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Copper-Catalyzed Difunctionalization of Allenes with Sulfonyl Iodides Leading to (*E*)-α-Iodomethyl Vinylsulfones

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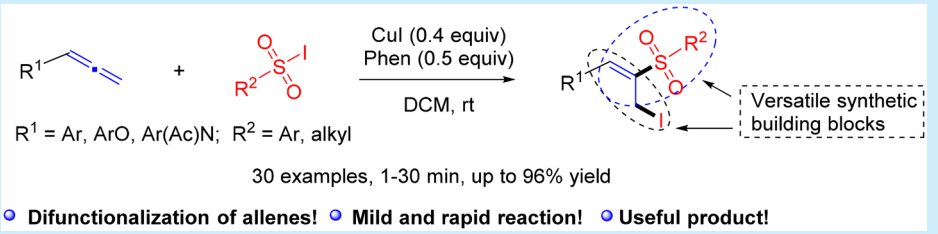
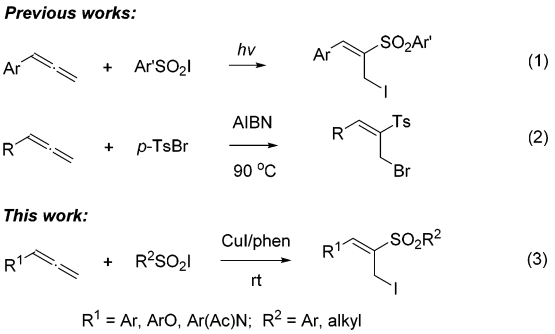
Supporting Information



ABSTRACT: A highly regioselective iodosulfonylation of allenes in the presence of CuI and 1,10-phenanthroline has been developed for the synthesis of various useful (*E*)-α-iodomethyl vinylsulfones in moderate to excellent yields. This practical reaction is fast, operationally simple, and in particular, proceeds under very mild conditions to afford the target products with high regio- and stereoselectivity. The selectivity was illustrated by a conceptual DFT analysis.

Allenes are interesting and potential small organic molecules that possess a special functional group of two cumulative carbon−carbon double bonds. They have been widely used in difunctionalization reactions in modern synthetic organic chemistry for rapid and straightforward access to synthetically complex molecules in a single procedure via a variety of different difunctional strategies.[1,2] A number of reagents as the difunctional groups donors were introduced to the allenes, such as sulfonyl halides,[3,4] *N*-fluorobenzenesulfonimide,[5] diboron reagents,[6−10] borylsilane,[11] silylstannanes,[12] aminals,[13] diorganoselenium reagents,[14,15] diphenyl disulfide,[16] allyl bromide,[17] cyanoformates,[18] chloroformates,[19] selenol esters,[20] acyl- and alkynylstannanes,[21] benzamides,[22−24] and areneselenosulfonates.[25] However, achieving the difunctionalization reaction of allenes with high regioselectivity, stereoselectivity, and chemoselectivity is very challenging work because diverse reactive sites are available in allenes.[3,6,26−31]

Vinylsulfone-containing compounds have been found to be widespread in biological molecules, such as cysteine protease inhibitors,[32] HIV-1 inhibitors,[33] covalent protease inhibitors,[34] and inhibitors of a transpeptidase required for cell wall protein anchoring and virulence in *Staphylococcus aureus*.[35] The difunctionalization of allenes through the halosulfonylation of allenes represents a particularly useful contribution to vinylsulfone-containing molecule synthesis because both the allylic halide and vinylsulfone moieties in the resulting α-halomethyl vinylsulfones can be further used as versatile building blocks in synthetic organic chemistry and transformed into high-value vinylsulfone-containing chemicals.[36,37] They also possess great synthetic potential due to the presence of a halo group. However, a review of the literature reveals that only two works[3,4] have been carried out toward allenes with sulfonyl halides. In 1974, Truce and co-workers[3] reported the 1:1 adducts of sulfonyl iodides and allenes under photochemical conditions (eq 1). Further work by Kang's group[4] has



(1) (2) (3)

extended the scope of the difunctional reaction to the use of sulfonyl bromides and allene substrates. They described a regioselective radical addition of 4-methylbenzenesulfonyl bromide to substituted terminal allenes in the presence of azodiisobutyronitrile (AIBN) at 90 °C. Only five kinds of tosyl-substituted allylic bromides were obtained in yields of 63−87% (eq 2).

As can be seen, the use of an AIBN reagent and a photochemical conditions restricted their practical utility on a

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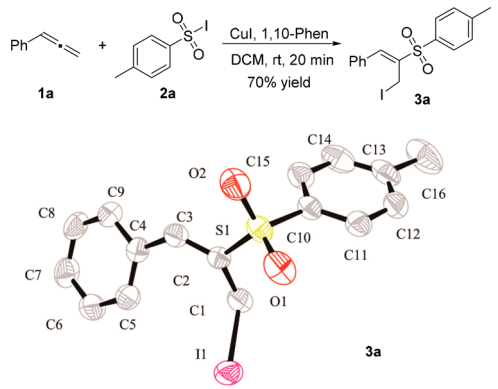
larger scale process. Therefore, the development of a reliable and practical halosulfonylation strategy for the difunctionalization of allenes under mild conditions to achieve the highly regioselective transformations is highly desirable. We report here a mild and practical method for the rapid synthesis of various useful (*E*)-α-iodomethyl vinylsulfones via an iodosulfonylation of allenes in the presence of CuI and 1,10-phen under mild conditions by employing sulfonyl iodides serving as both iodine and sulfonyl sources (eq 3). This operationally simple and highly selective reaction proceeds very fast under very mild conditions.

Recently, we aimed at developing new sulfuryl halide reactions for synthesis of reactive sulfonyl-containing compounds under mild conditions.[38] As part of our ongoing program of discovering new reaction patterns of sulfonyl halides,[38] an important but relatively rarely studied iodosulfonylation reaction of allenes was focused. Initially, phenylallene (**1a**) and 4-methylbenzenesulfonyl iodide (**2a**) were selected as model substrates (Scheme 1). After many attempts, the desired

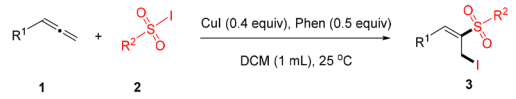
Scheme 1. Synthesis and Single-Crystal X-ray Structure of 3a

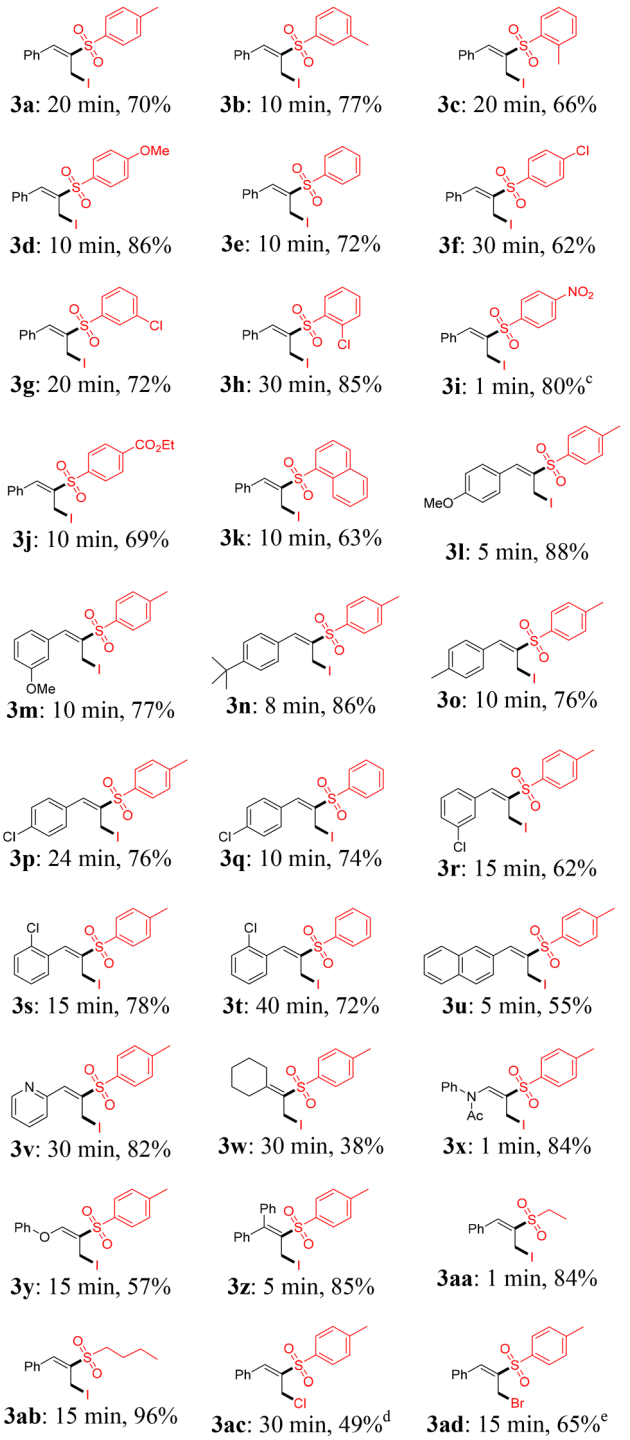


product (*E*)-1-((3-iodo-1-phenylprop-1-en-2-yl)sulfonyl)-4-ethylbenzene (**3a**) was isolated in 70% yield when we treated the mixture of **1a** and **2a** with 0.4 equiv of CuI and 0.5 equiv of 1,10-phen in dichloromethane (DCM) solvent at 25 °C for 20 min. Furthermore, the accurate structure of the iodosulfonylated product **3a** was confirmed by single-crystal X-ray diffraction analysis (Scheme 1). Notably, product **3a** was predominantly formed with high selectivity.

After extensive screening of different reaction parameters (Table S1), optimum conditions were identified to be CuI (0.4 equiv) as catalyst, 1,10-phen (0.5 equiv) as ligand, and DCM as solvent at room temperature (see Table S1, entry 2). With the optimal reaction conditions in hand (Table S1, entry 2), we set out to investigate the substrate scope of this intermolecular regioselective difunctionalization reaction (Scheme 2). The substitution effect on the aromatic ring of the arylsulfonyl iodides **2** was examined first. It was found that a variety of different substitution including electron-donating groups (EDGs) (e.g., **3a**–**c**, −Me, and **3d**, −OMe) and electron-withdrawing groups (EWGs) (**3f**–**h**, −Cl, **3i**, $-NO_2$, and **3j**, $-CO_2Et$) at the *para*-, *ortho*-, or *meta*-positions as well as the benzenesulfonyl iodide were well tolerated in the reaction with **1a** and afforded the desired sulfonyl-substituted primary (*E*)-allylic iodides **3a**–**j** in moderate to good yields (62–86%). Of note, a moderate yield (63%) of **3k** was achieved in the case of starting material naphthalene-1-sulfonyl

Scheme 2. Extension of Reaction Scope[a,b]





[a]Unless otherwise indicated, all reactions were carried out with **1a** (0.45 mmol), **2a** (0.3 mmol), CuI (0.4 equiv), and 1,10-phen (0.5 equiv) and in commercial DCM (1 mL) at 25 °C. [b]Isolated yield. [c]Reaction was performed at −20 °C. [d]CuCl (1.0 equiv) was used instead of CuI. [e]CuBr (0.7 equiv) was used instead of CuI.

iodide. Next, we studied the impact of allene end substitution on the reaction. Good to high yields of **3l**–**t** (62–88%) were

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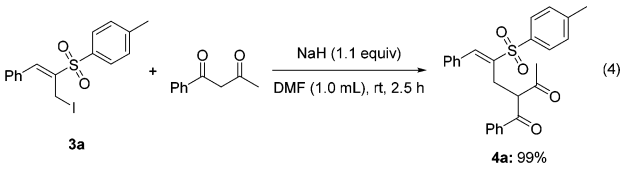
obtained in the cases of 1-arylallenes bearing an EDG (**3l**−**m**, −OMe, **3n**, −^{t}Bu, or **3o**, −Me) and a weak EWG (**3p**−**t**, −Cl) on the substituted phenyl group moiety. Notably, 1-naphthylallene showed a slightly lower reactivity than that of phenylallene and produced the corresponding product **3u** in 55% yield. To our delight, on expanding the functional group tolerance, allenylpyridine and vinylidenecyclohexane were smoothly converted to the desired products **3v** and **3w** in 82 and 38% yields, respectively.

Having observed the wide substrate scope, we tested some special allenes, including the *N*-allenylamine, *O*-allenyl ether, and 1,1-diphenylallene. As a result, they were proven to be suitable substrates for this reaction, giving the corresponding difunctionalized products **3x**−**z** in 84, 57, and 85% yields, respectively. To our delight, aliphatic sulfonyl iodide starting materials ethanesulfonyl iodide and butane-1-sulfonyl iodide gave excellent yields of the addition products **3aa** (84%) and **3ab** (96%). The sulfuryl chloride and bromide could also undergo the additions to phenylallene to produce corresponding (*E*)-α-chloromethyl- and (*E*)-α-bromomethyl vinylsulfones **3ac** and **3ad** in relative lower yields of 49% and 65%, respectively. It is noteworthy that no difunctionalized products at other locations of the allenes were observed for all tested cases in the intermolecular regioselective difunctionalization reaction in Scheme 2. It should be also noted that this new method has a scope limitation: the addition of sulfonyl iodides to general monoalkyl allenes resulted in a mixture of products without selectivity, thereby possibly impacting its synthetic significance.

Previous works demonstrated that the useful primary allylic iodide moiety could be attacked by various nucleophiles leading to other useful functional small organic molecules.[4,39] To explore the applications for this type of compounds is a very practical and meaningful work. Our preliminary attempts showed that the alkylation product **4a** was obtained in a yield of 99% by the reaction of **3a** and 1-phenylbutane-1,3-dione in the presence of 1.1 equiv of NaH in 1.0 mL of DMF after 2.5 h (eq 4).[39] The experiments disclosed that this type of



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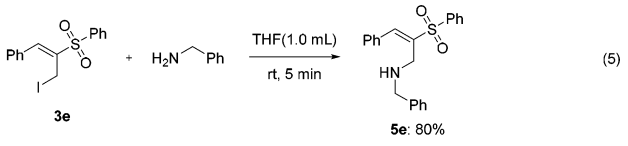

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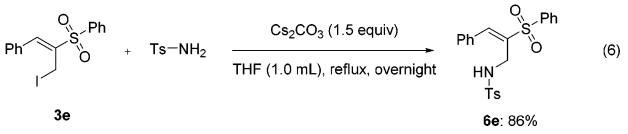
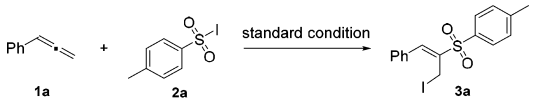


(6)

iodoalkanes, such as **3e**, could also be attacked by other nucleophilic reagents under different reaction conditions, including phenylmethanamine and 4-methylbenzenesulfonamide, resulting in β,γ-unsaturated amines **5e** (80%) and **6e** (86%), which are versatile and essential building blocks in organic chemistry (eqs 5 and 6).[4,40]

Many works have disclosed that the copper-catalyzed addition reaction of the olefins and alkynes with sulfonyl halides maybe proceed through the free-radical pathway. To clarify the mechanism of the iodosulfonation of allenes, control experiments were conducted with two different radical scavengers. The results reveal that the reactions were suppressed in the presence of 1 equiv and 3 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and galvinoxyl (Galv) radical scavengers, respectively, which suggested that a radical species might be involved in this reaction (Scheme 3).

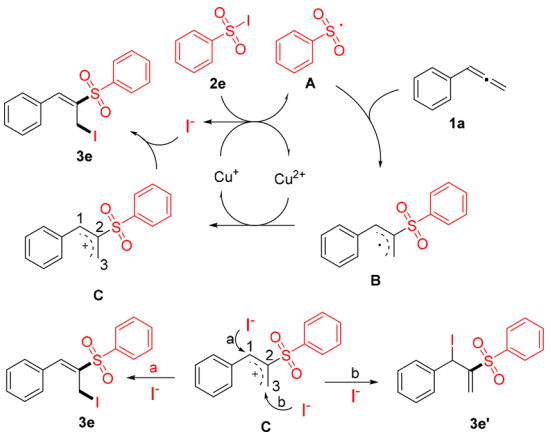
Scheme 3. Radical-Trapping Experiments



without radical inhibitors	70%
with TEMPO (1.0 equiv)	8%
with TEMPO (3.0 equiv)	0%
with Galv (1.0 equiv)	26%
with Galv (3.0 equiv)	0%

Based on the results of the current study and the literature, the mechanism of the regioselective radical addition of sulfonyl iodides to the substituted allenes is proposed in Scheme 4. It is

Scheme 4. Proposed Mechanism



presumed that sulfonyl radical **A** and a highly charged iodine ion generate first with the help of CuI and Phen.[41−46] Then the addition of tosyl radical to the central carbon atom of the allene moiety leads to the extensively radical delocalized intermediate **B**,[23] which is further oxidized to a extensively delocalized carbocation **C** in the propagating step, followed by the iodation at the terminal position regioselectively to afford the (*E*)-α-iodomethyl vinylsulfones **3**.[3,4,47] To explain the regioselectivity, a conceptual DFT[48] analysis (by means of electron density as the fundamental property) is performed to obtain the order of electrophilic attack of C1 and C3 of the intermediate **C**. The calculated Fukui function values $f(r)^+$, calculated using NPA charges at B3LYP/6-311+G(d,p) level, of C3 and C1 are 0.156 and 0.106, respectively, illustrating that the C3 is much more electrophilic than C1. Further energy calculations for optimized **3e** and **3e′** show that the **3e** is more stable than **3e′** by 7.57 kcal/mol. These calculated results are entirely consistent for the experimental findings.

In summary, an efficient and practical method has been developed for rapid synthesis of useful (*E*)-α-iodomethyl

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vinylsulfones through a highly selective iodosulfonylation of allenes in the presence of CuI and 1,10-phen in moderate to excellent yields under mild conditions. These reactions underwent very rapidly and tolerated diverse functionalities on various readily available starting materials. Furthermore, preliminary application exploration disclosed that the resulting α,β-unsaturated allylic iodide derivatives are useful synthons for the synthesis of multifunctional vinylsulfones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01765.

Screening of reaction conditions, experimental procedures, X-ray diffraction data, and ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

Accession Codes

CCDC 1846775 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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