led to evident improvement on the yield of **3a** (entries 13-14, Table 1). Finally, the variation on the amount of BPO was not able to further improve the reaction (entries 15-16, Table 1). An additional entry employing molecular iodine as the halogen source in the presence of catalytic amount of CuI resulted in the production of complex mixture (entry 17, Table 1). The *Z*-configuration of **3a** was clearly assigned by full spectroscopic analysis and the comparison of related data with those of E-isomer reported in literature.[4c] The X-ray analysis on the single crystal of the synthesized product **3i** was a further confirmation on the assignment (Fig. 1).

Table 1 Optimization on the reaction conditions for the *Z*-selective iodosulfonylation[a]



1a 2a 3a

Entry	Oxidant	Solvent	Yield(%)[b]
1[c]	BPO	DMSO	nr
2	no	DMSO	trace
3	BPO	DMSO	57
4	TBHP	DMSO	21
5	H_2O_2	DMSO	trace
6	BPO	DMF	trace
7	BPO	EL	nr
8	BPO	EtOH	nr
9	BPO	H_2O	nr
10	BPO	CH_2Cl_2	nr
11	BPO	toluene	nr
12[d]	BPO	DMSO	59
13[e]	**BPO**	**DMSO**	**85**
14[f]	BPO	DMSO	82
15[g]	BPO	DMSO	70
16[h]	BPO	DMSO	75
17[i]	BPO	DMSO	nr

[a]General conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), CuI (0.2 mmol), oxidant (0.2 mmol), stirred at rt for 12 h in 2.0 mL solvent, nr = no reaction; EL = ethyl lactate. [b]Yield of isolated product based on **1a**. [c]No CuI was employed. [d]The CuI loading was 0.3 mmol. [e]The loading of **2a** was 0.3 mmol. [f]The loading of **2a** was 0.4 mmol. [g]The loading of BPO was 0.1 mmol. [h]The loading of BPO was 0.3 mmol. [i]Catalytic amount of CuI (10 mol%) in the presence of 1 eq mole of I_2 (0.2 mmol), and complex mixture was formed.

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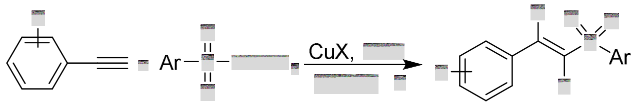
To examine the application scope, the synthesis of diverse *Z*-halogenated vinyl sulfones **3** was conducted by employing a variety of different terminal alkynes **1** and sulfonohydrazides **2**. As shown in Table 2, under the optimized conditions, a number of *Z*-alkene products **3** were smoothly synthesized with generally good to excellent yields. Aryl terminal alkynes and sulfonohydrazides containing various functional groups such as alkyl, alkoxyl, halogen et al were all well tolerated. Considerably lower yield of related product was acquired when phenylacetylene containing strong electron withdrawing group was used (**3ai**, Table 2). A highly notable fact of the present protocol lied in its universal applicability not only for the synthesis of iodinated products (**3a**-**3s**, Table 2), but also

Table 2 Scope of the *Z*-selective alkyne halosulfonylation[a]



1 2 3

R	Ar	X	Product	Yield (%)[b]
H	4-$CH_3C_6H_4$	I	**3a**	85
H	Ph	I	**3b**	71
4-CH_3	Ph	I	**3c**	86
3-CH_3	Ph	I	**3d**	74
3-F	Ph	I	**3e**	65
2-F	Ph	I	**3f**	63
4-Cl	Ph	I	**3g**	81
4-Br	Ph	I	**3h**	83
4-CH_3O	4-$CH_3C_6H_4$	I	**3i**	79
4-Cl	4-$CH_3C_6H_4$	I	**3j**	73
4-Br	4-$CH_3C_6H_4$	I	**3k**	80
4-CH_3	4-$CH_3OC_6H_4$	I	**3l**	68
4-Cl	4-$CH_3OC_6H_4$	I	**3m**	66
4-CH_3	4-ClC_6H_4	I	**3n**	71
4-Cl	4-ClC_6H_4	I	**3o**	56
4-CH_3	4-CNC_6H_4	I	**3p**	69
4-CH_3	4-$NO_2C_6H_4$	I	**3q**	65
4-Cl	2-$CH_3C_6H_4$	I	**3r**	58
4-CH_3	2-FC_6H_4	I	**3s**	61
4-CH_3	Ph	Br	**3t**	83
4-CH_3O	Ph	Br	**3u**	72
4-Cl	Ph	Br	**3v**	64
3-CH_3	Ph	Br	**3w**	78
H	4-$CH_3C_6H_4$	Br	**3x**	73
4-CH_3	4-$CH_3C_6H_4$	Br	**3y**	75
4-Cl	4-$CH_3C_6H_4$	Br	**3z**	62
4-Br	4-$CH_3C_6H_4$	Br	**3aa**	59
4-CH_3	2-naphthyl	Br	**3ab**	76
4-Cl	2-naphthyl	Br	**3ac**	71
H	Ph	Cl	**3ad**	70
4-CH_3	Ph	Cl	**3ae**	68
4-Cl	Ph	Cl	**3af**	59
4-Br	Ph	Cl	**3ag**	62
4-Br	4-$CH_3C_6H_4$	Cl	**3ah**	62
4-CN	4-$CH_3C_6H_4$	I	**3ai**	30

[a]General conditions: **1** (0.2 mmol), **2** (0.3 mmol), CuX (0.2 mmol) and BPO (0.2 mmol) in DMSO (2 mL), stirred at room temperature for 12 h. [b]Yield of isolated product based on **1**.

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the brominated (**3t**-**3z**, **3aa**-**3ac**, Table 2) and chlorinated products (**3ad**-**3ah,** Table 2). Therefore, along with the hardly accessible *Z*-selectivity,[11] the general application scope to different halogen sources remarks another desirable feature of the present alkyne halosulfonylation protocol.[12] No expect halosulfonylation was observed when 1,2-diphenylethyne, a typical internal alkyne, aliphatic terminal alkyne or phenylacetylenes containing sensitive groups (3-hydroxyl phenylacetylene, 3-aminophenylacetylene and 2-formyl phenylacetylene, respectively) were subjected with tosyl hydrazine and CuI and standard reaction conditions. In addition, the reactions employing methanesulfonohydrazide didn't provide expect transformation, either.

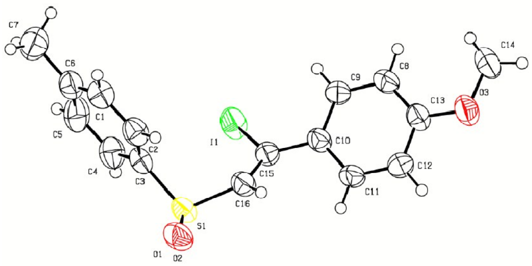
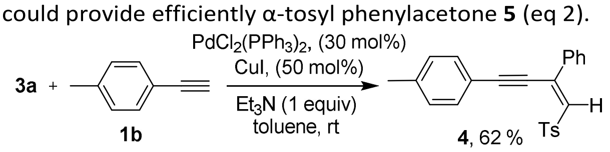
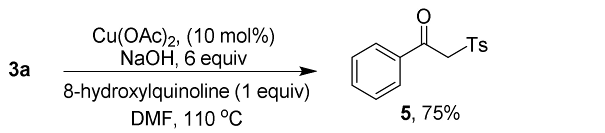


Figure 1 X-Ray single crystal structure of **3i**

Considering the rare availability of these *Z*-halogenated vinyl sulfones determined by the lack of synthetic methodology, primary investigation on their synthetic applications of the Z-vinyl sulfone was then conducted. For example, products **3a** could undergo Sonogashira coupling reaction with terminal alkyne **1b** to provide corresponding conjugate *Z*-enyne **4** (Eq1). In addition, the copper-catalyzed C(sp^2)-I hydroxylation of **3a** could provide efficiently α-tosyl phenylacetone **5** (eq 2).

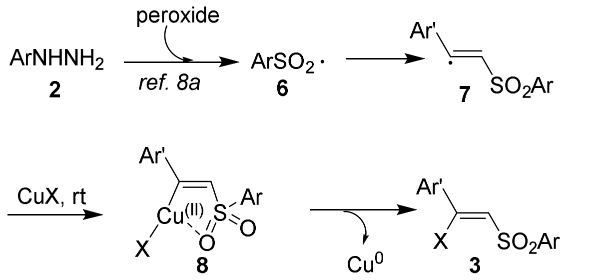


(1)



(2)

To illustrate the possible routes of transformation, the mechanism has been proposed on the basis of the outcomes obtained in our work and related literatures (Scheme 2).[5d,8a] In known reports of alkyne difunctionalization involving the sulfonyl reagents, the sulfone radical is a generally recognized intermediate. As proposed in the previous *E*-selective halosulfonylation of alkynes using sulfonohydrazides in the presence of a peroxide and FeX_3 (X = Cl, Br),[8a] the sulfonyl radical **6** is proposed to be produced from the sulfonohydrazide in the presence of peroxide (BPO). With the activation CuX, the reaction of alkyne with sulfonyl radical **6** provides vinyl sulfone radical **7**. The incorporation of **7** to CuX may then results in the formation of Cu(II)-species **8** via oxidative addition. The Cu---O interaction forming cyclic structure in **8** accounts for the *Z*-selectivity of this vinyl sulfone formation. Subsequently, the reductive elimination of **8** provides *Z*-halogenated vinyl sulfone products **3**.



Scheme 2 The proposed reaction mechanism

Conclusions

In conclusion, by employing Cu(I) halides as the halogen sources and sulfonohydrazides as reaction partners, the hardly accessible *Z*-selective halosulfonylation of terminal alkynes has been successfully achieved in the presence of BPO at room temperature. The novel *Z*-stereoselectivty, mild reaction conditions and the general tolerance to halogen sources (Cl, Br, I) have featured the high potential of the present method in the synthesis of diverse halogenated vinyl sulfones.

Acknowledgments

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11 CCDC 1474142 (**3i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

12 According to the TLC analysis, small amount of *E*-isomers were observed in some entries, but none of them were isolable by column chromatography (very low yield) in the present scale of experiment.

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Stereoselective *Z*-halosulfonylation of terminal alkynes using sulfonohydrazides and CuX (X = Cl, Br, I)

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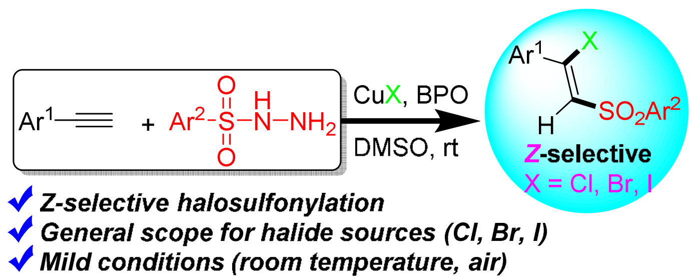

The unconventional *Z*-selective halosulfonylation of terminal alkynes has been achieved by using CuX (X= Cl, Br, I)/sulfonohydrazides at rt. Providing a practical and new route for the synthesis of diverse halogenated vinyl sulfones.