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Advanced Synthesis & Catalysis

Regio- and Stereoselective Chloro Sulfoximidations of Terminal Aryl Alkynes Enabled by Copper Catalysis and Visible Light

Peng Shi,[a] Yongliang Tu,[a] Duo Zhang,[a] Chenyang Wang,[a] Khai-Nghi Truong,[b] Kari Rissanen,[b] and Carsten Bolm[a,*]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany
Phone: (+49)-241-8094675;
E-mail: carsten.bolm@oc.rwth-aachen.de
[b] University of Jyvaskyla, Department of Chemistry, P.O. Box 35, Survontie 9B, FI-40014 Jyväskylä, Finland

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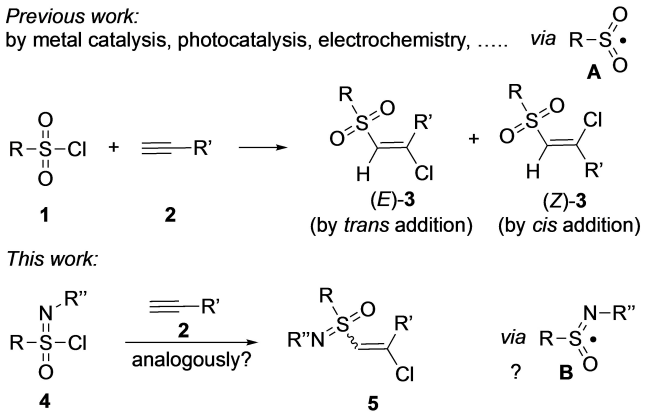
Abstract: By visible-light photoredox catalysis with copper complexes, sulfoximidoyl chlorides add to terminal aryl alkynes to give the corresponding (*E*)-*β*-chlorovinyl sulfoximines with exclusive regio- and stereoselectivities in high yields. Two representative products have been characterized by X-ray crystal structure analysis. Radicals appear to be decisive intermediates. As demonstrated by two subsequent reactions, the products can be derivatized.

Keywords: alkyne addition; copper catalysis; difunctionalization; vinyl sulfoximine; visible-light photoredox catalysis

Difunctionalizations of alkynes leading to olefins have attracted much attention.[1] To be of synthetic value, reactions with unsymmetric substrates require high regio- and stereoselectivities. For achieving this goal, various activation modes involving metal catalysts, visible light, or electrochemistry, for example, have been investigated.[2] Mechanistically, most additions can be characterized by radical and nucleophilic pathways. For synthetic purposes, alkyne difunctionalizations with sulfur-based reagents proved particularly useful. In this context, chlorosulfonylations of alkynes (Scheme 1, top) have continuously been studied in the last decades. Very early work stems from Amiel, who described the application of both copper(I) and copper (II) salts in catalyzed additions of sulfonyl chlorides **1** to alkynes **2**.[3] As a result, he obtained *trans*- and *cis*-addition products **3** in variable ratios. For the diastereoselectivity the solvent and the presence of chloride ions played an important role. Free sulfonyl radicals **A** were suggested to dominate the reaction path. By modifying the copper catalyst, Liang and co-workers achieved exclusive *cis* additions to give (*Z*)-*β*-chlorovinyl sulfones from terminal alkynes.[4,5] Also iron salts have been used for promoting such additions.[6] More recently, sulfonyl chloride additions to alkynes have been initiated by visible light photoredox catalysis.[7,8] An example is Han's work, who observed highly stereoselective *trans* additions affording (*E*)-*β*-chlorovinyl sulfones by using an iridium catalyst/blue light combination for the activation.[8a]

In each of the aforementioned examples, sulfonyl radicals **A** have been proposed to be key intermediates. In contrast to this very well-established field, nothing can be known about the reaction behaviour of the structurally closely related sulfoximidoyl radicals **B** (Scheme 1, bottom). Undoubtfully, analogous addition reactions of sulfoximidoyl chlorides **4** to alkynes **2** are of interest as they should lead to specifically substituted vinyl sulfoximines **5** with numerous potential applications in organic synthesis.[9,10] Realizing this opportunity, we decided to investigate such transformations and report the first results here.

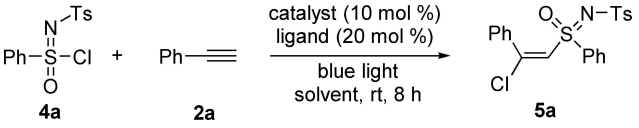
In light of the very impressive advances in visible-light photoredox catalysis with copper complexes,[11] we decided to focus on studying the potential of such systems. For an initial screening and optimization of the reaction conditions, *N*-tosyl-protected sulfoximidoyl chloride **4a** and phenylacetylene (**2a**) were



Scheme 1. (Top) previous work utilizing sulfonyl radicals **A**; (bottom) envisaged reactions *via* sulfoximidoyl radical **B** and discovered transformation described here.

selected as starting materials. To our delight, both compounds reacted when irradiated in THF for 8 h at room temperature with blue LED light in the presence of copper(II) chloride (10 mol%) and dtbpy (dtbpy = 4,4'-di-*tert*-butyl-2-2'-bipyridine, 20 mol%) providing addition product **5a** in 10% yield (Table 1, entry 1).

Table 1. Optimization of the reaction conditions for the synthesis of **5a** starting from **4a** and **2a**.[a]



entry	catalyst	ligand	solvent	yield (%)
1	$CuCl_2$	dtbpy	THF	10
2	$CuCl_2$	dtbpy	DMF	trace
3	$CuCl_2$	dtbpy	Toluene	trace
4	$CuCl_2$	dtbpy	EtOH	trace
5	$CuCl_2$	dtbpy	CCl_4	24
6	$CuCl_2$	dtbpy	dioxane	15
7	**$CuCl_2$**	**dtbpy**	**DCM**	**52**
8	$NiCl_2$	dtbpy	DCM	trace
9	$PdCl_2$	dtbpy	DCM	trace
10	$Cu(OAc)_2$	dtbpy	DCM	43
11	**CuCl**	**dtbpy**	**DCM**	**65**
12	CuBr	dtbpy	DCM	47
13	CuI	dtbpy	DCM	38
14	$Cu(OTf)_2$	dtbpy	DCM	40
15	CuCl	Xphos	DCM	trace
16	CuCl	1,10-phen	DCM	75
17	**CuCl**	**dmbp**	**DCM**	**80**
18[b]	CuCl	dmbp	DCM	78

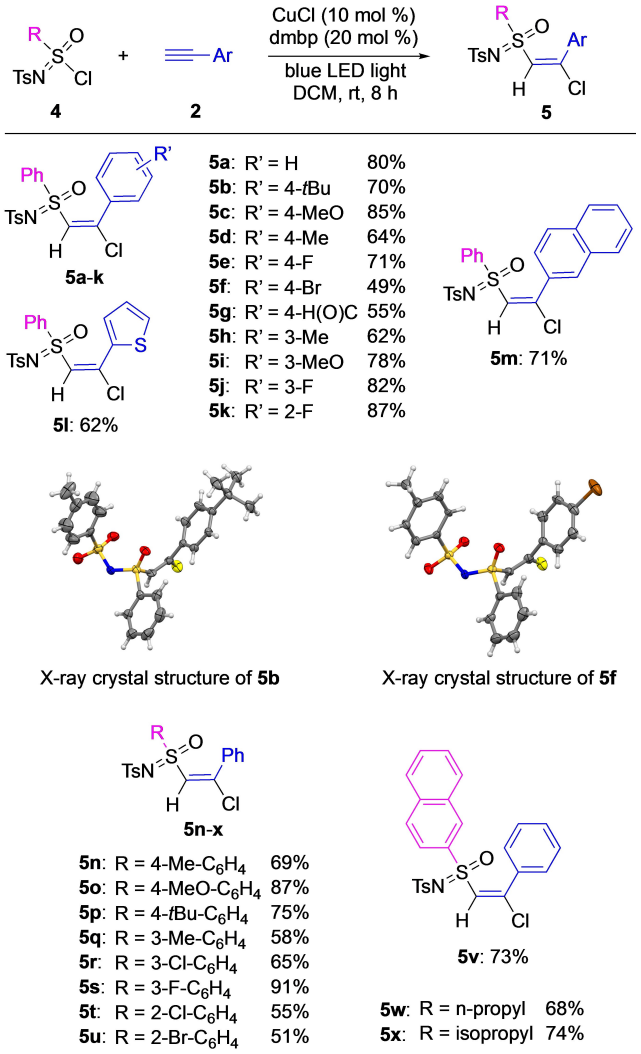
[a] Reaction conditions: **4a** (0.20 mmol), **2a** (0.40 mmol), catalyst (0.02 mmol, 10 mol%), ligand (0.04 mmol, 20 mol%) in the solvent (1.0 mL) at room temperature for 8 h.
[b] Under Ar atmosphere.

Encouraged by this result, several solvents were tested (Table 1, entries 1–7), and among THF, DMF, toluene, EtOH, CCl_4, 1,4-dioxane, and DCM, the latter proved optimal leading to **5a** in 52% yield (Table 1, entry 7). Substituting $CuCl_2$ by $NiCl_2$ and $PdCl_2$ proved ineffective (Table 1, entries 8 and 9). Other copper salts led to product formation, but generally, the yield of **5a** was lower than with $CuCl_2$ (Table 1, entries 10–14). The only exception was copper(I) chloride which gave **5a** in 65% yield (Table 1, entry 11). Changing the ligand from dtbpy to Xphos (Xphos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) inhibited the catalysis with CuCl (Table 1, entry 15). In contrast, combination of CuCl with 1,10-phen (1,10-phenanthroline) and dmbp (6,6-di-methyl-2,2-bipyridine) gave better results with yield for **5a** of 75% and 80%, respectively (Table 1, entries 16 and 17). Providing an inert atmosphere by performing the catalysis with CuCl/dmbp under argon had almost no effect leading to **5a** in 78% yield (Table 1, entry 18). Thus, the optimal conditions established for the addition of **4a** to **2a** to give **5a** (in 80% yield) involved the use of a combination of 10 mol% of copper(I) chloride and 20 mol% of dmbp to be applied in DCM under irradiation with blue LED light for 8 h at room temperature (Table 1, entry 17).[12]

Next, the substrate scope was evaluated. Scheme 2 shows the results. First, the alkyne **2** was varied and reactions with sulfoximidoyl chloride **4a** were studied. In general, all products **5a–m** were obtained in good to high yields ranging from 49–87%. The reactions were highly regio- and diastereoselective providing single isolated products. Substrates with electron-donating substituents on the arene gave slightly higher yields of the corresponding products than those with electron-withdrawing groups. For example, while alkyne **4c** with a 4-methoxy substituent gave **5c** in 85% yield, the analogous compound bearing a 4-formyl group led to **5g** in only 49% yield. The position of the substituent was of minor importance as revealed by the results for the three fluoro-substituted products, which were obtained in yields of 71% (**5e**, *para*), 82% (**5j**, *meta*), and 87% (**5k**, *ortho*), respectively. Also, 2-thiophenyl and 2-naphthyl-containing alkynes **2l** and **2m** reacted well with **4a** affording **5l** and **5m** in yields of 62% and 71%. Performing the addition of **4a** to **2a** on a 2 mmol scale gave **5a** in 64% yield.[13]

The molecular structures of two representative products in the series, **5b** and **5f**, were determined by X-ray crystal structure analysis,[14] and both showed the formation of *trans* addition products (Scheme 2). The regioselectivities corresponded to sulfur additions at the terminal positions of the alkynes.

Subsequently, reactions between phenylacetylene (**2a**) and a number of sulfoximidoyl chlorides including those with *S*-aryl and *S*-alkyl groups leading to



Scheme 2. Substrate scope and X-ray crystal structures of products **5b** and **5f**.

products **5n–x** were studied. Those results are shown in Scheme 2 too.

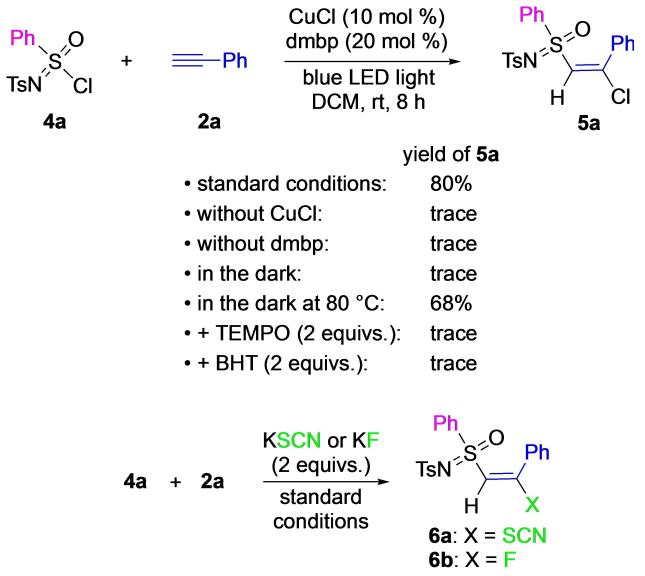
In the series, electronic effects induced by *S*-aryl substituents appeared to be of minor importance, and the product yields were mainly dominated by steric factors. Thus, with the exception of *S*-3-fluorophenyl-containing product **5s**, which was isolated in 91% yield, the average results for substrates with *para*-substituted *S*-aryl groups (**5n–p**) were generally better than those for products with *ortho*-substituted *S*-aryls (**5t** and **5u**). *S*-2-Naphthyl-containing addition product **5v** was isolated in 73% yield. Also *S*-alkyl sulfoximidoyl chlorides (specifically **4w** and **4x**) could be applied, and the corresponding products **5w** and **5x** were obtained in 68% and 74%, respectively.

To gain insight into the reaction details and to verify potential reaction pathways, several control experiments were performed. Again, phenylacetylene (**2a**) and sulfoximidoyl chloride **4a** served as representative substrates. The observations are summarized in Scheme 3.

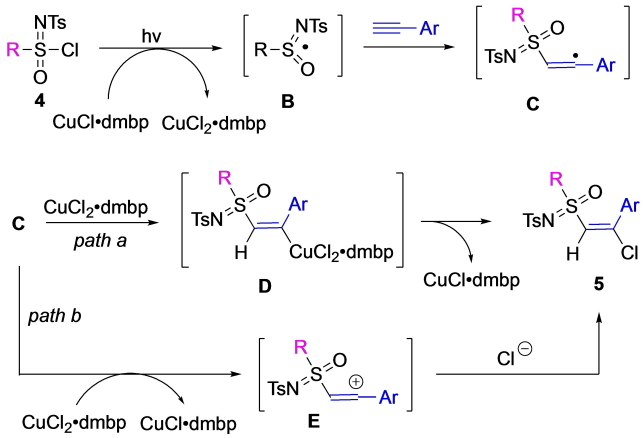
First, under standard conditions, the presence of CuCl and ligand, as well as the LED irradiation were critical. As shown in individual experiments any change along these lines led to a significant drop in yield of **5a** from the previously determined 80% to only a trace amount. However, that was different, when the reaction was performed at 80 °C instead of the commonly applied ambient temperature. Now, **5a** was obtained in 68% yield in the dark. Hence, under standard conditions visible light was essential, but the addition of **4a** to **2a** could also be initiated by raising the reaction temperature. The presence of both 2.0 equivs. of either TEMPO or BHT inhibited the product formation suggesting a relevance of radicals. Finally, performing the catalysis under standard conditions and offering 2.0 equivs. of thioisocyanate (SCN^-) or fluoride (F^-) ions (in form of their K^+ salts) as nucleophiles did not result in the formation of the corresponding addition products **6a** or **6b** (as analyzed by TLC and ESI MS). This result indicated that cationic intermediates were unlikely.

Based on these observations and considering the results from other studies, in particular those related to additions of sulfonyl radicals to alkynes[3–8] and visible light photocatalysis with copper complexes,[11] the mechanism depicted in Scheme 4 can be proposed.

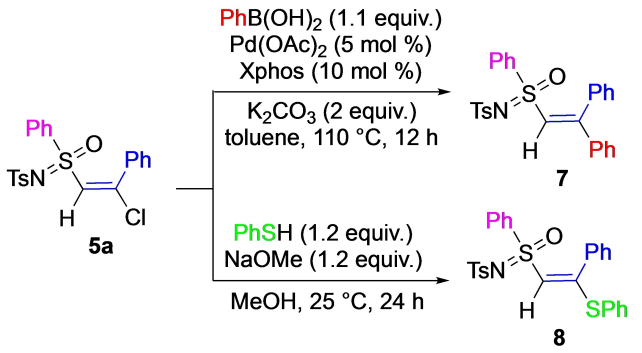
The product formation is initiated by generation of sulfoximidoyl radical **B** from sulfoximidoyl chloride **4** upon irradiation with visible light in the presence of the copper complex. In this process, which can also be



Scheme 3. (Top) standard conditions and variations thereof; (middle) use of TEMPO and BHT (2,6-di-*tert*-butyl-*p*-cresol) as additives; (bottom) attempts to use other nucleophiles.



Scheme 4. Plausible mechanism for the product formation.



Scheme 5. Product modifications.

promoted (in the dark) by raising the temperature, the original ligand-bound copper(I) complex is oxidized to give the corresponding copper dichloride complex. Addition of radical **B** to the alkyne is regioselective and leads to a new radical species **C**, which can subsequently follow two pathways. On path a, **C** interacts with the previously generated ligand-bound copper(II) complex to give a copper(III) intermediate **D**, which upon reductive elimination provides product **5**. Presumably, the pronounced stereoselectivity of the reaction is determined in the formation of intermediate **D**, where the sterically demanding sulfoximidoyl substituent is *trans* to the large copper(III) group. Retention of configuration in the reductive coupling step would then lead to the observed *E*-isomer of **5**. TEMPO or BHT would interfere with any of the involved radicals thereby inhibiting the product formation. The alternative route to **5** (path b) involves radical **C** too, this time, however, **C** is oxidized by $CuCl_2 \cdot$dmbp to give cation **E**. The resulting copper(I) complex can re-enter the catalytic cyclic, and cation **E** reacts with chloride ions to afford addition product **5**. Although path b cannot rigorously be excluded, we regard it less likely based on the results of the trapping experiments with other nucleophiles reported in Scheme 3, where neither **6a** nor **6b** were detected. Furthermore, the high stereoselectivity in the formation of **E** would be difficult to rationalize.[15,16]

With the goal to demonstrate the synthetic applicability of products **5** by subsequent functional group modifications, two structural changes were investigated (Scheme 5). In both cases, **5a** served as representative starting material. Applying Suzuki-type cross-coupling conditions with phenyl boronic acid as reagent and a palladium(II)/Xphos combination led to arylated product **7** in 81% yield.[17] The formation of thioether **8** was achieved by treatment of **5a** with a mixture of thiophenol and sodium methoxide in methanol, which provided **8** in 85% yield.

In summary, we developed a visible-light photoredox process with copper complexes as catalysts leading to vinylic sulfoximine derivatives by highly regio- and stereoselective additions of sulfoximidoyl chlorides to terminal arylalkynes. The molecular structures of two representative products were determined by single crystal X-ray diffraction analysis. A wide range of functional groups is tolerated, and the yields are good. Mechanistic studies suggest the involvement of radicals as key intermediates. By two subsequent functional group modifications, potential synthetic applications have been exemplified.

Experimental Section

General procedure for preparation of vinyl sulfoximines 5 as exemplified for the synthesis of 5a. A mixture of **4a** (65.8 mg, 0.2 mmol), **2a** (40.8 mg, 0.4 mmol), CuCl (2.0 mg, 0.02 mmol), dmbp (7.4 mg, 0.04 mmol), and DCM (1.0 mL) in a sealed 5 mL glass vial was irradiated with blue LED light at room temperature for 8 hours. Then, the reaction mixture was concentrated in vacuo. Finally, the resulting product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 6/1–4/1) to give 69.0 mg (80% yield) of product **5a** as a white solid.

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[12] Shortening the reaction time from 8 h to 1 h, 3 h, and 5 h led to incomplete conversions. Extending it to over-night had no significant effect on the yield.

[13] Attempts to **4a** under standard conditions onto 1-phenyl propyne and 1,2-diphenylethylene representing internal alkynes remained unsuccessful.

[14] CCDC 2034819 (for **5b**) and CCDC 2034818 (for **5f**) contain the supplementary crystallographic data for these structures. 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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[16] Generating the sulfoximidoyl radical from sulfoximidoyl chloride **4a** by metal-free methods and to add it to **2a** proved possible, but the outcome remained unsatisfying. Thus, heating **2a** and **4a** in the presence of AIBN (1.5 equiv.) in DCM to 80 °C for 12 h, gave **5a** in 13% yield. Alternatively, stirring **2a** and **4a** with BEt_3 (0.3 equiv.) under dioxygen at ambient temperature in MeCN for 12 h, gave **5a** in traces (< 5% yield). For a guiding reference of the latter approach, see: K. Gilmore, B. Gold, R. J. Clark, I. V. Alabugin, *Aust. J. Chem.* **2013**, *66*, 336–340.

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COMMUNICATIONS

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