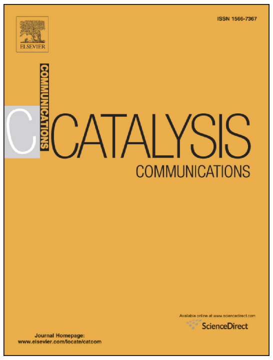

h-BN@Copper(II) nanomaterial catalyzed cross-coupling reactions between sulfoximines and N-(phenylthio)-succinimide under mild condition

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***h*-BN@Copper(II) nanomaterial catalyzed cross-coupling reactions between sulfoximines and *N*-(phenylthio)-succinimide under mild condition**

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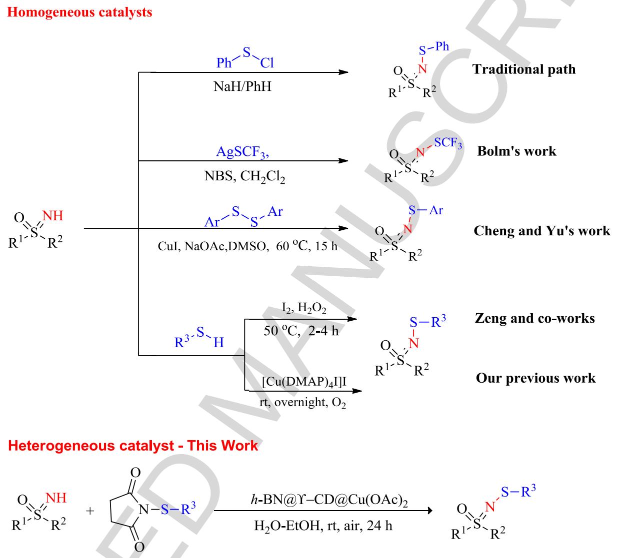
Abstract

A novel and efficient method for the synthesis of *N*‑S substituted sulfoximines has been established with *h*-BN-supported copper(II) nanomaterial as the catalyst. Catalyzed by this heterogeneous catalyst, the desire products were obtained with wide scope of substrates, good to excellent yields, free ligand and low-toxicity solvent. Moreover, after being reused ten times, there is almost no significant loss of its catalytic activity.

Keywords *N*-sulfenyl sulfoximines, hexagonal boron nitride, copper, cross-coupling**,** recyclable, water

1. Introduction

As a class of important organosulfur-nitrogen containing compounds, sulfoximines have attracted considerable attention since the discovery of the sulfonimidoyl function in 1949 [1]. In general, sulfoximines are one kind of monoaza analogues of sulfones, and the amphoteric nitrogen offers an additional point for the structure modification [2]. Due to the high reactivity of the nitrogen and stereogenic sulfur atom, sulfoximines have been applied as useful building blocks for organocatalysts [3], chiral auxiliaries [4, 5] and chiral ligands [6, 7]. Recently, sulfoximines were also used as directing group in transition metal-catalyzed C-H functionalizations [8, 9]. Furthermore, sulfoximines also showed potential biological activity in many sides [10].



Scheme 1 Pathway for the construction of N-S substituted sulfoximines

With the increasing importance in organic synthesis and chemical industry, more and more efforts were focused on the synthesis of sulfoximine derivatives. Inspiringly, a number of modern and efficient methods about N-H bond modification of sulfoximines have been reported and the N-C bond formations of sulfoximines were well developed. For example, the *N*-alkylations [11], *N*-arylation [12, 13], *N*-cyanation [14, 15], *N*-acylation [16, 17] and *N*-alkynylation [18, 19] have been established in the past few ten years. Those reports greatly enriched the structural complexity and molecular multiplicity of sulfoximines. Conventionally, *N*-sulfenyl sulfoximines were synthesized from the reactions of *N*-sulfenyl sulfoximines and arylsulfonyl chloride [20]. Recently, some new synthetic routes about *N*-sulfenyl sulfoximines were reported. In 2015, *N*-trifluoromethylthiolated sulfoximines were synthesized by Carsten Bolm’s team [21]. Somewhat later, copper-catalyzed *N*-thioetherification of sulfoximines were obtained [22]. More recently, Zeng and co-works reported iodine and hydrogen peroxide-catalyzed intermolecular S–H/N–H dehydrocoupling reaction in sulfoximines [23]. Almost at the close of time, our team also focuses on the modification of sulfoximines and a one-pot cascade N-S bond formation method to prepare directly *N*-sulfenyl sulfoximines with thiophenols were established [24]. Compared with the traditional sulfoximines synthesis methods (arylsulfonyl chloride was needed), those homogeneous catalysts have been established for the construction of such structures, but they may be also limited by the catalyst recovery, difficulty in separation and create hazardous waste. With the development of catalysis chemistry, many researches were focused on the heterogeneous catalyst which was considered as a valuable tool to overcome these issues.

In the modern era of organic synthesis, there are increasing demands for using environmentally benign catalysts and solvents in chemistry reactions, and high molecular materials are gaining more and more attention in heterogeneous catalysis system due to their excellent abilities in catalyst separation and recovery, mild reaction conditions and low-toxic nature [25, 26]. Among these materials, hexagonal boron nitride (*h*-BN) interestingly exhibits excellent activity. It is similar in many ways to graphene with high thermal tolerance, excellent chemical stability and wide band gap independent of morphology [27, 28]. In addition, *h*-BN was also considered as a supporting material to synthesize heterogeneous catalyst. Last year, we had developed a novel and green heterogeneous nanomaterial *h*-BN@γ-CD@$Cu(OAc)_2$ as an efficient and recoverable catalyst which was used in the multicomponent 1,3-dipolar cycloaddition reaction [29]. Due to our continuous interest in the heterogeneous catalyst and sulfoximines, here we introduce this efficient catalyst into the aqueous cross-coupling reaction to synthesis *N*-sulfenyl sulfoximines.

2. Experimental

General Procedure for the Synthesis of *N*-Thiosuccinimides: *N*-Chlorosuccinimide (1.0 equiv.) was added to a stirred solution of thiol (1.0 equiv.) in anhydrous toluene (4 mL toluene/1.0 mmol thiol) at 25 °C under an argon atmosphere. The color of the resulting heterogenous mixture was transformed to yellow-orange after stirring at 25 °C for 45 min. A solution of Et_3N (1.0 equiv.) in anhydrous toluene (1.6 mL toluene/1.0 mmol of Et_3N) was then added over 45 min with a syringe pump. The resulting heterogeneous mixture was stirred at 25 °C for 12 h and then diluted with diethyl ether (12 mL ether/1.0 mmol of thiol). The resulting white precipitate was filtered off. The filtrate was concentrated under reduced pressure to produce a yellow/orange semisolid residue, which was purified by silica gel column chromatography to obtain the *N*-Thiosuccinimides.

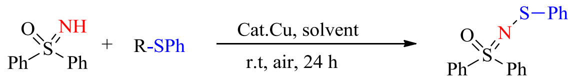
General Procedure for the Synthesis of *N*-Sulfenyl sulfoximines (3aa-3ja): To a 25 ml round-bottom flask equipped with a magnetic stir bar, commercially available solutions of EtOH:H_2O=1:1 (3mL : 3mL) were added to a mixture of sulfoximines (50 mg, 0.23 mmol, 1.00 equiv.), *N*-tiosuccinimides (142.8 mg, 0.69 mmol, 3.00 equiv.) and *h*-BN@γ-CD@Cu (20 mol%, 240 mg) under air. The reaction mixture was stirred at rt for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and washed with ethyl acetate to recycle the *h*-BN@γ-CD@Cu.The filtrate was diluted with H_2O (10 mL), extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4 .After that concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel using a mixture of PE/EtOAc and 0.3% trimethylamine as the eluent to obtain the *N*-sulfenyl sulfoximines products.

The *h*-BN@γ-CD@Cu was prepared according to reported procedure [29].

3. Results and discussion

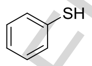
At the beginning of our investigation, the reaction conditions were screened with diphenyl sulfoximine (**1aa**) as the model substrate. First, in the presence of *h*-BN@γ-CD@Cu(OAc)$_{2,}$ diphenyl sulfoximine was reacted with different sulfur sources such as benzenethiol (**2a**), 1,2-diphenyldisulfane (**2b**), *S*-phenyl 4-methylbenzenesulfonothioate (**2c**), trimethyl(phenylthio)silane (**2d**), *S*-phenyl ethanethioate (**2e**) and *S*-phenyl methanesulfonothioate (**2f**) in the mixture solvents H_2O-EtOH at room temperature for 24 h. Regrettably, the expected product *N*-sulfenyl sulfoximine (**3aa**) was not observed (Table 1, entries 1-6). On the contrary, when **1aa** was treated with *N*-(phenylthio)-succinimide (**2g**), compound **3aa** was obtained with 93% yield (Table 1, entry 7). For the optimization of the amount of *h*-BN@γ-CD@Cu(OAc)$_2$ used in the model reaction, 0.2 equivalent (the contents of Cu^{2+})was found to be adequate, as neither larger nor smaller amount showed better yields (Table 1, entries 8-10). Next, we searched the optimal ratio of the reaction substrate in this reaction and 1:3 equivalent weights of **1aa** and **2g** was the superlative proportion to prepare product (Table 1, entries 11–13). In addition, when the mixed solvents were replaced by a single organic solvent or water will result in a decrease in yields (Table 1, entries 14–17). Furthermore, some common copper salts were also tested in this reaction and the yield of **3aa** was significantly reduced compared with *h*-BN@γ-CD@Cu(OAc)$_2$ (Table 1, entries 18–22).

Table 1 Optimization of the reaction conditions [a]



1aa **2a-2g** **3aa**

Entry	R-SPh (equiv)	Cat. Cu	Solvent	Yield (%)
1	2a	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	0
2	2b	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	0
3	2c	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	0
4	2d	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	0
5	2e	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	0
6	2f	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	0
7	2g	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	93
8	2g	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	65[b]
9	2g	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	75[c]
10	2g	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	92[d]
11	2g (1.2)	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	65
12	2g (1.5)	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	69
13	2g (2.0)	*h*-BN@ Cu(II)	$Et(OH)_2:H_2O=1:1$	80
14	2g	*h*-BN@ Cu(II)	$Et(OH)_2$	50
15	2g	*h*-BN@ Cu(II)	H_2O	75
16	2g	*h*-BN@ Cu(II)	Isopropanol	30
17	2g	*h*-BN@Cu(II)	DCM	trace
18	2g	CuI	$Et(OH)_2:H_2O=1:1$	13
19	2g	Cu_2O	$Et(OH)_2:H_2O=1:1$	26
20	2g	CuO	$Et(OH)_2:H_2O=1:1$	15
21	2g	$CuNO_3$	$Et(OH)_2:H_2O=1:1$	35
22	2g	$Cu(OAc)_2$	$Et(OH)_2:H_2O=1:1$	34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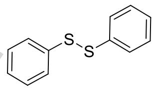
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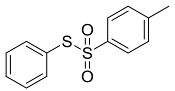
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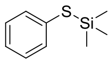
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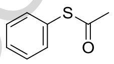
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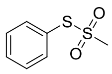
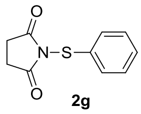
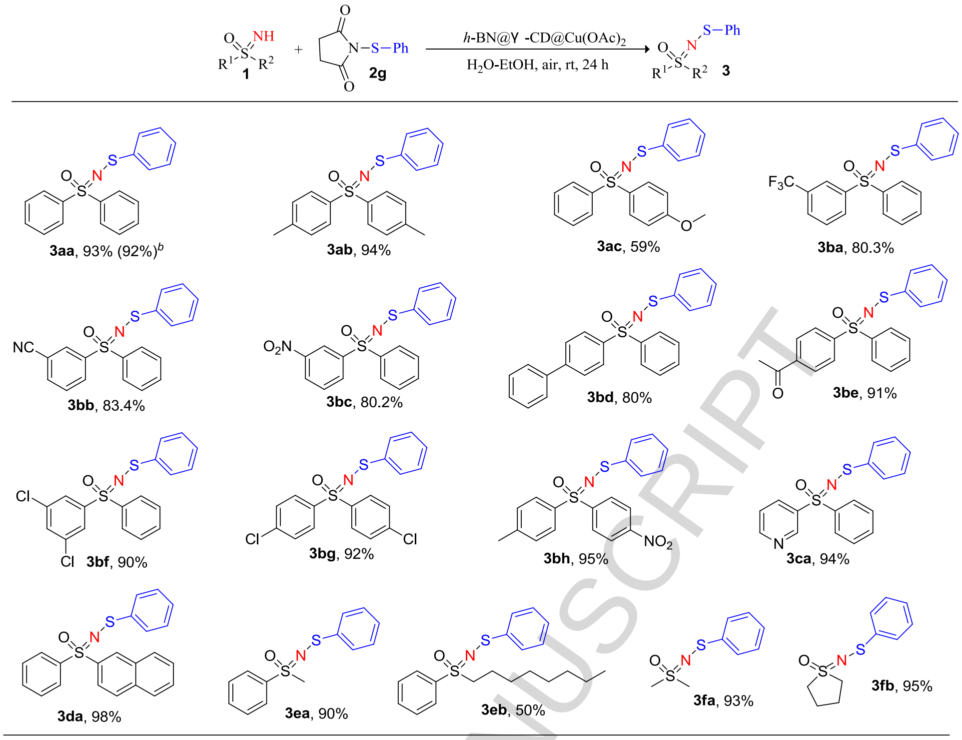

2f


2g

[a]Reaction condition: **1aa** (50 mg, 0.23 mmol), **2** (0.69 mmol, 3 equiv), cat Cu (the contents of Cu^{2+}, 0.046 mmol, 0.2 equiv), in solvent (6 mL), r.t, under air, 24 h; [b] Cat. Cu (0.05 equiv); [c] Cat. Cu (0.1 equiv); [d] Cat. Cu (0.3 equiv); [e] Isolated yields.

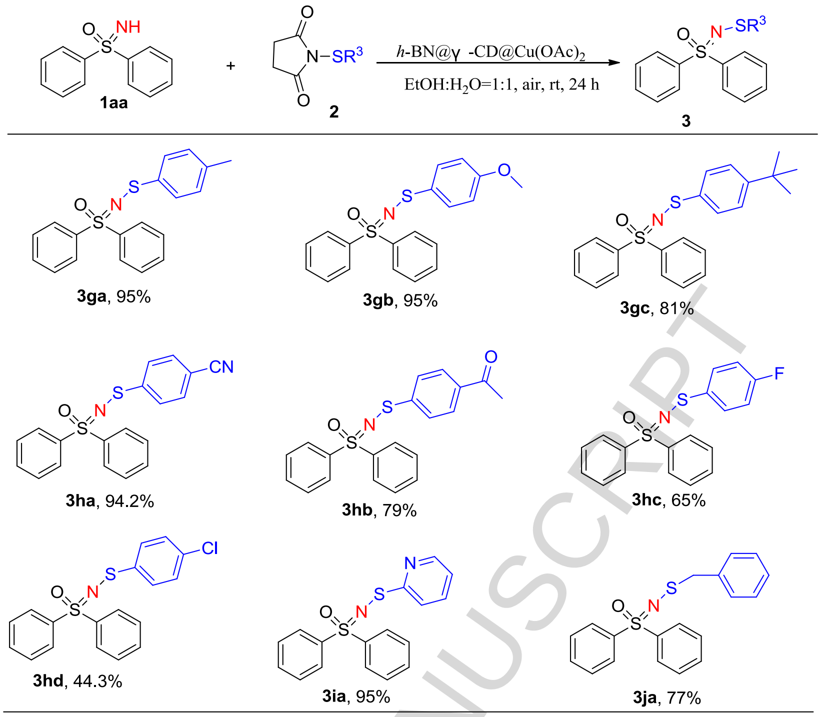
Table 2 Reaction of sulfoximines with *N*-(phenylthio)-succinimide [a]



[a] Reaction condition: **1a** (50 mg, 0.23 mmol), **2** (0.69 mmol), cat Cu (the contents of Cu^{2+}, 0.046 mmol, 0.2 equiv), in EtOH:H_2O (3 mL:3 mL), rt, under air, 24 h; Isolated yields; [b] Isolated yield at 5 mmol scale reaction.

With the optimal reaction condition in hand, a range of reactions were carried out to expand the scope of substituted sulfoximine, the results were shown in Table 2. First, diphenyl sulfoximines with either electron-donating or electron-withdrawing groups were reacted with *N*-(phenylthio)-succinimide. The desired products were obtained in good to excellent yields and the electrical effects have no significant effect on those reactions (Table 2, **3aa-3bh**). Additionally, *S*-phenyl-*S*-pyridyl-sulfoximine (Table 2, **3ca**) and *S*-phenyl-*S*-naphthalene-sulfoximine (Table 2, **3da**) were reacted smoothly to deliver the desired pruducts. Inspiringly, both of *S*-aryl-*S*-alkyl-sulfoximines and dialkyl sulfoximines were efficiently coupled with *N*-(phenylthio)-succinimide in moderate to excellent yields (Table 2, **3ea-3fb**). The practicability of this procedure was evaluated with **1aa** (1.086 g, 5 mmol), giving the product **3aa** in 92% yield and the amount of catalyst was decreased to 0.1 equiv.

Table 3 Reaction of diphenyl sulfoxime with *N*-thiosuccinimides [a]



[a] Reaction condition: **1a** (50 mg, 0.23 mmol), **2** (0.69 mmol), cat Cu (the contents of Cu^{2+}, 0.046 mmol, 0.2 equiv), in EtOH:H$_2$O (3 mL:3 mL), rt, under air, 24 h; Isolated yields

In addition, substituted *N*–(phenylthio)-succinimides were tested in this reaction. *N*–(phenylthio)-succinimide with electron-donating groups- methyl, methoxyl, *tertiary*-butyl (Table 3, **3ga-3gd**) or electron-withdrawing groups- cyano, cyanyl (Table 3, **3ha** and **3hb**) all afforded the expected products with good to excellent yields. However, the halogens, especially chlorinum substituted *N*–(phenylthio)-succinimide generate the desired product in lower yield (Table 3, **3hc** and **3hd**). Moreover, *N*–(pyridylthio)-succinimide and *N*–(benzylthio)-succinimide also successfully transformed to the products in high yield (**3ia, 3ja**).

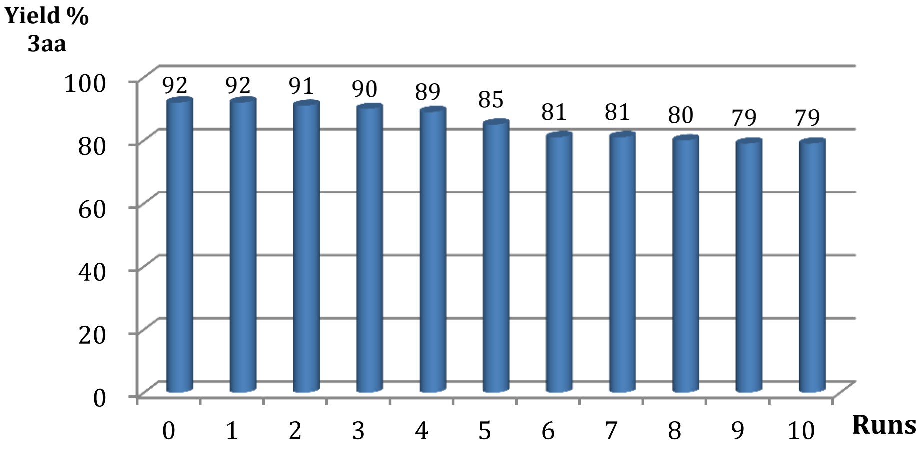


Fig. 1 Reuse of catalyst in the synthesis of **3aa**

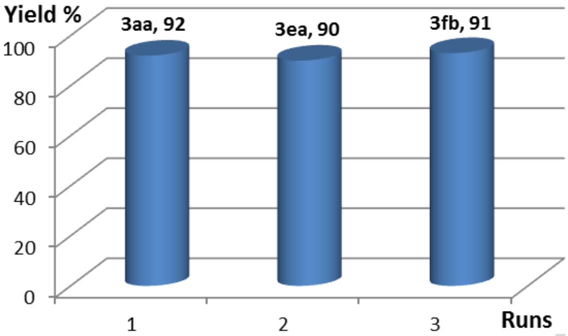


Fig. 2 Recyclability of *h*-BN@γ-CD@Cu(OAc)$_2$ in the reactions between **1** and **2g**

The further study to check the recovering and reusing of catalyst were also performed. After completion of the reaction, *h*-BN@γ-CD@Cu(OAc)$_2$ was separated by filtration, and washed with ethyl acetate until all the produce residuals were completely removed. The catalyst was reused directly in the new reaction. As the number of cycles increasing, the yield decreased slightly. But, it is worthy noting that, a good yield 79% was obtained even if the catalyst was recycled for 10 times (Figure 1). In addition, the recycling experiments were also carried out in which the substrate would be changed after each catalytic run. As shown in Figure 2, performing the reaction between **1aa** and **2g**, the desired product **3aa** was obtained with 92% yield. Then, the catalyst was separated and treated with *S*-phenyl-*S*-methyl-sulfoximine (**1ea**) and **2g**, delivering **3ea** in 90% yield. With the same operation, the catalyst was continuously used in the reaction between **1fb** and **2g**, an excellent yield 91% of **3fb** occurred. Thus, it is reasonable to believe that the catalyst can be repeatedly used and the using of recycle catalyst between different types of substrates has no significant influence.

4. Conclusion

In conclusion, we have successfully reported the heterogeneous *h*-BN supported copper-mediated cross-coupling reaction to synthesis *N*-sulfenyl sulfoximines. This synthesis offers the corresponding products with good yields and excellent functional group tolerance. More importantly, this catalyst can be easily separated by filtration and even if recycled ten times, the activity was almost no significant decrease. In addition, the catalyst can be used between different types of substrates in the recycling experiments. The study to apply this catalyst in other environmentally friendly recyclable reaction is ongoing in our laboratory.

Acknowledgements

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Highlights

- The synthesis of *N*-sulfenyl sulfoximines catalyzed by *h*-BN@γ-CD@$Cu(OAc)_2$ is developed
- This methodology has a broad substrate scope and good to excellent yields.
- The catalyst could be reused ten times.
- The reaction was performed under aqueous solution and room temperature