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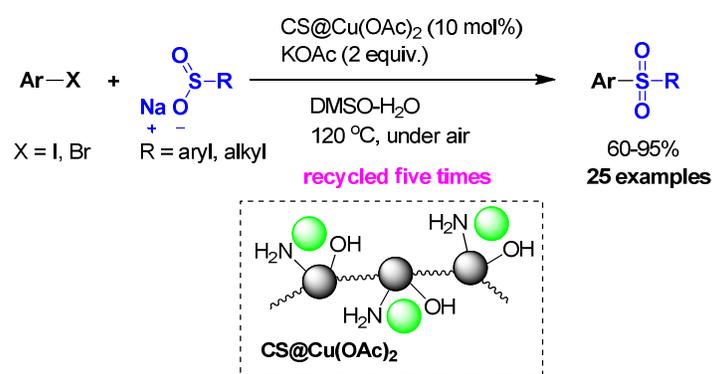


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## A highly active and easily recoverable chitosan@copper catalyst for the C-S coupling and its application in the synthesis of Zolimidine

Chao Shen,<sup>a,b</sup> Jun Xu,<sup>b</sup> Wenbo Yu,<sup>b</sup> and Pengfei Zhang<sup>\*b</sup>

Chitosan@copper catalyst displays high efficiency as an easily recoverable catalyst for C-S couplings and the synthesis of Zolimidine.



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# A highly active and easily recoverable chitosan@copper catalyst for the C-S coupling and its application in the synthesis of Zolimidine

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Aryl sulfones were synthesized using a highly active and easily recoverable heterogeneous Cu catalyst which was prepared by simply stirring an aqueous suspension of chitosan in water with copper salt. The chitosan@copper catalyst catalyzed coupling reactions of aryl halides with sodium sulfonates readily to give the corresponding sulfones in good to excellent yields. The highly active catalyst can be reused many times without losing catalytic activity. In addition, by using this protocol, the marketed drug Zolimidine (antiulcer) could be synthesized easily.

## Introduction

C-S coupling reaction plays a significant role in organic synthesis and constitutes a key step in the synthesis of many molecules that are of biological and material interest.<sup>1</sup> Sulfones are an important class of sulfur-containing compounds which have been identified in a broad range of biologically important molecules.<sup>2</sup> Various sulfones derivatives have been found to possess anti-tumor,<sup>3</sup> anti-inflammatory,<sup>4</sup> anti-microbial,<sup>5</sup> anti-HIV<sup>6</sup> and some other properties.<sup>7</sup> In the past few decades, a lot of significant methods to construct sulfones have been subsequently developed.<sup>8</sup> Among these approaches, the nucleophile substitution reaction of halide with thiol, followed by oxidation of the corresponding sulfide<sup>9</sup> and metal-catalyzed coupling reactions between sodium sulfonates and aryl halides or aryl boronic acids<sup>10</sup> are the most common. However, in many of these transformations, harsh reaction conditions, toxic reagents and oxygen-free techniques are required. Thus, development of alternative, inexpensive, air and moisture insensitive and recyclable catalysts for the synthesis of sulfones is highly desirable in the context of environmental and industrial concerns.<sup>11</sup>

Metal catalysts anchored on a heterogeneous support have received tremendous attention recently.<sup>12</sup> The heterogeneous processes have the advantages such as ease of separation of prod-

uct, reusability of catalyst, better steric control of the reaction intermediate and so on. These merits prompted researchers to immobilize a homogeneous catalytic site on various supports such as silica,<sup>13</sup> zeolites,<sup>14</sup> magnetic-materials,<sup>15</sup> and polymers.<sup>16</sup> Recently, Chitosan (CS) have generated significant attention for their green and essential roles in transition metal catalyzed reactions.<sup>17</sup> Several groups have reported the catalytic activity of chitosan-supported metal complexes used as catalyst for C-C bond forming reactions such as Suzuki cross-coupling reaction (CS-supported Pd catalyst),<sup>18</sup> Henry reaction (CS-supported Ti catalyst),<sup>19</sup> hydroformylation reaction (CS-supported Rh catalyst)<sup>20</sup> and for C-N bond forming reactions such as Click Chemistry (CS-supported Cu catalyst).<sup>21</sup> While few examples describing the C-S coupling in CS-supported heterogeneous systems were reported, and the subject still represents a real challenge.

Continuing our longstanding interest in developing novel C-S bond-forming reactions for the efficient construction of heterocyclic frameworks,<sup>22</sup> we are interested in developing green chemistry protocol for coupling reaction.<sup>23</sup> Herein, we describe a simple and efficient synthesis of a chitosan-supported, recyclable, and inexpensive copper catalyst for construction of aryl sulfones and its application to synthesis of the marketed drug Zolimidine.

## Results and discussion

### Catalyst synthesis and characterization

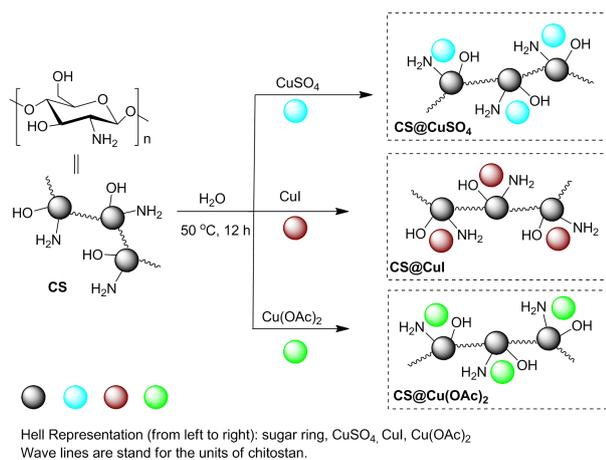
The CS supported copper salt (CuSO<sub>4</sub>, CuI and Cu(OAc)<sub>2</sub>) employed for the C-S coupling were synthesized according to the following representative procedure: the catalyst was prepared by suspending chitosan in an aqueous solution of CuSO<sub>4</sub>, CuI or Cu(OAc)<sub>2</sub> for 3 h under neutral conditions at 50 °C for 12 hours respectively. After adsorption of the copper, the solid was preconditioned by washing thoroughly to remove any loose Cu compounds and dried under vacuum at 50 °C overnight to give the chitosan@copper catalyst (Scheme 1).

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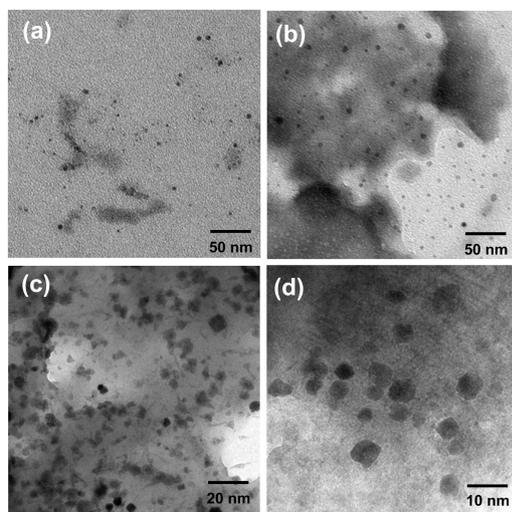
† Electronic Supplementary Information (ESI) available: <sup>1</sup>H NMR spectra, <sup>13</sup>C NMR spectrum, GC/MS profile, HRMS profile. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.



**Scheme 1** Preparation of CS@copper catalysts.

Catalyst have been characterized by Infra-red analyses (FT-IR), Thermogravimetric analysis (TG), X-ray Diffraction (XRD), Transmission electron microscopy (TEM) and inductively coupled plasma-atomic emission spectrometry (ICP-AES). Using these methods, the possible structures of chitosan-supported Cu catalysts were proposed in Scheme 1. FT-IR of the chitosan catalysts were carried out and the pure chitosan powder exhibited characteristic absorption bands of O-H and N-H stretching vibrations of amine groups at  $3440\text{ cm}^{-1}$ . For the CS@copper catalysts, the peak at  $3426\text{ cm}^{-1}$  becomes sharper and stronger compared to chitosan. The peaks at around  $1085$ ,  $1384$ ,  $1606$ ,  $2877$ - $2925\text{ cm}^{-1}$  correspond to C-OH, C-N, N-H, and C-H stretching models of the chitosan molecules, respectively (Figure S1-4, ESI<sup>†</sup>). The FT-IR of the copper catalysts demonstrates that -NH<sub>2</sub> and -OH coordination with metal Cu. The catalysts were also characterized by TG to study its thermal behavior and stability at elevated temperatures (Figure S5, ESI<sup>†</sup>). TG curve of chitosan shows three different mass loss stages. It is clear that CS@copper catalysts also involves three mass loss stages during thermal decomposition. However, the thermal stability is less than chitosan because of decrease in the number of primary amino gr-



**Figure 1** TEM images of (a) CS@CuSO<sub>4</sub>, (b) CS@CuI, (c) CS@Cu(OAc)<sub>2</sub> and (d) recovered CS@Cu(OAc)<sub>2</sub> after the fifth run.

**Table 1** Optimization of reaction conditions.<sup>a</sup>

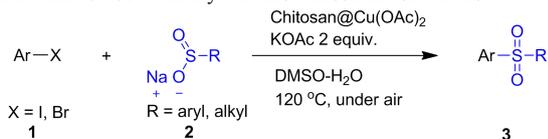
Entry	Catalyst	Base	Solvent /H <sub>2</sub> O(1:1)	Time (h)	Yield (%) <sup>b</sup>
1	CS@CuSO <sub>4</sub>	Na <sub>2</sub> CO <sub>3</sub>	DMSO	3	60
2	CS@CuSO <sub>4</sub>	Na <sub>2</sub> CO <sub>3</sub>	DMSO	24	70
3	CS@CuI	Na <sub>2</sub> CO <sub>3</sub>	DMSO	3	72
4	CS@CuI	Na <sub>2</sub> CO <sub>3</sub>	DMSO	24	72
5	CS@Cu(OAc) <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub>	DMSO	3	64
6	CS@Cu(OAc) <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub>	DMSO	24	85
7	CS + Cu(OAc) <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub>	DMSO	48	trace
8	CS@Cu(OAc) <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	DMSO	24	62
9	CS@Cu(OAc) <sub>2</sub>	CS <sub>2</sub> CO <sub>3</sub>	DMSO	24	25
10	CS@Cu(OAc) <sub>2</sub>	KOAc	DMSO	24	91
11	CS@Cu(OAc) <sub>2</sub>	KOH	DMSO	24	trace
12	CS@Cu(OAc) <sub>2</sub>	NaOH	DMSO	24	trace
13	CS@Cu(OAc) <sub>2</sub>	Et <sub>3</sub> N	DMSO	24	70
14	CS@Cu(OAc) <sub>2</sub>	KOAc	DMF	24	82
15	CS@Cu(OAc) <sub>2</sub>	KOAc	Toluene	24	65
16	CS@Cu(OAc) <sub>2</sub>	KOAc	Dioxane	24	70
17	CS@Cu(OAc) <sub>2</sub>	KOAc	H <sub>2</sub> O	48	trace
18	CS@Cu(OAc) <sub>2</sub>	KOAc	DMSO	24	52 <sup>c</sup>

<sup>a</sup> Reaction was carried out with 4-iodoanisole **1a** (1 mmol), sodium benzenesulfinate **2a** (1.2 mmol), base (2 mmol) and chitosan@copper salts (loading 10 mol%) in solvent (3 mL, 1:1), 120 °C under air. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction was performed at 100 °C.

roups after coordination with metal Cu. Importantly, the TG shows that these catalysts are stable up to 200 °C, suggesting that their high thermal stability allows them to be compatible with most organic reactions. The signals pertaining to copper metal were not detected by XRD (Figure S6, ESI<sup>†</sup>), presumably due to its complexation with chitosan or its low percentage amount. The TEM analysis showed that the average diameter of the copper nanoparticles' diameter was about 3-8 nm and the dispersion of the Cu particles was very well (Figure 1a-c). The copper loading levels of catalysts, which was measured by ICP-AES, were 1.95, 1.50, and 1.46 mmol/g, respectively.

### Catalytic studies

After characterization of the composite, the catalytic activities of chitosan@copper catalysts were examined in coupling reaction of 4-iodoanisole (1.0 equiv.) with benzenesulfinic acid sodium salt (1.2 equiv.). First, the reaction was explored using catalysts in DMSO-H<sub>2</sub>O (1:1) mixture at 120 °C for using Na<sub>2</sub>CO<sub>3</sub> as a base. While every copper source tested exhibits reasonable activity, no product is detected over three days in the absence of a copper catalyst. No apparent correlation exists between metal oxidation state and catalytic activity: CS@CuSO<sub>4</sub> and CS@CuI produce identical GC yields (Table 1, entry 2 vs. 4), and CS@Cu(OAc)<sub>2</sub> is superior to CS@CuSO<sub>4</sub> (entry 6 vs. 2). The CS@Cu(OAc)<sub>2</sub> afford the highest overall 85% isolated yields. Surprisingly, no product formation when Chitosan and Cu(OAc)<sub>2</sub> acetate were added *in situ* (Table 1, entry 7). With CS@Cu(OAc)<sub>2</sub> as the catalyst, some inorganic and organic bases were further screened. The reaction with K<sub>2</sub>CO<sub>3</sub> and CS<sub>2</sub>CO<sub>3</sub> as the base resulted in the formation of **3a** in 63 and 25% yield, respectively. Gratifyingly, adding 2 equiv of KOAc increased the yield of the product to 91% (Table 1, entry 10). However, with KOH or NaOH as the base, no target

**Table 2** Reaction between aryl halides and sodium sulfonates.<sup>a</sup>

Entry	Ar	X	R	Yield(%) <sup>b</sup>
1	Ar = <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	I	Ph	91 (3a)
2	Ar = <i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	I	Ph	90 (3b)
3	Ar = <i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	I	Ph	82 (3c)
4	Ar = <i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	I	Ph	83 (3d)
5	Ar = <i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	I	Ph	80 (3e)
6	Ar = <i>p</i> -CH <sub>3</sub> CO-C <sub>6</sub> H <sub>4</sub>	I	Ph	75 (3f)
7	Ar = <i>p</i> -HO-C <sub>6</sub> H <sub>4</sub>	I	Ph	80 (3g)
8	Ar = Ph	I	Ph	91 (3h)
9	Ar = <i>m</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	I	Ph	82 (3i)
10	Ar = <i>o</i> -Me-C <sub>6</sub> H <sub>4</sub>	I	Ph	71 (3j)
11	Ar = <i>o</i> -COOMe-C <sub>6</sub> H <sub>4</sub>	I	Ph	65(3k)
12	Ar = <i>p</i> -C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub>	I	Ph	72 (3l)
13	Ar = Ph	I	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	90 (3b)
14	Ar = <i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	I	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	87 (3m)
15	Ar = <i>o</i> -Me-C <sub>6</sub> H <sub>4</sub>	I	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	85 (3n)
16	Ar = Ph	I	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	81 (3c)
17	Ar = <i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	I	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	77 (3o)
18	Ar = <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	I	Me	93 (3p)
19	Ar = Ph	I	Me	95 (3q)
20	Ar = <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	Br	Ph	72 <sup>c</sup> (3a)
21	Ar = <i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	Br	Ph	70 <sup>c</sup> (3b)
22	Ar = <i>m</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Br	Ph	65 <sup>c</sup> (3i)
23	Ar = <i>o</i> -Me-C <sub>6</sub> H <sub>4</sub>	Br	Ph	61 <sup>c</sup> (3j)
24	Ar = Ph	Br	Ph	69 <sup>c</sup> (3h)
25	Ar = Ph	Br	Me	60 <sup>c</sup> (3q)

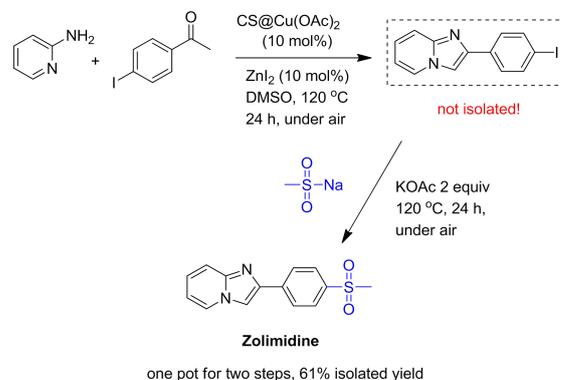
<sup>a</sup> Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), CS@Cu(OAc)<sub>2</sub> (120 mg, loading 10 mol%), KOAc (2 mmol), DMSO : H<sub>2</sub>O (3 ml 1:1) 120 °C under air. <sup>b</sup> Isolated yield. <sup>c</sup> 140 °C, 48 h.

product was obtained. When Et<sub>3</sub>N was used as base an 70% isolated yield of desired product was obtained (Table 1, entry 13). Further experimentations revealed that this C-S cross-coupling reaction was effective in polar aprotic organic solvent/H<sub>2</sub>O (1 : 1) mixtures such as DMF. In stark contrast, the coupling reaction proceeded less efficiently in nonpolar solvent such as dioxane and toluene (Table 1, entries 15 and 16). While trying the reaction using only water as solvent, no product was obtained (Table 1, entry 17). In addition, reaction temperature have a significant effect on the yield of **3a**. For example, when the temperature was decreased from 120 °C to 100 °C, the yield was decreased from 91% to 52% (Table 1, entry 18).

Under the optimized reaction conditions, we further studied the scope of the reaction with respect to aryl iodides and the results are summarized in Table 2. Aryl iodide bearing either an electron-donating group or electron-withdrawing reacted smoothly with sodium benzenesulfinate to afford the corresponding products in moderate to high yields. Generally, substrates with electron-donating groups were more reactive than those with electron-withdrawing groups (Table 2, entries 2-12). Steric hindrance on the phenyl ring of aryl iodides has a significant influence on the transformation. For instance, **3b** could be obtained in 90% yield, while the yield of **3j** was only 71% (Table 2, entries 2 vs. 10). It is noteworthy that the aryl iodides with the

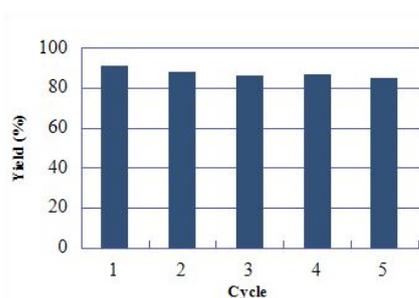
*p*-acetyl-, hydroxyl- or ester group could also be successfully transformed into the corresponding target products (Table 2, entries 6,7 and 11). Next, the sodium arylsulfonates with *p*-methyl and *p*-chloro group afforded the corresponding products in good yields under the optimized reaction conditions (Table 2, entries 13-17). Interestingly, when the cross-coupling reactions using sodium methanesulfinate are performed, the product **3q** and **3r** are obtained in excellent yields (Table 2, entries 18-19). Since the coupling reactions of unactivated aryl bromides with sodium sulfonates were reportedly unsuccessful under the most of previous conditions, we next checked these substrates using our catalytic system. To our delight, many aryl bromides worked well in our hands although higher reaction temperature and longer reaction time were required in comparison with aryl iodides (Table 2, entries 20-25).

The compatibility of this reaction with various functional groups provides potential to be incorporated into a synthetic protocol combined with other processes for further decoration. This is illustrated in a newly designed one-pot synthesis of imidazo[1,2-*a*]pyridine rings which are present in a number of commercial drugs such as zolpidem, alpidem, olprinone, zolimidine, necopidem and saripidem.<sup>24-25</sup> For example as shown in Scheme 2, *p*-iodoacetophenone was successfully applied to prepare Zolimidine through a C-H/N-H oxidative cross-coupling/cyclization and subsequently C-S cross-coupling with sodium methanesulfinate. It was noted that the CS@Cu(OAc)<sub>2</sub> efficiently promoted the transformations without isolation of the intermediate in satisfying yield.



**Scheme 2** Application of the CS@Cu(OAc)<sub>2</sub>-catalyzed C-S coupling in the one-pot synthesis of Zolimidine.

As transition metal catalysts are often expensive and display toxicity, from both an economical and environmental point of view, the recovery and recycling of the catalyst is a major concern with a transition-metal catalyzed reaction for sustainability.<sup>26</sup> Taking advantage of the good solubility of products and the insolubility of catalyst in solvent, a simple filtration was sufficient to separate the catalyst solution from the products. The recyclability of the catalyst was then studied in the C-S coupling reaction and the results are shown in Figure 2. In the recycling experiment, the separated CS@Cu(OAc)<sub>2</sub> was recharged with fresh substrate for the next run under the same reaction conditions. It was notable that the catalyst still remained catalytically active after being reused five times. The C-S coupling reaction at the 4th and 5th runs gave the desired product in 87% and 85% yields (Figure 2).



**Figure 2** Catalyst recycling for C-S coupling reaction. Reaction conditions: see Table 1, Entry 10. The catalyst was recovered by simple filtration after reaction.

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To verify whether the observed catalysis is derived from CS@Cu(OAc)<sub>2</sub> catalyst or leached copper species, the reaction of 4-iodoanisole with benzenesulfonic acid sodium salt was carried out under the conditions described in Table 1 and the catalyst was removed from the reaction mixture by hot filtration after 6 hours (at this time, approximately 50% conversion). After removal of the catalyst, the reaction was carried out again and no more product conversion was further observed even during extended time (for detailed leaching study see ESI†). No Cu metal was detected in the solution by ICP analysis. Furthermore, the TEM image of the catalyst taken after the fifth cycle of the reaction does not show significant change in the morphology and the size of the catalyst (3-8nm) (Figure 1d), which indicates the retention of the catalytic activity after recycling. The copper content was measured to be 5.83% before the reaction and 5.80% after the five reactions by ICP analysis. These results confirm the fact that chitosan provides enough binding sites on the surface to minimize deterioration and supports the heterogeneous nature of the reaction.

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## Conclusions

In conclusion, we have developed a simple, green and efficient protocol for the coupling reaction of aryl halides with sodium sulfonates readily to give the corresponding aryl and alkyl sulfones in good to excellent yields and a wide range of functional group tolerance. In particular, the easily recoverable and efficient chitosan@copper catalysts in this catalytic system can be reused five times without significant loss of catalytic performance. By using this protocol, the marketed drug Zolimidine (antiulcer) could be easily synthesized in a concise route. Further mechanistic studies on this transformation are currently ongoing in our laboratory.

## 40 Experimental section

Chitosan powder (MW: 10,000-50,000, deacetylation degree 95%, purchased from Aladdin reagent (Shanghai) Co., Ltd.) was used without further purification. Aryl halides and sulfonic acid salts were purchased from Alfa Aesar. Other chemicals were obtained commercially and used without any prior purification. All products were isolated by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90 °C), unless otherwise noted. Melting points were determined on an X-5 Data microscopic melting point apparatus. <sup>1</sup>H NMR and <sup>13</sup>C NMR

spectra were recorded on a Bruker Advance 400 spectrometer at ambient temperature with CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> as solvent unless otherwise noted and tetramethylsilane (TMS) as the internal standard. Mass spectra (GC-MS) were acquired on an Agilent 5975 spectrometer. IR spectra were recorded on a Nicolet 380 FT-IR spectrophotometer using KBr discs. Transmission electron microscopy (TEM) images were taken on FEI T20 microscope. ICP-AES metal determinations were carried out on a Perkin-Elmer Optima 3100 XL inductively coupled plasma atomic emission spectrometer. The small-angle X-ray diffraction (SAXRD) data were taken on a German Bruker D4 X-ray diffractometer with Niltered Cu Ka radiation (40 kV, 40 mA). Thermogravimetric analyses were performed with a SII Nano Technology EXTAR TG/DTA7220 thermal analyzer at 10 °C/min in nitrogen atmosphere (10 ml/min). 5 mg of each sample in an alumina pan was analyzed in the 40-900 °C temperature range.

### General procedure for synthesis of chitosan@copper catalyst.

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Chitosan (5 g) was suspended in 100 mL of water. To this suspension, 1 g of copper salt was added and stirring was continued for 3 h. The catalyst was separated using centrifuge (5000 rpm 5 min), dried under vacuum at 50 °C.<sup>21</sup> The catalyst was characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM), Infrared Spectroscopy (IR), Thermogravimetric analyses (TG) and plasma-atomic emission spectrometry (ICP-AES).

### 30 General procedure for CS@Cu(OAc)<sub>2</sub>-catalyzed coupling of aryl halides and sodium benzenesulfonate.

A mixture of aryl halide (1 mmol), sodium benzenesulfonate (1.2 mmol), CS@Cu(OAc)<sub>2</sub> (120 mg, loading 10 mol%), KOAc (2 mmol), 3 mL of DMSO-H<sub>2</sub>O (1:1) in a sealed tube was heated to 120 °C under air. The reaction was monitored using thin layer chromatographic technique. After complete disappearance of aryl halide, the reaction was cooled and the catalyst was filtered off, then the solvent was evaporated and further purification has done by column chromatography on neutral alumina using ethyl acetate/hexanes as the eluent to afford the product. All compounds were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectroscopy, which are consistent with those reported in the literature<sup>10</sup>(ESI†).

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### The catalyst recycling experiment.

To check if the CS@Cu(OAc)<sub>2</sub> is recyclable, the C-S coupling reaction was repeated five times with the same catalyst sample, which was recovered after each reaction. The initial amount of catalyst was 120 mg (loading 10 mol%). Reactions were carried out for 24 h. After the reaction, the catalyst was filtered off, washed with ethyl acetate and water twice, then dried for 3 h at 60 °C. It was then stored at ambient conditions over night and used again.

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### General procedure for one-pot synthesis of Zolimidine.

A mixture of 2-aminopyridine (113 mg, 1.2 mmol),

*p*-iodoacetophenone (246 mg, 1 mmol), CS@Cu(OAc)<sub>2</sub> (120 mg, loading 10 mol%), and ZnI<sub>2</sub> (0.1 mmol) in DMSO (3 mL) was stirred at 120 °C for 24 hours under ambient air. Then sodium methanesulfinate (122 mg, 1.2 mmol) and KOAc (196 mg, 2 mmol) were added. The reaction was stirred at 120 °C for another 24 hours under air. After cooling the reaction mixture, the catalyst was filtered and washed with ethyl acetate and water. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) as eluent. Yellowish white solid (166 mg, 61% yield).

## Acknowledgments

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