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Mechanistic aspects of copper (II)-catalyzed synthesis of sulfones from sulfinate salts and aryl halides under C-S coupling

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ABSTRACT

Copper(II)-catalyzed synthesis of sulfones from sulfinate salts and aryl halides was investigated by means of a combination of experiment and DFT calculation. Experimental results demonstrated the wide applicability of the title approach. The reaction mechanisms are revealed by *in-situ* IR and theoretical study. It reveals remarkable ligand effect the bidentate amine plays in the reaction, that is, it initially activats the C-I bond of iodobenzene so as to enhance the whole catalytic process.

1. Introduction

Aryl sulfone is an important class of compounds which play a major role in pharmaceuticals and agrochemicals [1]. Especially, their versatile bioactivities e.g. anti-HIV [2], anti-tumor [3] and anti-inflammatory [4] continue to attract much attention in medical industry. Sulfones can be prepared via quite a few routes, among which the oxidation of sulfides [5] and the sulfonylation of arenes [6] are classic. However, these two routes suffer from some disadvantages, e.g. low yield and fastidiousness about the substrate. Further, for the oxidation route, the harsh condition required and limited applicability of organometallic catalyst concerning various functional groups are also annoying. Recently, metal-catalyzed coupling reaction is becoming the most powerful tool for functionalization of arylated compound [7]. Compared with other metal-catalyst, copper-complex is more promising for coupling of sulfinate salts with aryl halides due to the benign condition needed and the wide applicability for various functional groups including olefin, amine *etc* [8]. In 1995, Suzuki et.al. [9] first reported the sulfones were synthesized by using 1.5 equiv of CuI as catalyst in DMF at 110 °C; the afterward work done by Wang [10] and Ma [11] improved this strategy by introducing diamine and proline ligands. Up till now, various ligands such as anion-functionalized ionic liquid [12], 1,10-phenanthroline [13], D-Glucosamine [14] and chitosan [15] have been developed for promoting the coupling of sulfinate salts with aryl halides. In contrast to the vast number of reports on Ullmann C—N and C—O coupling reaction, there are only a few reports on C-S coupling of sulfinate salts with aryl halides, and detailed mechanism study is still lacking.

Recently, considerable effort has been made to elucidate the mechanism of Ullmann C—N coupling reaction. The oxidation addition/reductive elimination mechanisms are widely accepted [16], in which the ligand-Cu^{I}-nucleophile intermediates were identified as the active species for the C—N coupling process [17]. Moreover, the oxidative addition of ligand-Cu^{I}-nucleophile intermediates with aryl halides was identified as the rate-determining step [16][16d]. By contrast, analogous mechanistic studies on Ullmann C-S [18] coupling reaction received less attention. Shyu et. al. [18][18a] reported that several Cu-thiolate intermediates in the C-S coupling of thiophenol with aryl halide were observed by *in situ* ESI–MS study. Weng and Hartwig et. al. [18][18b] prepared ligand-Cu^{I}-thiophenolato complexes and examined their reactivity in the copper-catalyzed thioetherification of aryl halides. Upon comparing several proposed mechanisms for Ullman reaction, e.g. oxidative addition/reductive elimination, σ-bond metathesis, single-electron transfer (SET) and halogen-atom transfer (HAT) mechanisms, Zhang et. al. [18][18c] found that HAT is the most favorable mechanism for Ullmann C-S coupling of thiophenol with

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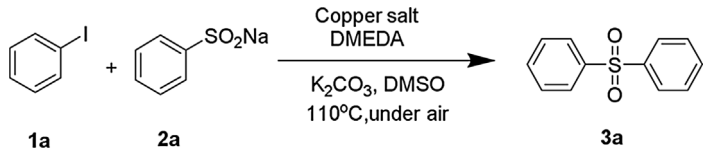
Table 1
Ullmann C-S coupling of iodobenzene with sodium benzenesulfinate [a].



Entry	Copper Salt	Solvent	Yield (%)[b]
1	CuCl	DMSO	85
2	CuBr	DMSO	83
3	CuI	DMSO	74
4	$CuSO_4{\cdot}5H_2O$	DMSO	71
5	$Cu(OAc)_2$	DMSO	95
6[c]	$Cu(OAc)_2$	DMSO	0
7[d]	$Cu(OAc)_2$	DMSO	0
8	$Cu(OAc)_2$	DMF	84
9	$Cu(OAc)_2$	Methanol	31
10	$Cu(OAc)_2$	DMSO:H_2O (1:1)	0

[a] reaction conditions: iodobenzene 1a (1.0 mmol), sodium benzenesulfinate 2a (1.2 mmol), copper salt (0.01 mmol), DMEDA (0.02 mmol), K2CO3 (2.0 mmol), solvent (5 mL), 110 °C, under air, 2 h.
[b] Isolated yield.
[c] No ligand.
[d] No K_2CO_3.

aryl halide. However, the mechanism of C-S coupling of sulfinate salts with aryl halides remains a mystery. The previously reported mechanisms for Ullmann reactions imply that different nucleophiles may react via different mechanisms. In this work, we reveal the mechanistic aspects for Ullmann C-S coupling of sulfinate salts with aryl halides catalyzed by Cu(II)-complexes. Several conceivable pathways were considered and the influence of diamine-type ligand on the synthesis of aryl sulfones will be discussed.

2. Result and discussion

Initial experimental investigations focused on the influence of diamine-type ligand structure on the catalytic activity. The coupling of iodobenzene (1.0 equiv.) and sodium benzenesulfinate (1.2 equiv.) was adopted as the model reaction, and detailed ligand screening are shown in Fig. 1. By using 10 mol% of cyclohexane-1,2-diamine (**L1**) and ethylenediamine (**L2**), the sulfone was obtained in good yields. When *N,N'*-dimethylehylenediamine (DMEDA, **L3**) was used as ligand, the yield increased to 95%. Ligand containing secondary amine serves as more active catalysts as compared to those with primary amine group. We speculated that ligands possessing primary amine is less electron-donating such that the so formed complex is less active. Accordingly, secondary-amine-ligand **L5** possessing two electron-withdrawing benzene groups is also less active. Moreover, due to steric hindrance, **L4** is difficult to bound with copper for forming stable chelate, resulting in less reactivity of associated system. The other bidentate N-ligand 1,10-phenanthroline (**L6**) gave good result with 88% yield.

For Ullmann C-S coupling of iodobenzene with sodium benzenesulfinate, various copper sources and solvent were studied in presence of DMEDA. The detained results were summarized in Table 1. Comparison of different copper sources, i.e. CuI, CuBr, CuCl, $CuSO_4{\cdot}5H_2O$ and $Cu(OAc)_2$, showed that $Cu(OAc)_2$ was the best copper source (Table 1, Entry 1–5). This suggested that the oxidation state of copper may have no influence on the formation of catalyst precursor, which have also been observed previously [19]. However, copper source without the ligand was completely inactive (Table 1, Entry 6). In addition, base is found to be essential in this protocol for the formation of C-S bond (Table 1, Entry 7). Next, a serious of solvents were tested and it was found that polar aprotic solvents were favorable for this C-S coupling (Table 1, Entry 5,8–10). The detailed kinetic profiles were obtained using *in-situ*

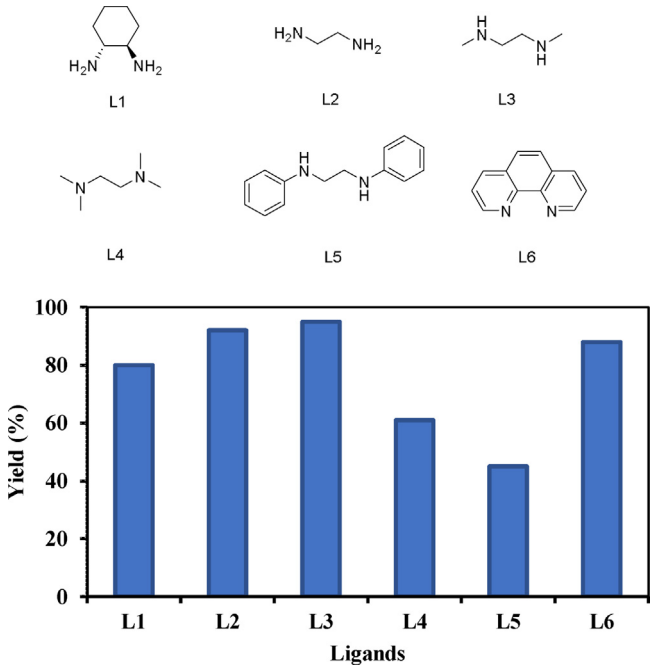
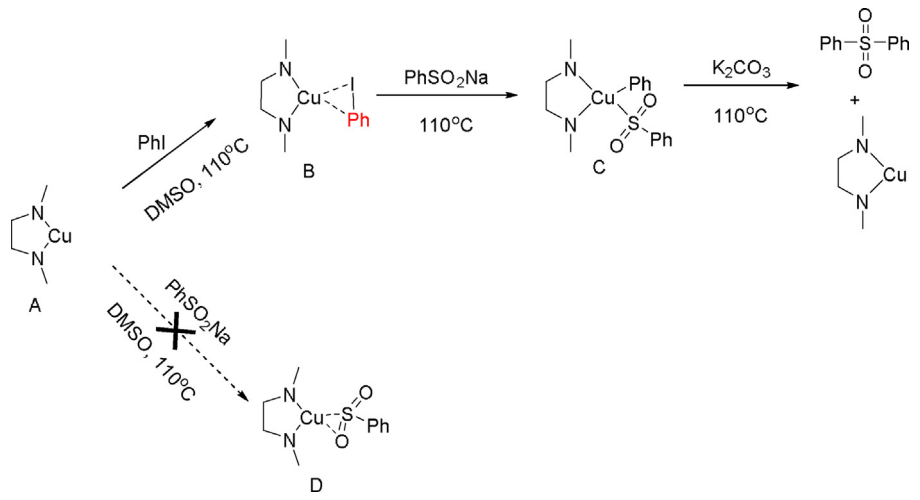


Fig. 1. Ligand screening in copper-catalyzed synthesis of sulfones from sulfinate salts and aryl halides [a].
[a]reaction conditions: iodobenzene 1a (1.0 mmol), sodium benzenesulfinate 2a (1.2 mmol), Cu(OAc)2 (0.01 mmol), ligand (0.02 mmol), K2CO3 (2.0 mmol), DMSO (5 mL), 110 oC, under air, 2 h. The yield of product is isolated yield.

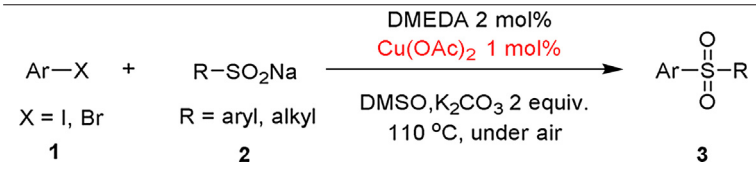
IR. As shown in Fig. 2, all these three copper-catalyzed reactions exhibit zero-order character, and the initial rates of $Cu(OAc)_2$, CuCl and CuI were 0.019 mM/min, 0.012 mM/min and 0.0094 mM/min, respectively. Clearly, $Cu(OAc)_2$ outperforms the other two copper salts.

Further study focused on testing the scope of $Cu(OAc)_2$/DMEDA catalyzed C-S coupling reaction. As showed in Table 2, to our delight, both aryl sulfonate and alkyl sulfonate react efficiently with iodobenzene and targeted product was obtained with excellent yields (Table 2, Entry 1–4). Moreover, it is notable that the sulfonates with electron-donating groups are more reactive than the ones with electron-withdrawing groups. For aryl iodide, neither



Scheme 1. Proposed mechanism.

Table 2
$Cu(OAc)_2$/DMEDA catalyzed C-S coupling reaction [a].



Entry	Ar	X	R	Yield (%)[b]
1	Ph	I	Ph	95 (3a)
2	Ph	I	4-MeC_6H_4	96 (3b)
3	Ph	I	4-ClC_6H_4	82 (3c)
4	Ph	I	Me	97 (3d)
5	4-$MeOC_6H_4$	I	Ph	93 (3e)
6	4-MeC_6H_4	I	Ph	92 (3b)
7	4-HOC_6H_4	I	Ph	88 (3f)
8	4-ClC_6H_4	I	Ph	87 (3c)
9	4-$NO_2C_6H_4$	I	Ph	90 (3 g)
10	4-$CF_3C_6H_4$	I	Ph	94 (3 h)
11	4-$CH_3COC_6H_4$	I	Ph	81 (3i)
12	3-$NO_2C_6H_4$	I	Ph	85 (3j)
13	2-MeC_6H_4	I	Ph	71 (3k)
14	2-$MeOOCC_6H_4$	I	Ph	64 (3l)
15	Ph	Br	Ph	47 (3a)

[a] reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $Cu(OAc)_2$ (0.01 mmol), DMEDA (0.02 mmol), K_2CO_3 (2.0 mmol), DMSO (5 mL), 110 °C, under air, 2 h.
[b] Isolated yield.

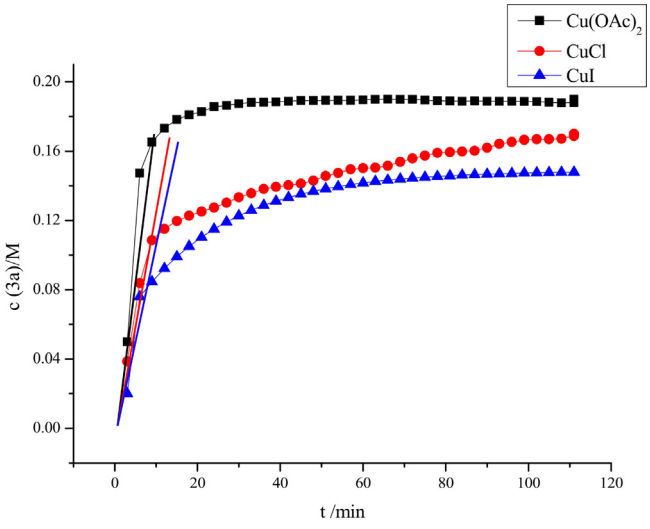


Fig. 2. Kinetic profiles of C-S coupling catalyzed by Cu species.

electron donating nor withdrawing groups substituted on the ring have obvious influence on the yields (Table 2, Entry 5–11), while the steric hindrance by *ortho*-substituents decreases the reaction efficiency (Table 2, Entry 12–14). In line with the previous study [9,10], the reactivity of aryl bromide is lower than iodobenzene (Table 2, Entry 15).

To elucidate the reaction mechanisms, we used *in-situ* IR to monitor the stoichiometric reaction of DMEDA-ligated copper **A** with iodobenzene or sodium benzenesulfinate. Initially, DMEDA-ligated copper **A** formed in situ by the stoichiometric reaction of DMEDA and $Cu(OAc)_2$ in DMSO at 110 °C. As shown in Fig. 3a, after the addition of iodobenzene, the peak at 731 cm^{-1} concerning Ar-I stretch vibration migrated to 742 cm^{-1}. Then, the addition of sodium benzenesulfinate to the mixture resulted in the ConcIRT migration of S=O stretching from 1130 cm^{-1} to 1158 cm^{-1}. Finally, when the K_2CO_3 was added into the reaction system, the new peak at 1119 cm^{-1} regarding S=O stretching was formed. However, when sodium benzenesulfinate was first added to mixture, the *in-situ* IR had no obvious change. Thus, a prototypical reaction mechanism for C-S coupling of iodobenzene with sodium benzene-

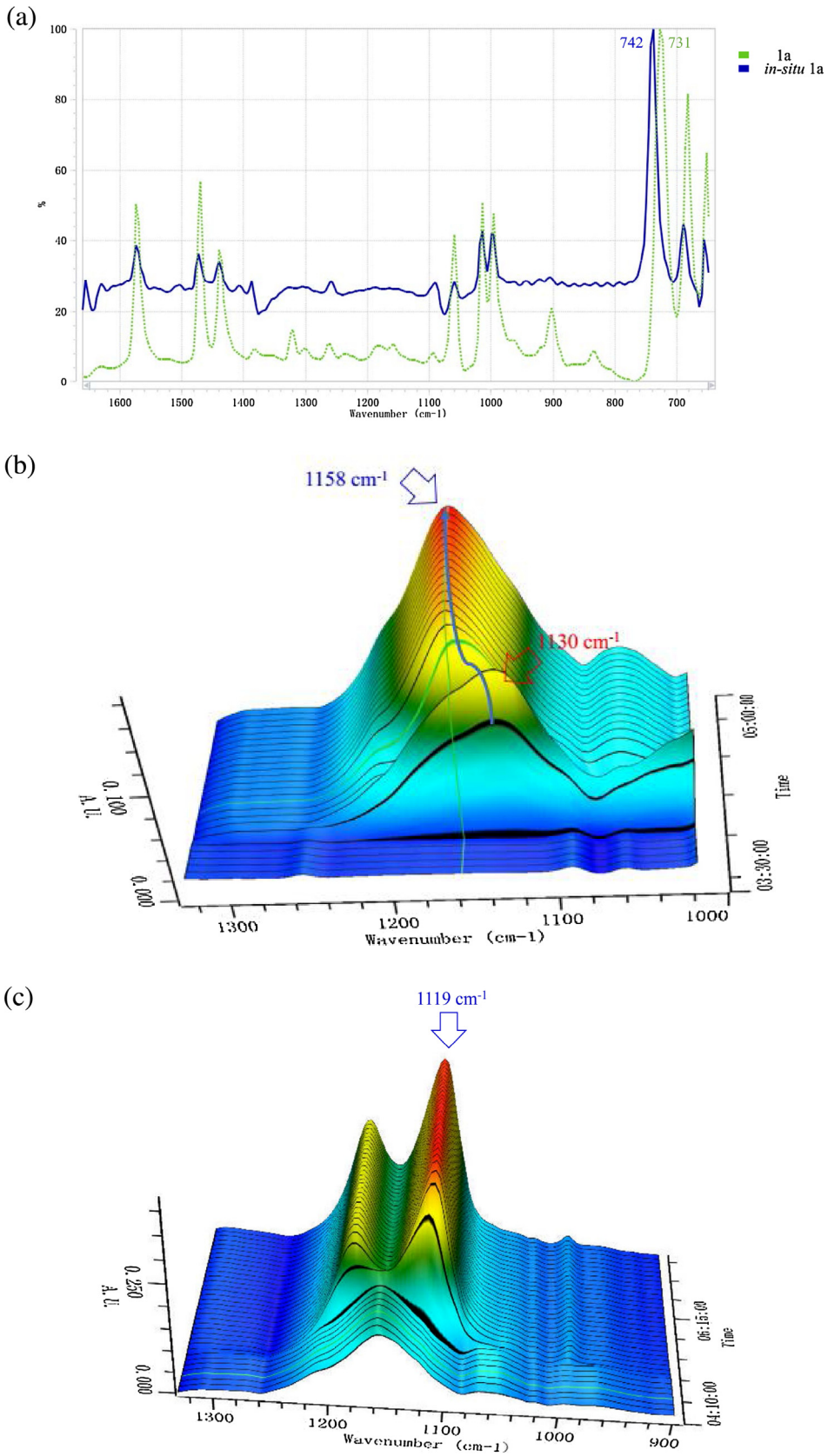


Fig. 3. (a) ConcIRT spectra of *in-situ* **1a**. (b) Overall three-dimensional Fourier transform IR (3D-FTIR) profile of the reaction between complex **B** and **2a**. (c) 3D-FTIR profile of the reaction between complex **C** and K_2CO_3.

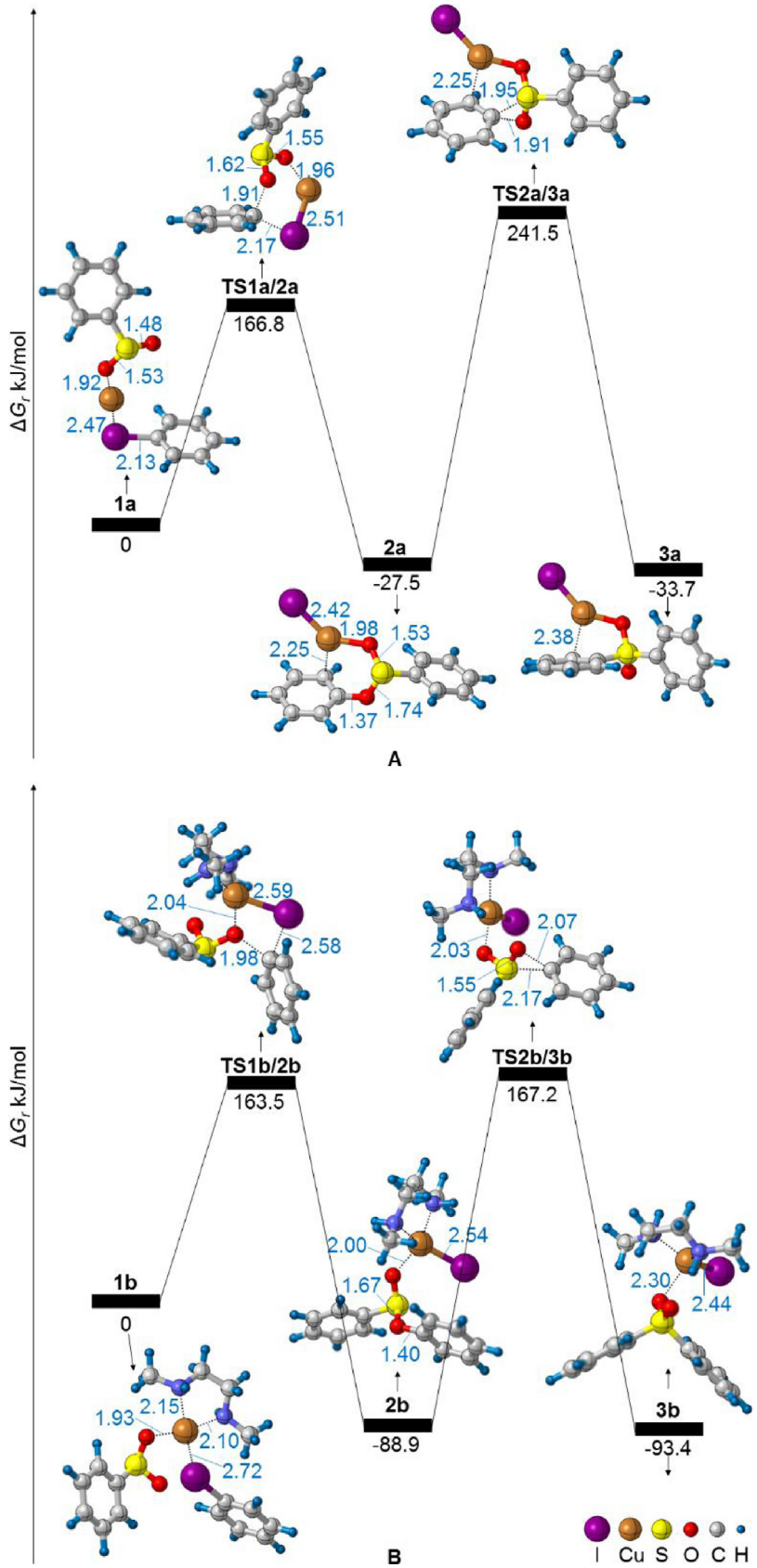


Fig. 4. PES and selected structural information for route 1; **A** is for bare Cu^{2+} catalyzed reaction, while **B** is for the Cu(II)-catalyzed one.

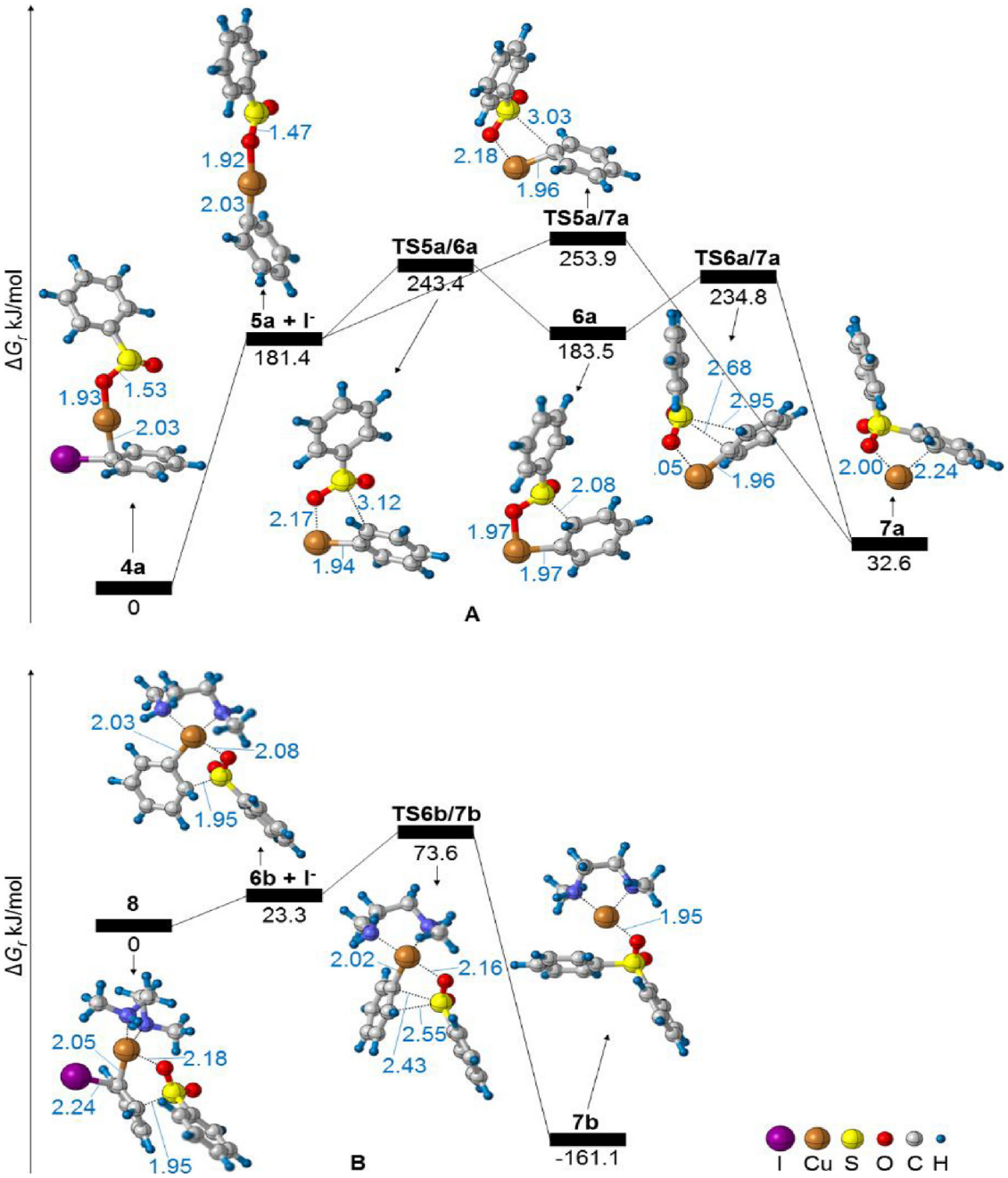


Fig. 5. PES and selected structural information for route 2; **A** is for bare Cu^{2+} catalyzed reaction, while **B** is for the Cu(II)-catalyzed one.

sulfinate catalyzed by copper is proposed, as shown in Scheme 1. Initially, complex **B** is formed via oxidative addition of complex **A** with iodobenzene, which activates Ar-I bond. The nucleophilic reaction of complex **B** with sodium benzenesulfinate generates complex **C**. This results in the cleavage of Ar-I bond, which is proved by consumption of the peak at 731 cm^{-1} (see Fig.S2 in the SI). With the addition of base to mixture, the final product was obtained by reductive elimination and DMEDA-ligated copper was regenerated.

Next, the reaction mechanisms were interrogated by density functional theory (DFT) calculation. For the Ullmann reaction, the oxidative addition/reductive elimination mechanism is widely accepted[16d,e]. However, the mechanism of C-S coupling of sulfinate salts with aryl halides remains unknown. Thus, we first studied the influence of diamine-type ligand on the synthesis of aryl sulfones. Ligand **L2**, which gives the best performance according to the experimental results, was thus used for modeling the Cu(II)-catalyzed reaction; the latter will be compared with the bare Cu^{2+} catalyzed system. In order to obtain common information about the reaction mechanism, the production of diphenylsulfone was selected as the model. Two possible routes, e.g. oxidative addition/reductive elimination and σ-bond metathesis, were considered, and the potential energy surfaces (PESs) as well as some structural information of relevant species are shown in Figs. 2 and 3, respectively.

For route 1 (σ-bond metathesis mechanism), the C-S coupling concerts with activation of the C_6H_5-I bond. As shown in Fig. 4A, for bare Cu^{2+} catalyzed reaction, the transformation starts from an encounter complex **1a**, in which the copper atom interacts with the iodine atom of iodobenzene and one oxygen atom of benzenesulfinate. By surmounting **TS1a/2a**, the C_6H_5-I bond is

activated under formation of the Cu-I and C_6H_5—O bonds, forming **2a**. Subsequently, the phenyl group of original iodobenzene migrates from the oxygen atom to the sulfur atom, producing the product complex **3a**, the dissociation of which releases neutral diphenylsulfone and CuI^+. The Cu(II)-catalyzed reaction, Fig. 4B, structurally resemble the bare Cu^{2+} catalyzed reaction one, i.e. **1b** → **TS1b/2b** → **2b** → **TS2b/3b** → **3b**. However, both reaction pathways are too energetically demanding to be available.

For route 2 (oxidative addition/reductive elimination mechanism), the C-S coupling is achieved in a stepwise manner, that is, the C_6H_5-I bond activation takes place first which is followed by coupling of the left moieties. As shown in Fig. 5**A**, for bare Cu^{2+} catalyzed reaction, the transformation starts from encounter complex **4a**, in which the copper atom interacts with the *ipso* carbon of iodobenzene and one oxygen atom of benzenesulfinate. By barrierlessly liberating an iodine anion, the intermediate **5a** is formed. From **5a**, the production of diphenylsulfone can be achieved via either a direct C-S coupling via **TS5/7a**, or an alternative two-step transformation, i.e. **5a** → **6a** → **7a**. The latter one is energetically more pronounced. Yet these two pathway suffers from the inefficient C_6H_5-I bond activation as the process **4a** → **5a** is energetically too demanding. Further, for Cu(II)-catalyzed reaction, only one pathway has been found. Starting from the encounter complex **8**, the elimination of I^- can be achieved when 23 kJ/mol energy is supplied, generating **6b**, and the product complex **7b** can be produced via only one step. Obviously, the stepwise C-S coupling (route 2) is more competitive than the concerted one (route 1), and the process **8** → **6b** → **7b**, that is, oxidative addition/reductive elimination mechanism corresponds to the energetically most favorable pathway.

Comparing the pathways shown in Fig. 5A and B, one cannot escape from the conclusion: it is the remarkable ligand effect that decreases the energy required to activate the C_6H_5-I bond, so as to enable the whole C-S coupling process, highly consistent with the experimental observation.

3. Conclusion

In summary, in this work, we have presented the combined experimental/theoretical study of the copper (II)-catalyzed synthesis of sulfones from sulfinate salts and aryl halides under C-S coupling. Experimental results clearly demonstrate the wide applicability of the title approach; a stepwise C-S coupling process is monitored by *in-situ* IR and initialized by the activation of Ar-I bond; theoretical study reveals the remarkable ligand effect the bidentate amine plays in the reaction, that is, it promotes the decreasing of energy required for activating the C-I bond of iodobenzene so as to enhance the whole process.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mcat.2017.12.016.

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