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Iron(III) Chloride-Mediated Regio- and Stereoselective Chlorosulfonylation of Alkynes and Alkenes with Sodium Sulfinates

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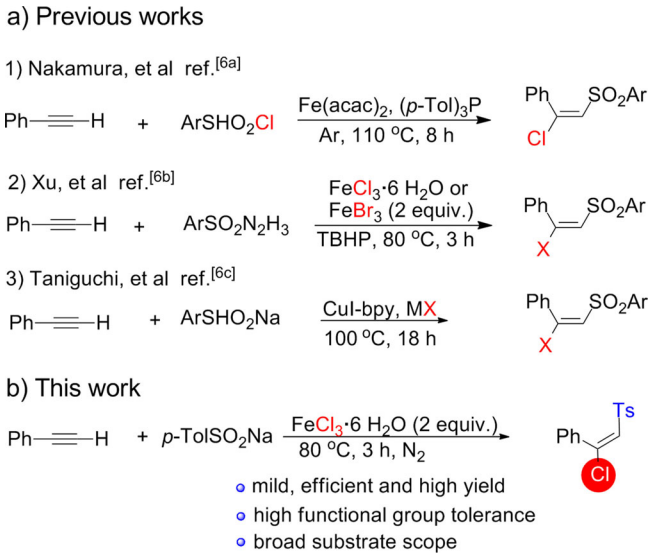
Abstract: The atom-economic and one-pot regio- and stereoselective addition of sodium arenesulfinates to either alkynes or alkenes can be achieved with an iron(III) chloride hexahydrate [$FeCl_3 \cdot 6H_2O$] catalytic system to afford β-haloalkenyl and β-chloroalkyl sulfones in moderate to good yields.

Keywords: alkenes; alkynes; β-chloroalkyl sulfones; β-haloalkenyl sulfones; sodium arenesulfinates

Introduction

As basic starting materials, halide-functionalized alkenyl compounds are versatile substrates in organic transformations.[1,2] Nonetheless, they are costly to buy due to their rare availability. On the other hand, vinyl sulfone derivatives are valuable organic intermediates in the fields of organic,[3] medicinal[4] and materials chemistry.[5] For example, they are efficient Michael acceptors[3b] as well as being good 2π partners in cycloaddition reactions.[3g] Also, vinyl sulfone derivatives can be readily exchanged by entities such as hydrogen, alkyl, hydroxy, and carbonyl groups, and are versatile reactive synthons in organic synthesis.[3a,c,e] Given the importance of vinyl sulfones and the utility of halides, it is of great interest to make use of the two moieties in organic synthesis.

Difunctionalization of alkynes is the most efficient and direct method for the synthesis of β-haloalkenyl sulfones (Scheme 1).[6] Transition metal-catalyzed difunctionalization of alkynes with sulfonyl chlorides has achieved various degrees of success in the control of selectivity. In 2013, Xu et al. disclosed a method for the synthesis of β-haloalkenyl sulfones using alkynes and sulfonyl hydrazides as starting materials, where an iron halide was employed as the halide source.[6b] However, the two methods have drawbacks such as the need for special ligands and moisture-sensitive transition metal catalysts as well as poor tolerance towards functional groups. In recent years, sodium sulfinates have attracted significant attention, more than that of sulfonyl chlorides or sulfonyl hydrazides, because sodium sulfinates are more air- and moisture-stable. In 2014, Taniguchi et al. reported the



Scheme 1. Methods for the synthesis of β-haloalkenyl sulfones.

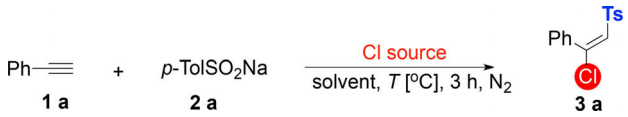
direct activation of alkynes with organic sodium sulfinates for the preparation of β-haloalkenyl sulfones, but there was the requirement for a special ligand. It is well known that $FeCl_3$ releases Cl ions in some radical reactions.[7] In the light of this information, we envisaged that the combination of sodium sulfinates with $FeCl_3$ may result in the chlorosulfonylation of alkynes.

In this work, β-haloalkenyl sulfones are synthesized with good to excellent yield in the iron halide-mediated regio- and stereoselective halosulfonylation of alkynes with sodium sulfinates. It is noted that the reaction also works well for alkenes with excellent tolerance toward functional groups, affording the corresponding difunctionalization derivatives in good yields.[8] The starting materials are simple and commercially available, and the system shows excellent selectivity and yields. The approach is superior to the methods reported so far in the literature, in which ligands and air-sensitive reagents were used.

Results and Discussion

We initiated our study by using phenylacetylene (**1a**) and 4-$MeC_6H_4SO_2Na$ (**2a**) as substrates to optimize the reaction. As shown in Table 1, when $FeCl_3$ (2.0 equiv.) is adopted, the reaction gives no formation of the target product, i.e., (*E*)-1-[(2-chloro-2-phenylvinyl)sulfonyl]-4-methylbenzene (**3a**) (Table 1, entry 3). To our delight, when 2.0 equiv. of $FeCl_3{\cdot}6H_2O$ is used under the optimized conditions, **3a** is generated in 94% yield (Table 1, entry 9), and 2.0 equiv. of $FeCl_3{\cdot}6H_2O$ proved to be the most suitable for the reaction (Table 1, entries 9 and 21). The application of $FeCl_3$ (2.0 equiv.), $CuCl_2$ (2.0 equiv.) or $FeCl_2$ (2.0 equiv.) in combination with 12 equiv. H_2O was tested under the same conditions, (Table 1, entries 1, 6 and 8), and only 90% yield of **3a** is formed when 2.0 equiv. $FeCl_3$ are employed. Then we optimized the amount of H_2O, and found that 12 equiv. H_2O are the best (Table 1, entries 4–7). We also used $CuCl_2{\cdot}2H_2O$ instead of $FeCl_3{\cdot}6H_2O$ under the optimized conditions (Table 1, entries 2 and 9), and the product was generated in 23% yield. All the results indicate that H_2O and Fe(III) play an essential role in the reaction. A selection of solvents, i.e., CF_3CH_2OH, DMF, DMSO, toluene, CH_3CN and C_2H_5OH was screened, and the results indicate that 2.0 mL of CF_3CH_2OH are the best (Table 1, entries 9–14, 24 and 25). The result may be ascribed to the fact that CF_3CH_2OH is miscible with water in any proportions and is also a strongly protic solvent. Furthermore, with the decrease of reaction temperature, there is decline in product yield. Since the increase of temperature from 80 °C to 120 °C does not result in any increase of product yield, we take 80 °C as the optimal temperature (Table 1, entries 15–18). When the reaction is conducted in air rather than in nitrogen, there is a decline of product yield from 94% to 40%, plausibly due to the influence of oxygen on the generation of sulfonyl radicals (Table 1, entry 19). In the study of the effects of 4-$MeC_6H_4SO_2Na$ (**2a**) loading and reaction time, we found that the maximum **3a** yield is achieved at a phenylacetylene/4-$MeC_6H_4SO_2Na$ molar

Table 1. Optimization of the reaction conditions.[a]



1 a 2 a 3 a

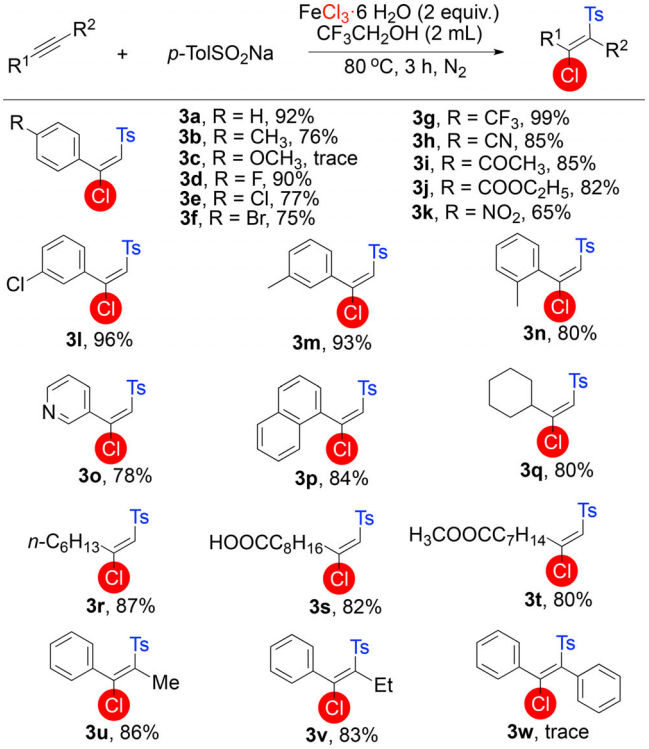
Entry	Cl source [2 equiv.]	Solvent [2 mL]	*T* [°C]	Yield [%][b]
1[d]	$CuCl_2$	CF_3CH_2OH	80	trace
2	$CuCl_2{\cdot}2H_2O$	CF_3CH_2OH	80	23
3	$FeCl_3$	CF_3CH_2OH	80	N.D.[c]
4[e]	$FeCl_3$	CF_3CH_2OH	80	24
5[f]	$FeCl_3$	CF_3CH_2OH	80	62
6[d]	$FeCl_3$	CF_3CH_2OH	80	90
7[g]	$FeCl_3$	CF_3CH_2OH	80	88
8[d]	$FeCl_2$	CF_3CH_2OH	80	N.D.
9	**$FeCl_3{\cdot}6H_2O$**	**CF_3CH_2OH**	**80**	**94**
10	$FeCl_3{\cdot}6H_2O$	DMF	80	26
11	$FeCl_3{\cdot}6H_2O$	DMSO	80	39
12	$FeCl_3{\cdot}6H_2O$	toluene	80	63
13	$FeCl_3{\cdot}6H_2O$	CH_3CN	80	78
14	$FeCl_3{\cdot}6H_2O$	C_2H_5OH	80	89
15	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	25	18
16	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	60	78
17	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	100	91
18	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	120	93
19[h]	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	80	40
20[i]	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	80	82
21[j]	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	80	74
22[k]	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	80	92
23[l]	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	80	93
24[m]	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	80	89
25[n]	$FeCl_3{\cdot}6H_2O$	CF_3CH_2OH	80	92

[a] Reactions were carried out at 80 °C with phenylacetylene (0.5 mmol), 4-$MeC_6H_4SO_2Na$ (0.75 mmol), Cl source in a selected solvent (2 mL) under dry nitrogen with stirring for 3 h.
[b] Yield was determined by GC analysis, and dodecane was used as the internal standard.
[c] N.D. = not detected.
[d] H_2O (12 equiv.).
[e] H_2O (4 equiv.).
[f] H_2O (8 equiv.).
[g] H_2O (16 equiv.).
[h] Under an air atmosphere.
[i] 4-$MeC_6H_4SO_2Na$ (1.2 equiv.).[j] $FeCl_3{\cdot}6H_2O$ (1.5 equiv.).
[k] For 6 h.
[l] For 9 h.
[m] CF_3CH_2OH (1.0 mL).
[n] CF_3CH_2OH (3.0 mL).

ratio of 1/1.5 and in a reaction time of 3 h (Table 1, entries 9, 20, 22 and 23).

Shown in Table 2 are the results of reacting a variety of substituted alkynes with 4-Me$C_6H_4SO_2Na$.

Table 2. Scope of the alkynes.[a]



[a] Reactions were carried out with alkynes (0.5 mmol), *p*-TolSO_2Na (0.75 mmol), and $FeCl_3·6H_2O$ (1.0 mmol) in CF_3CH_2OH (2.0 mL) under stirring in dry nitrogen at 80 °C for 3 h.

It is obvious that electron-withdrawing groups, slightly electron-donating groups and steric groups at the phenyl ring are well tolerated (**3a**, **3b** and **3d**–**3k**). The X-ray structure of **3d** is shown in Figure 1. However, strong electron-donating groups are not compatible in this system, implying a Friedel–Crafts-type oxidation process (**3c**).[9] Functional groups at the *meta* or *ortho* positions do not affect the reaction (**3l**–**3n**). To our delight, C–X groups (X = Cl, Br, CN, NO_2, $COCH_3$, $COOC_2H_5$) are well tolerated in the reaction, signifying that these compounds have great potential for further functionalization (**3e**–**3l**). In addition, *p*-F- and *p*-CF_3-substituted phenylacetylenes are compatible under the adopted conditions, which is a favorable factor for pharmaceutical and materials chemistry (**3d**, **3g**). Moreover, a pyridine- or naphthalene-substituted alkyne is suitable for this transformation, affording the desired **3o** and **3p** products in 78% and 84% yields, respectively. When chains or rings of aliphatic alkynes are applied, (*E*)-1-[(2-chloro-2-cyclohexylvinyl)sulfonyl]-4-methylbenzene (**3q**) and (*E*)-1-[(2-chlorooct-1-en-1-yl)sulfonyl]-4-methylbenzene (**3r**) are generated in 80% and 87% yields. To our surprise, chains of aliphatic alkynes with a wide range of functional groups such as carboxyl and ester are well tolerated, giving the target products in 80–82% yields (**3s** and **3t**). With internal alkynes the chlorosulfonylation products **3u** and **3v** are obtained in 83% and 86% yields, but 1,2-diphenylethyne only gives **3w** in trace amounts, this phenomenon may be ascribed to the effect of steric hindrance.

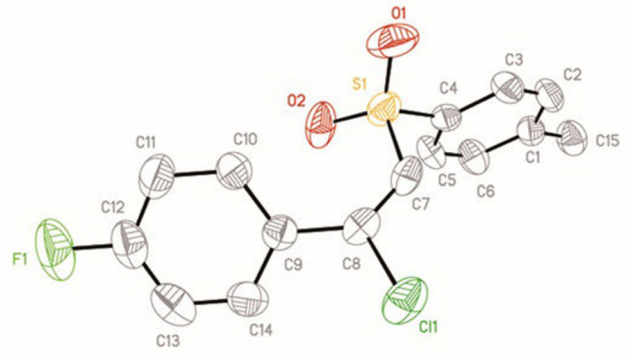


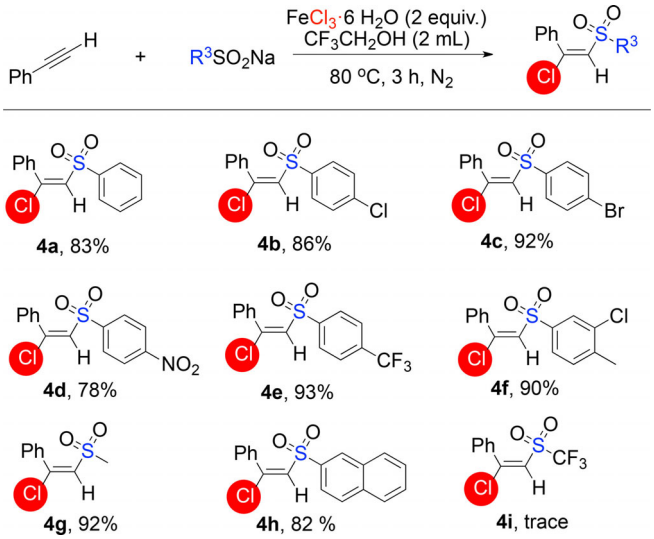
Figure 1. ORTEP drawing of compound **3d**. Hydrogen atoms are omitted for clarity; ellipsoids are drawn at 50% probability. Selected bond lengths [Å] and angles [°]: S1–O1 1.426(3), S1–O2 1.435(3), S1–C4 1.756(4), S1–C7 1.757(3), Cl1–C8 1.750(3), C8–C7 1.326(5), C8–C9 1.463(5), C8–C7–S1 127.3(3), C7–C8–Cl1 115.7(3), C9–C8–Cl1 113.6(3), C4–S1–C7 102.53(17).

The results of reacting phenylacetylene compounds with a number of sodium sulfinates under the optimized condition are depicted in Table 3. Gratifyingly, the introduction of CH_3, H, CF_3, NO_2 and halogen groups to the phenyl ring of sodium sulfinates is well tolerated, and the sulfonylation products are isolated in good to excellent yields (**4a**–**4f**). Moreover, aliphatic and naphthalene-substituted sodium sulfinates also react efficiently with phenylacetylene, affording the corresponding β-haloalkenyl sulfones (**4g** and **4h**). Unfortunately, sodium trifluoromethanesulfinate is not suitable for this reaction (**4i**).

To our delight, there is no need to change any of the reaction conditions to pave the way for using alkenes as reaction partners (Table 4). Substitution at the *para* position affords the desired products **5a**–**5d** in excellent yields. Strong electron-donating groups are again not compatible (**5e**). Substitution at the *meta* position does not affect the reaction (**5f**). Chains of aliphatic alkene are well tolerated (**5g** and **5h**). However, the internal alkene 1,2-diphenylethene fails in the reaction to give the desired product (**5i**) due to steric hindrance.

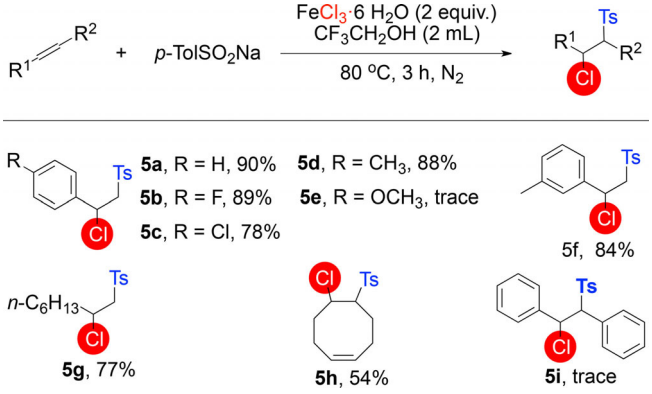
Control experiments were conducted to gain insights into the reaction mechanism (Scheme 2). In the case of Scheme 2 Eq. (1), there is no formation of the

Table 3. Scope of the sodium sulfonates.[a]

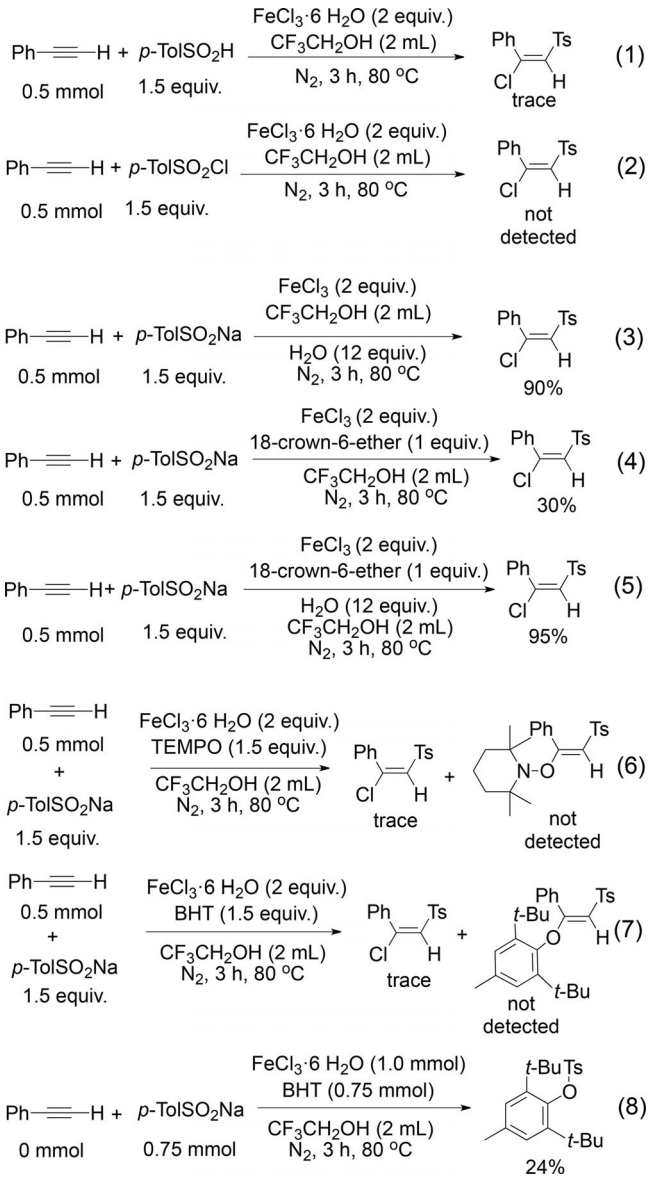


[a] Reactions were carried out with phenylacetylene (0.5 mmol), sodium sulfinates (0.75 mmol), and $FeCl_3·6H_2O$ (1.0 mmol), in CF_3CH_2OH (2.0 mL) under stirring in dry nitrogen at 80 °C for 3 h.

Table 4. Scope of the alkenes.[a]



[a] Reactions were carried out with alkene (0.5 mmol), *p*-$TolSO_2Na$ (0.75 mmol), $FeCl_3·6H_2O$ (1.0 mmol), in CF_3CH_2OH (2.0 mL) stirred under nitrogen atmosphere at 80 °C for 3 h.



Scheme 2. Control reactions.

expected products, and the possibility of H_2O promoting the conversion of sodium *p*-toluenesufinate to the corresponding nucleophile sulfinic acid can be discarded.[10] Another possible mechanism for the generation of the desired product is *via* the formation of a sulfonyl chloride, followed by the addition of the sulfonyl chloride to alkynes.[6a] To examine such a possibility, we performed the reaction using *p*-$TolSO_2Cl$ instead of *p*-$TolSO_2Na$ (0.75 mmol). As monitored by GC and GC-MS, there is no generation of the target product [Scheme 2, Eq. (2)], and the result shows that such a route is invalid. As discussed above, it is interesting to find out that H_2O plays an important role in this reaction. Scheme 2 Eq. (4) implies that H_2O could serve as a bridge to dissolve the two different phases. Under the conditions of Scheme 2 Eq. (4), we added extra 12 equiv. of H_2O, and the product was generated in 95% yield [Scheme 2, Eq. (5)]. Combining the results of Table 1 with Scheme 2 Eqs. (3)–(5), it is deduced that CF_3CH_2OH is soluble in the organic phase as well as miscible with H_2O at any proportions. With the salt also soluble in H_2O, there is promotion of the reaction in the inorganic phase as well as in the organic phase. In an experiment of phenylacetylene with 4-$MeC_6H_4SO_2Na$ under the optimized conditions with the extra addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (butylated hydroxytoluene), there is no generation of **3a** or any formation of trapping reagent adduct [Scheme 2, Eqs (6) and (7)]. Surprisingly, when the reaction was conducted in

the absence of phenylacetylene and with the addition of BHT under the optimized conditions, there was a 24% yield of BHT-sulfonyl [Scheme 2, Eq. (8)]. In an XPS analysis of Fe after the reaction (Figure 2),

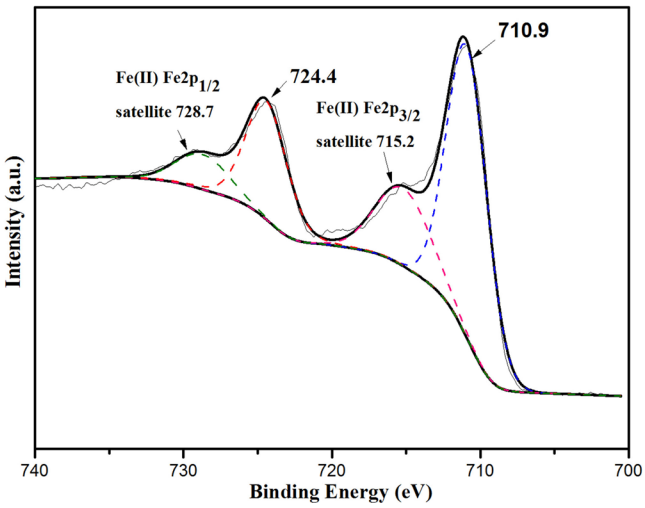
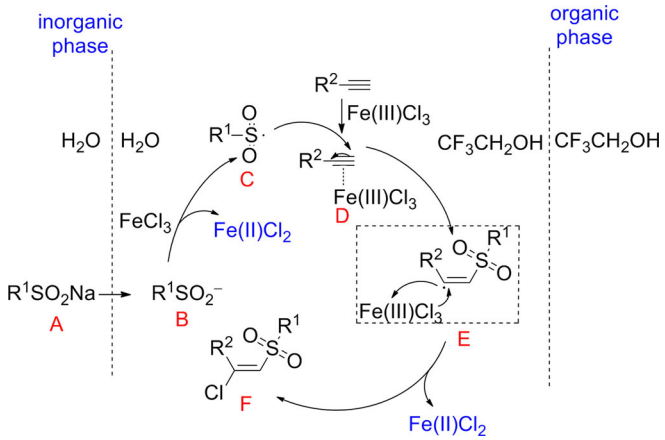


Figure 2. XPS Fe 2p spectrum of Fe after reaction under the optimized conditions.

there are signals at 710.9 and 724.4 eV binding energy corresponding to Fe $2p_{3/2}$ and Fe $2p_{1/2}$, respectively. These peaks could be deconvoluted into two sets of peaks, i.e., 710.9 and 724.4 eV due to Fe in the +2 state, and 715.2 and 728.7 eV due to the satellite signals. The binding-energy difference between the main and satellite peaks is 4.3 eV, which is in good agreement with the reported data.[11a,d] The XPS data support the fact that $FeCl_3{\cdot}6H_2O$ acts as an oxidant in this reaction.[11] In addition, GC and GC-MS information for the reaction of 1-ethynyl-4- fluorobenzene with $4\text{-MeC}_6H_4SO_2Na$ confirms that the one-pot regio- and stereoselective addition of sodium sulfinates to alkynes can proceed efficiently with the $FeCl_3{\cdot}6H_2O$ catalytic system (see Charts in the Supporting Information).

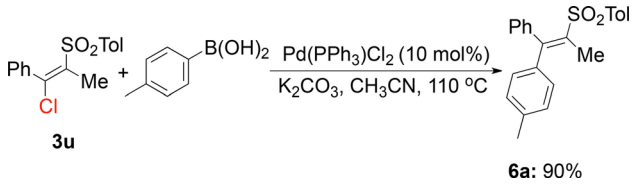
On the basis of the obtained results and the information available in the literature,[6b] we propose a possible mechanism for the reaction (Scheme 3). Initially, sulfonyl radicals (**C**) are generated *via* the assistance of the iron catalyst, where iron halide acts as a Lewis acid to activate alkynes. Subsequently, the addition of sulfonyl radicals to the Fe-coordinated alkynes (**D**) from the opposite side of the Fe moiety at the terminal position leads to the regio- and stereoselective formation of the transition state (**E**). Eventually, reductive elimination of **E** occurs to afford the product *E*-β-halovinyl sulfones (**F**) together with the regeneration of the Fe(II) catalyst.

In order to explore the potential applications of the obtained functionalized tetrasubstituted alkenes for



Scheme 3. A possible reaction mechanism.

synthetic purposes,[12] we performed a palladium-catalyzed cross-coupling reaction of β-chloroalkenyl sulfones with *p*-tolylboronic acid according to the reported procedure, and the arylation coupling product **6a** was obtained with 90% yield (Scheme 4).[12a]



Scheme 4. Transformation of β-haloalkenyl sulfones *via* Suzuki coupling.

Conclusions

We have reported the preparation of β-haloalkenyl sulfones and β-chloroalkyl sulfones with good to excellent yields through iron halide-mediated regio- and stereoselective halosulfonylation of alkynes and alkenes with sodium sulfinates. This protocol uses the $FeCl_3{\cdot}6H_2O$ catalyst as Cl source as well as oxidant, and avoids the use of air-sensitive reagents and special ligands. Furthermore, the reaction is easy to operate and the starting materials are simple and commercially available. Considering the utility of the resulting compounds, the protocol has potential for wide application in the construction of biologically active molecules, catalysis ligands, and functional materials.

Experimental Section

General

All solvents used in the reactions were freshly distilled. The reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitro-

gen unless specified otherwise. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a 400 MHz spectrometer with the sample dissolved in $CDCl_3$. ^{1}H NMR chemical shifts are reported using TMS as internal standard while ^{13}C NMR chemical shifts are reported relative to $CDCl_3$. The electron ionization method was used for HR-MS measurements, and the mass analyzer type was double-focusing.

General Procedure for the Preparation of Sodium Sulfinates

Sulfinic acid sodium salts $C_6H_4SO_2Na$, sodium 4-chlorobenzenesulfinate, sodium 3-chloro-4-methylbenzenesulfinate, sodium methanesulfinate and sodium trifluoromethanesulfinate were purchased from Alfa-Aesar with purity equal to or greater than 98.0%. They were used as received without further purification. Sodium 4-bromobenzenesulfinate was prepared by heating 5.0 g of sodium sulfite, 4.12 g of 4-bromobenzenesulfonyl chloride, and 3.36 g of sodium bicarbonate in 20 mL of water at 80 °C for 8 h. After cooling to room temperature, water was removed under vacuum. Recrystallization of the residue in ethanol afforded the product as a white solid; yield: 2.76 g (70%). Similarly, other sodium arenesulfinates (sodium 4-nitrobenzenesulfinate, sodium 4-(trifluoromethyl) benzenesulfinate, sodium naphthalene-2-sulfinate) were prepared from the corresponding sulfonyl chlorides.

Procedure for the Suzuki Coupling Reaction of 3u with *p*-Tolylboronic Acid

Under an argon atmosphere, 0.5 mmol (*E*)-1-[(1-chloro-1-phenylprop-1-en-2-yl)sulfonyl]-4-methylbenzene **3u** was added to a mixture of 0.6 mmol *p*-tolylboronic acid, 0.05 mmol $Pd(PPh_3)_2Cl_2$ and 0.6 mmol K_2CO_3 in 3 mL CH_3CN. After stirring at 110 °C for 30 min, the reaction mixture was quenched with saturated NaCl, extracted with ethyl acetate (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration under vacuum, the crude product was purified with flash chromatography on silica gel (ethyl acetate/petroleum ether = 1/20) to give **6a**.

General Procedure for the Preparation of β-Haloalkenyl Sulfones and β-Chloroalkyl Sulfones

$FeCl_3{\cdot}6H_2O$ was purchased from Sinophsrm Chemical Reagent Co., Ltd with a purity equal or greater than 99.0%. CF_3CH_2OH was purchased from Aladdin with purity equal or greater than 99.8%. For the reaction of alkynes compounds with sodium sulfinates: a mixture of alkyne compound (0.5 mmol), sodium sulfinate (0.75 mmol), $FeCl_3{\cdot}6H_2O$ (1 mmol) in CF_3CH_2OH (2 mL) was stirred at 80 °C under a nitrogen atmosphere for 3 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with aluminum heating sleeve. The reaction temperature was directly read from the screen of the IKA apparatus and was not calibrated. Removal of the solvent under reduced pressure gave the crude product; and the pure product was obtained by passing the crude product through a short silica gel column using hexane/EtOAc as eluent.

Crystallographic Information

CCDC 1510491 (**3d**) 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.

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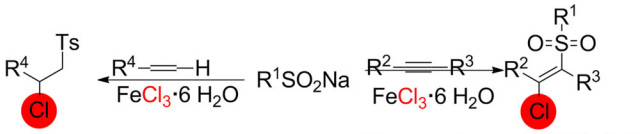

9 examples up to 90% yield

32 examples up to 99% yield

- mild, efficient and high yield
- high functional group tolerance
- broad substrate scope