Organic LETTERS

Letter

pubs.acs.org/OrgLett

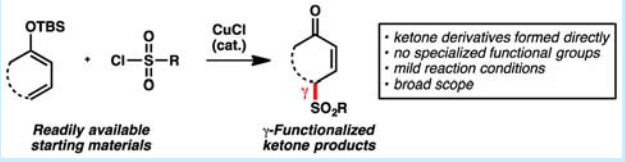
Copper-Catalyzed γ-Sulfonylation of α,β-Unsaturated Carbonyl Compounds by Means of Silyl Dienol Ethers

Xiaoguang Liu, Xiaohong Chen, and Justin T. Mohr*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, United States

Supporting Information

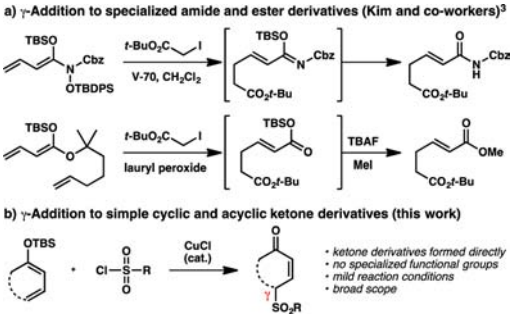
ABSTRACT: A regioselective method for the introduction of sulfonyl groups at the γ-carbon of enone systems is reported. Using a copper catalyst and readily available sulfonyl chlorides, a range of silyl dienol ethers are sulfonylated in good yield under mild reaction conditions. The sulfone derivatives formed are poised for further synthetic manipulations as demonstrated by regioselective alkylations.



Unsaturated carbonyl compounds are valuable synthetic intermediates owing to the aggregation of multiple locations poised for further functionalization. Perhaps most notably, the α- and β-carbons may be substituted readily by engaging the polarized alkene in a conjugate addition reaction followed by an enolate alkylation. Substitution of the more remote γ-carbon of an enone has proven substantially more challenging. Considerable effort, including in our own laboratory,[1] has been directed toward achieving this goal, often relying on dienolate intermediates.[2] These approaches have met with some success, but are generally limited to a narrow range of suitable electrophilic partners and often require strongly basic reaction conditions. Consequently, a general solution to the problem of ketone γ-functionalization has remained elusive.

In 2004, Kim and co-workers[3] introduced an elegant, radical-based strategy for γ-functionalization relying on specifically engineered hydroxamic acid or ester derivatives that contain an internal reactive moiety that enables decomposition of a putative radical intermediate, obtaining excellent results for the synthesis of amides and esters (Scheme 1a). The substrate design constraints limit the scope of the transformation and notably exclude ketones and most cyclic systems as viable radical acceptors.[4] To further our efforts in the area of γ-functionalization, we aimed to address this issue with the express goal of creating γ-functionalized enone products that are largely inaccessible through dienolates or the Kim system.

Scheme 1. Strategy for Carbonyl γ-Functionalization



Sulfones are generally useful synthetic intermediates[5] and are central moieties in a variety of useful biologically active compounds (Figure 1). Given the value of sulfones and the general deficiency of existing methods to form γ-C−S bonds,[3,4,6] we selected γ-sulfonyl enones to test our strategy for ketone γ-functionalization (Scheme 1b). We reasoned that the γ-sulfonyl enone would provide the opportunity to carry out a regiocontrolled γ-alkylation, a concept explored by Lansbury, Trost, and Paquette,[7] which is particularly attractive since it would facilitate access to various γ-alkylated enones. Moreover, sulfones have garnered significant recent attention as versatile substrates for enantioselective catalysis,[8] and as a result additional methods for installing these functional groups are of ever-increasing value. Herein, we report the results of our first efforts toward achieving the goal of ketone γ-C−S bond formation using a combination of readily available silyl dienol ethers, sulfonyl chlorides, and a Cu catalyst to access versatile sulfone products.

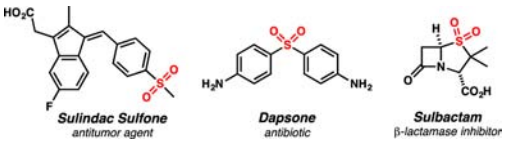


Figure 1. Biologically active sulfones.

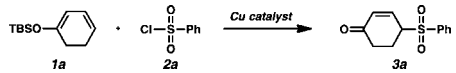
We chose cyclohexenone as a model substrate owing to literature reports of selective formation of the thermodynamically preferred extended dienolate isomer and trapping of this intermediate as an isolable dienol ether.[9] The first critical design element we sought to address was the nature of the oxygen substituent which could serve a number of roles depending on the precise reaction pathway. We reasoned that a group capable

Received: June 8, 2015
Published: July 1, 2015

DOI: 10.1021/acs.orglett.5b01675
Org. Lett. 2015, 17, 3572−3575

of sustaining a radical chain process would be ideal, and given the prevalence of enol silanes we first examined these derivatives. We found that the TBS-derived ether (**1a**, Table 1) was easily

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	catalyst (mol %)	solvent	temp (°C)	yield (%)	entry	catalyst (mol %)	solvent	temp (°C)	yield (%)
1	none	CH_3CN	80	0	7	CuCl (1)	CH_3CN	80	10
2	CuI (5)	CH_3CN	80	45	8	CuCl (10)	CH_3CN	80	91 (83)[b]
3	CuBr (5)	CH_3CN	80	40	9	CuCl (10)	C_6H_6	80	31
4	CuCl (5)	CH_3CN	80	74	10	CuCl (10)	dioxane	80	36
5	$CuCl_2$ (5)	CH_3CN	80	10	11	CuCl (10)	CH_3CN	60	20
6	Cu (10)	CH_3CN	80	52	12	CuCl (10)	CH_3CN	90	45

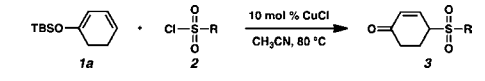
[a]Yields determined by ^1H NMR (using CH_2Br_2 as an internal standard) for reaction of dienol ether (0.25 mmol), $PhSO_2Cl$ (1.1 equiv), in solvent (1 mL) for 4 h. [b]In parentheses is the isolated yield for reaction on 0.50 mmol scale.

prepared and offered good stability that allowed purification and storage. With this material in hand, we turned our attention to identifying a suitable coupling partner. Truce and co-workers reported that sulfonyl chlorides add to diene systems in the presence of Cu catalysts,[10] and although this technique is rarely used,[11] recent interest in the chemistry of sulfonyl radicals prompted us to explore this system in detail.[12]

To adapt the Cu-catalyzed sulfonylation conditions to our more complex substrates, we first investigated a stoichiometric reaction with a 1:1:1 ratio of siloxydiene, $PhSO_2Cl$, and Cu salts. We were pleased to find that the desired γ-sulfonylation product (**3a**, Table 1) was formed, validating our regiocontrol hypothesis, although the yield was less than 10% and therefore the capacity for catalysis was in question. Fortunately, simply reducing the loading of Cu to 5 mol % increased the efficiency of the reaction dramatically and the sulfone formed in 45% NMR yield with CuI (entry 2). Screening additional Cu catalysts revealed CuCl to be most effective (entries 3−6). Increasing the CuCl loading to 10 mol % gave a very efficient reaction from which sulfone **3a** was isolated in 83% yield (entry 8). Several solvents were viable, but substantially higher yield was observed with acetonitrile (entries 8−10). This difference may be explained by the fact that the reaction is homogeneous only in acetonitrile. Finally, varying the temperature from 80 °C caused a substantial drop in yield over the 4 h reaction time (entries 11−12); at lower temperature unreacted starting material remained, and at higher temperature nonspecific decomposition occurred. We also investigated different silyl groups, but observed little difference from the initial TBS-derived compound.

Given the variety of commercially available sulfonyl chlorides, the scope of the transformation was readily elucidated (Table 2). Several arenesulfonyl chlorides varying in structure and electronics participated in the reaction with good results (**2a**−**2g**, entries 1−7). The reaction is readily scaled to produce multigram quantities of product with no decrease in efficiency (entry 1). We found that with certain sulfonyl halides (e.g., **2c**−**2e**) the product formed in low yield under our typical reaction conditions at 80 °C.[13] However, these problems were mitigated by performing the reaction at room temperature over longer reaction times (entries 3−5). Alkanesulfonyl halides **2h**−**2k** provided uniformly good results and the steric demands of the sulfonyl chloride appear to have little influence on the efficiency of the reaction (entries 8−12). Sensitive functional groups such as heterocycles, primary alkyl chlorides, or cyclopropanes may be

Table 2. Scope of Sulfonyl Chlorides[a]



1a 2 3

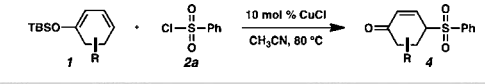
entry	sulfonyl chloride	product	% yield
1	**2a** R = H	**3a**	83 (85)[b]
2	**2b** R = Me	**3b**	87
3	**2c** R = NO_2	**3c**	56[c]
4	**2d** R = Me	**3d**	42[c]
5	**2e** R = *i*-Pr	**3e**	66[c]
6	**2f**	**3f**	53
7	**2g**	**3g**	55
8	**2h** R = Me	**3h**	69
9	**2i** R = *i*-Pr	**3i**	78[d]
10	**2j** R =	**3j**	66[e]
11	**2k** R =	**3k**	70
12	**2l**	**3l**	63

[a]Isolated yield (average of two runs) for reaction of dienol ether (0.50 mmol), sulfonyl chloride (1.1 equiv), in CH_3CN (2 mL) at 80 °C for 4 h. [b]Yield in parentheses for 10 mmol scale reaction. [c]Reaction at 22 °C for 10 h. [d]Contains 21% isomeric vinyl sulfone. [e]Contains 14% isomeric vinyl sulfone.

present without major complications (entries 7, 10, and 11). Camphorsulfonyl chloride (**2l**) engaged in the reaction as well, although no stereoinduction was apparent.

We turned next to the dienol ether reaction partner (**1**, Table 3). These materials were readily prepared from the corresponding enones by trapping the thermodynamically preferred γ-dienolate[1,9] or utilizing soft enolization techniques.[14] We were pleased to find that many dienol ethers participated in the reaction (entries 1−9), only moderately perturbed in cases where

Table 3. Scope of Cyclic Dienol Ethers[a]



1 2a 4

entry	dienol ether	product	% yield
1	**1a** R = H	**3a/4a**	85
2	**1b** R = Me	**4b** dr = 1.7:1	87
3	**1c** R = Bn	**4c** dr = 1.1:1	74
4	**1d** R = allyl	**4d** dr = 1.3:1	81
5	**1e** R = CH_2CO_2t-Bu	**4e** dr = 1.6:1	76
6	**1f**	**4f**	82[b]
7	**1g**	**4g** dr = 15:1	75
8	**1h**	**4h**	48[c]
9	**1i**	**4i**	38
10	**1j**	**4j**	56
11	**1k**	**4k**	50

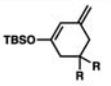
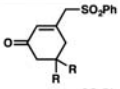
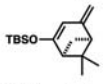
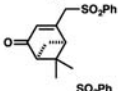
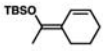
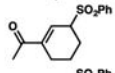
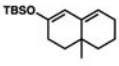
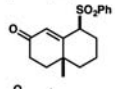
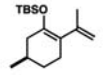
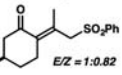
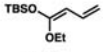
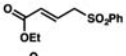
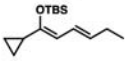
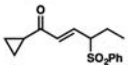
[a]Isolated yield (average of two runs) for reaction of dienol ether (0.50 mmol), $PhSO_2Cl$ (1.1 equiv), in CH_3CN (2 mL) at 80 °C for 4 h. [b]Contains 14% isomeric vinyl sulfone. [c]Contains 13% isomeric vinyl sulfone.

DOI: 10.1021/acs.orglett.5b01675
Org. Lett. 2015, 17, 3572−3575

sterically large substituents neighbored the reactive center (entries 8–9). Despite the demanding sterics, α-tertiary sulfone **4i** was isolated in respectable yield (entry 9). Lactam-derived dienol **1j** was employed to access dihydropyridone **4j**. In the case of the carvone-derived siloxydiene, sulfone **4k** was isolated as a single diastereomer, although the nature of the stereocontrol in this case is not clear at this point.

Pleased with the range of cyclohexanone derivatives that were accessible, we next sought to employ conjugated ethers that resided partially, or completely, outside of a ring (Table 4).

Table 4. Sulfonylation of Exocyclic Dienol Ethers[a]

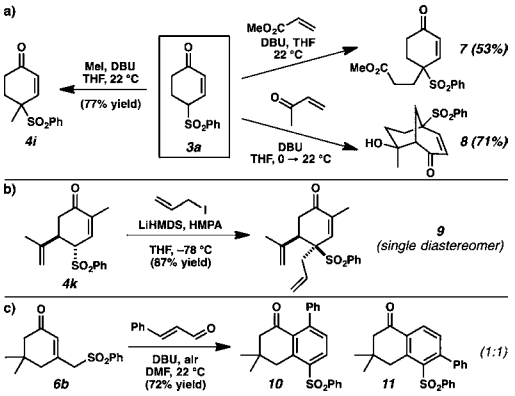
entry	dienol ether		product		% yield
1		**5a** R = H		**6a**	65[b]
2		**5b** R = Me		**6b**	71[b]
3		**5c**		**6c**	67[b]
4		**5d**		**6d**	61
5		**5e**		**6e**	57[b]
6		**5f**	 E/Z = 1:0.82	**6f**	70
7		**5g**		**6g**	79
8		**5h**		**6h**	66[b,c]

[a]Isolated yield (average of two runs) for reaction of dienol ether (0.50 mmol), $PhSO_2Cl$ (1.1 equiv), in CH_3CN (2 mL) at 80 °C for 4 h. [b]Isolated yield over two steps for reaction with 1.0 mmol of crude dienol ether. [c]Contains 10% isomeric vinyl sulfone.

Cyclohexenones bearing a β-methyl substituent are readily converted to the exocyclic methylene derivative (**5a–c**), although these compounds are quite sensitive. To circumvent this issue we often used crude dienol ether products directly;[14] the sulfonyl addition reaction was affected minimally, although yields (measured over two steps) are diminished somewhat due, in part, to substrate decomposition (entries 1–3). In the case of verbenone we observed no ring-opened products despite the strained ring system adjoining the reactive moiety (entry 3). Acyl cyclohexenes are accessible (entry 4) and in a decalin system the octalone product is isolated as a single diastereomer (entry 5). Pulegone-derived dienol ether **5f** participates in the transformation, indicating that a rigidly aligned diene system is not required for reactivity, and the sulfone geometric isomers are separable (entry 6).[14] Encouraged by this result, we explored acyclic substrates: both ethyl crotonate and a cyclopropyl vinyl ketone were transformed to the corresponding sulfones in good yield under our standard reaction conditions (entries 7–8).[2f]

Given the presence of two electron-withdrawing groups in our products, we reasoned that deprotonation would be facile and a subsequent alkylation event may be regioselective (Scheme 2a). This hypothesis was bolstered by studies in related systems by Lansbury and co-workers, although the generality of this strategy was not widely established.[7a,b] Indeed, methylation of sulfone **3a** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base was highly selective for the carbon adjacent to the sulfone and enone **4i** was isolated in 77% yield. The addition to methyl acrylate was

Scheme 2. Synthetic Transformations of Sulfones



also regioselective, forming ester **7** in 53% yield. When methyl vinyl ketone was employed, a stereoselective cascade conjugate addition/aldol sequence occurred leading to [3.3.1]bicycle **8** in 71% yield.[15] A similar transformation described by Paquette and co-workers required discrete conjugate addition and aldol steps.[7d,f] Allylation of carvone-derived sulfone **4k** with allyl iodide as an electrophile yielded enone **9** as a single diastereomer (Scheme 2b). Finally, engaging sulfonylated isophorone **6b** in the [3 + 3] benzannulation reaction recently disclosed by Menon and co-workers yielded tetralones **10** and **11** as a partially separable 1:1 mixture (Scheme 2c).[16]

Although our working hypothesis was based on the intermediacy of a sulfonyl radical,[10] we wished to gain empirical evidence in support of this supposition. Use of stoichiometric quantities of CuCl led to low yield, possibly due to excess Cu(I) behaving as a radical inhibitor. The reaction is air sensitive, perhaps due to decomposition of CuCl, although the reaction may be performed on the benchtop.[17] Addition of potential radical inhibitor butylated hydroxyl toluene (BHT) reduced the yield of the γ-sulfone, and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or $CuCl_2$ negated the addition reaction completely. In the absence of Cu, other radical initiators (2,2′-azobis-(isobutyronitrile) (AIBN),[18] benzoyl peroxide, or Et_3B/O_2) did lead to a significant amount of sulfone product. Tosyl fluoride, bromide, or iodide do not provide appreciable quantities of the γ-addition product under Cu-initiated conditions. The addition of NaI to a prototypical reaction with TsCl completely inhibited the addition and only cyclohexenone was observed. In the presence of allyltributylstannane, the addition reaction does proceed and allyl phenyl sulfone also is observed.[19]

The above data are all consistent with the postulated sulfonyl radical intermediate, but we have not succeeded in obtaining direct evidence for the putative alkoxyallyl radical intermediate that would form after addition. We noted that substrates containing strained rings (Table 2, entry 11 and Table 4, entries 3 and 8) showed no evidence of ring-opening under our standard reaction conditions, suggesting that if a radical intermediate does exist it may have a very short lifetime. To date we have found no byproducts that might be expected from a free silyl radical. In light of these observations it is tempting to consider an ionic mechanism with Cu behaving as a Lewis acid. We noted, however, that use of stoichiometric CuCl inhibited the reaction. To further probe this idea, we attempted to replace CuCl with TMSOTf, $AlCl_3$, $Ti(Oi\text{-}Pr)_4$, or $ZnBr_2$ since these Lewis acids are unlikely to participate in single electron chemistry, but observed no sulfonylation products. To assess the nucleophilicity of dienol ether **1a** we treated the substrate with BzCl or *p*-nitro-

DOI: 10.1021/acs.orglett.5b01675
Org. Lett. 2015, 17, 3572–3575

benzaldehyde in the presence of CuCl, but observed no addition products. Highly electrophilic sulfonyl chlorides **2c** and **2f** also do not react with dienol ether **1a** in the absence of CuCl. As a result of these experiments we consider an ionic mechanism unlikely, although we cannot rigorously rule out this possibility. Further mechanistic investigations are ongoing.

In conclusion, we have demonstrated the first regioselective addition to ketone-derived dienol ethers using a Cu(I) salt to form putative sulfonyl radicals from widely available sulfonyl chlorides. Through this process we obtain a wide variety of ketone products that are poised for further transformations controlled by versatile sulfone functionalities. Our system is amenable to both cyclic and acyclic substrates without the need to prepare any specialized amide or ester derivatives to facilitate radical termination. We are currently exploring further implementations of the radical/dienol coupling strategy to provide a more general solution to the problem of γ-functionalization of carbonyl systems.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01675.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jtmohr@uic.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding was provided by the UIC Department of Chemistry. We thank Profs. Vladimir Gevorgyan, Duncan Wardrop, Tom Driver, Laura Anderson, Daesung Lee, and Neal Mankad (UIC) for helpful discussions and use of reagents and equipment.

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(18) A small amount of the isobutyronitrile addition product formed as a side product in this case, consistent with a competing radical pathway.

(19) No allyl-containing enone products were observed.

DOI: 10.1021/acs.orglett.5b01675
Org. Lett. 2015, 17, 3572−3575