ORGANOMETALLICS

Use of Base Control To Provide High Selectivity between Diaryl Thioether and Diaryl Disulfide for C–S Coupling Reactions of Aryl Halides and Sulfur and a Mechanistic Study

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Supporting Information

ABSTRACT: Previous studies have reported that S-arylation produces diaryl disulfide when the precursors include sulfur powder and aryl halide using CuI as the catalyst. However, our research has revealed that the use of different bases in the above S-arylation process results in the coproduction of diarylsulfane and diaryldisulfane. In addition, we have demonstrated that the ratio of the two products can be controlled by selecting the alkalinity of the bases. ¹H NMR spectra showed that diaryldisulfane was the first product, which became the reagent in a reaction with aryl halide to form diarylsulfane through CuI catalysis. Various aryl halides were tested to enhance the selectivity between diarylsulfane and diaryldisulfane using various different bases, leading to the following principles. A weak



base, such as metal carbonate or acetate, results in the production of only diaryldisulfane; a strong base, such as metal hydroxide, results in the production of both diaryldisulfane and diarylsulfane. According to DFT calculations, hydroxide ions, which were exchanged for iodide and bonded with Cu, affected Cu electrons more strongly to reduce diaryl disulfide.

INTRODUCTION

Recently, C-N, C-S, and C-O coupling reactions have been performed using transition metals as catalysts. Such applications have been studied extensively because the resulting derivatives, such as phenol, aniline, and thiophenol, are important for synthesizing natural products, pharmaceuticals, and polymeric materials. Among them, scientists have paid particular attention to C-S coupling reactions because the derivatives exhibit biological activity. Liu and Huth^{1a} reported a series of *p*-(arylthio)cinnamide-based antagonists of the LFA-1/ICAM-1 interaction, represented by 1 (Chart1). This series of compounds was identified by screening for the inhibition of the LFA-1/ICAM-1 interaction with full length proteins. Silvestri^{1b} reported a series of arylthioindoles (ATIs) (Chart 1) that were effective inhibitors of the tubulin assembly and MCF-7 cell growth at nanomolar concentrations. In addition, aryl sulfides and their derivatives are important for their biological, pharmaceutical, and material interest.²

Conservative methods used in the formation of C–S bonds often require severe reaction conditions.³ To overcome this, attention has been focused on the evolution of catalytic systems for the S-arylation of thiols using aryl halides. Transition-metalcatalyzed cross-coupling reactions of aryl halides with arenethiol or alkanethiol are effective methods for forming carbon–sulfur bonds. Migita⁴ reported the first palladium-catalyzed coupling reaction of iodo- and bromoarenes with thiols, and various ligands⁵ have been tested for this reaction. Hartwig⁶ reported a highly efficient palladium-catalyzed system using the Josiphos ligand for the coupling of aryl chloride and triflates with thiols. Palladium-catalyzed coupling is a powerful method for forming aromatic carbon–sulfur bonds. Considering the current costs of Pd (\$600–700/ounce) and phosphine ligands, the search for less costly alternatives has led to the application of other transition metals such as nickel,⁷ iron,⁸ indium,⁹ cobalt,¹⁰ and copper^{11–14} for S-arylation. Copper salts in particular provide higher catalytic activity at a lower price than most of the other candidate materials. A variety of methods have been reported for the study of copper-catalyzed S-arylation, including (1) Cu-nanoparticle systems,¹¹ (2) ligand-free systems,¹² (3) ligand-based systems,¹³ and (4) systems using various sulfur reagents;¹⁴ method 4 deals mainly with the application of new reagents for S-arylation. Figure 1 outlines the fourth method using various sulfur reagents.

Among these methods, S-arylation from sulfur powder shows particular promise, due to its low coat and only faint odor. Jiang and Ma^{14k} reported several polysulfanes with various numbers of sulfur molecules as byproducts of S-arylation from sulfur powder (Figure 2a). Xu and Feng^{14j} reported that arenethiols could be synthesized after treating the coupling products with Zn and HCl (Figure 2b). We recently determined that the product of the above coupling reaction is diaryldisulfane, as identified by GC-MS using Na₂CO₃ as a base. Li¹⁴¹ and Srogl¹⁴ⁿ respectively reported that unsymmetrical sulfides were

Received: August 4, 2013

Chart 1. Examples of Sulfur-Containing Molecules with Biological Importance for Pharmaceuticals, Biologically Active Molecules, and Polymeric Materials



LFA-1/ICAM-1 Inhibitor

Table 1. Optimization of Cu Salts and Bases for C-S Coupling Reactions of 4-Iodotoluene and Sulfur Powder



			conversn, %"			
entry	Cu salt	base	ditolylsulfane	ditolyldisulfane	iodotoluene	
1	none	$Cs_2CO_3^a$	0	0	100	
2	CuI	$Cs_2CO_3^a$	<1	56	44	
3	CuBr	$Cs_2CO_3^a$	<1	58	42	
4	CuCl	$Cs_2CO_3^a$	<1	52	48	
5	Cu ₂ O	$Cs_2CO_3^a$	<1	23	73	
6	Cu ₂ S	$Cs_2CO_3^a$	<1	63	37	
7	CuO	$Cs_2CO_3^a$	0	0	100	
8	CuS	$Cs_2CO_3^a$	0	0	100	
9	$Pd(OAc)_2$	$Cs_2CO_3^a$	0	0	100	
10	PdCl ₂	$Cs_2CO_3^a$	0	0	100	
11	CuI	Cs ₂ CO ₃ ^c	32	25	43	
12	CuI	$Cs_2CO_3^{a,b}$	34	38	28	
13	CuI	K ₂ CO ₃	<1	48	52	
14	CuI	K ₃ PO ₄	7	54	39	
15	CuI	КОН	5	57	38	
16	CuI	NaOH	40	22	38	
17	CuI	LiOH·H ₂ O	44	43	12	
18	CuI	CH ₃ COOK	<1	48	52	
19	CuI	CH ₃ COONa	0	18	82	

^{*a*}Alfa reagent. ^{*b*}A drop of water was added. ^{*c*}Acros reagent. ^{*d*}Detection from ¹H NMR spectra. For example, 63% in entry 6 means that 63% of 4-iodotoluene transformed to ditolyldisulfane.

produced from aryl halide and diaryl disulfane. On the basis of this approach, this study sought to synthesize a symmetrical diaryldisulfane (from aryl halide and sulfur power using Cu salt and Na_2CO_3), which was then coupled with another aryl halide to obtain an unsymmetrical diarylsulfane. Jiang and Ma also described the production of arenethiol through the reaction of

diarylpolysulfane with NaBH₄. This study investigated the use of NaBH₄ as the base in the coupling reaction to obtain a symmetrical diarylsulfane. These results imply that there should be two products in the coupling reaction of aryl halide and sulfur powder: diarylsulfane and diaryldisulfane. In the coupling reaction of aryl halide with sulfur powder, diaryldisulfane was



Figure 1. C–S coupling reactions using various sulfur reagents: (a) S-arylation of arylboronic acid with alkanethiols,^{14b} N-thiol(alkyl, aryl, heteroaryl) imides,^{14a} or TMSCF₃,^{14c} (b) C–H activation and C–S cross-coupling of heterocycles with thiols,^{14d} (c) synthesis of unsymmetrical sulfides using ethyl potassium xanthogenate,^{14e,f} (d) methylthiolation of aryl C–H nonds with DMSO,^{14g} (e) synthesis of aryl methyl sulfones from aryl halides and DMSO,^{14h} (f) synthesis of arenethiols from aryl iodide and thiourea,¹⁴ⁱ (g) synthesis of arenethiols from aryl iodide, sulfur powder, and reductants,^{14j–L,t} and (h) synthesis of unsymmetrical sulfides from aryl iodides from aryl iodides and diaryldisulfanes.^{14m–p}

completely investigated^{14s} but the control of the ratio between products (diaryldisulfane and diarylsulfane) by the different bases and the mechanism were not studied. Thus, this study applied various bases in coupling reactions to determine the influence of the base on the coupling reaction and underlying mechanism.

RESULTS AND DISCUSSION

We first performed the optimization of Cu salts and bases for the C–S coupling reaction of 4-iodotoluene and sulfur powder (Table 1). Using Cs₂CO₃ (Alfa reagent, 99%) as the base with various Cu salts resulted in the production of only ditolyldisulfane. The catalytic rates in decreasing order were Cu₂S (63%) > CuBr (58%) > CuI (56%) > CuCl (52%) > Cu₂O (23%) ≫ CuO, CuS (0%). Cu₂S was the most effective Cu salt; however, the underlying mechanism remained unclear. We selected CuI for subsequent C–S coupling reactions due to its powerful catalytic activity and stability in air. Changing the catalyst to



Figure 2. S-arylation from sulfur powder and aryl iodide.

Pd(OAc)₂ or PdCl₂ (entries 9 and 10) was ineffective. With Cs₂CO₃ (99.5%) (entry 11) from Acros as the base, the production of ditolylsulfane (conversion 32%) and ditolyldisulfane (conversion 25%) was observed. It is believed that this was due to the deliquescence of the Cs₂CO₃ from Acros, and a comparison reaction was devised to provide entry 12. Cs_2CO_3 from Alfa was used with a drop of water for the C-S coupling reaction of 4-iodotoluene and sulfur powder, resulting in the production of ditolylsulfane (conversion 34%) and ditolyldisulfane (38%) with a slight increase in catalytic activity. One explanation may be that the water promoted the dissolution of Cs₂CO₃ in DMF, CsOH was produced from water and Cs₂CO₃ at 100 °C, and metal hydroxide helped the Cu salt to generate ditolylsulfane. To validate this assumption, KOH, NaOH, and LiOH·H2O were tested for the C-S coupling reaction of 4-iodotoluene and sulfur powder (entries 15-17), all of which produced ditolylsulfane and ditolyldisulfane. Other weak bases, such as K2CO3, CH3COOK, and CH₃COONa (entries 13, 18, and 19), were also used; only ditolyldisulfane was observed in the C-S coupling reaction of 4-iodotoluene and sulfur powder.

To reveal the reaction mechanism, we monitored the processes involved in the C–S coupling reaction of 4-iodotoluene and sulfur powder with Cs_2CO_3 (Acros) as the base using ¹H NMR spectra, as shown in Figures 3 and 4. When the reaction started, only 4-iodotoluene was observed (peaks 7.56 and 6.92 ppm, Figure 3a). After 30 min (Figure 3b), ditolyldisulfane was observed at 7.38 and 7.11 ppm. After 1 h, ditolylsulfane was observed at 7.22 and 7.09 ppm. The ratios of iodotoluene, diarylsulfane, and diaryldisulfane are shown in Figure 4. Ditolylsulfane was produced during 0.5–1 h, and ditolyldisulfane showed signs of decreasing after 1 h, suggesting that the first product was ditolyldisulfane, which was consumed to produce ditolylsulfane. To demonstrate this, diaryldisulfane and 4-iodotoluene were used as the precursors with various bases to produce ditolylsulfane, as shown in Table 2.

Entries 1-3 in Table 2 reveal that 4-iodotoluene, a base, and CuI were necessary for the formation of ditolylsulfane. Surprisingly, Cs₂CO₃ and K₂CO₃ influenced Cu catalysis in the synthesis of ditolylsulfane. Thus, Cs₂CO₃ and K₂CO₃ are both able to synthesize ditolyldisulfane and ditolylsulfane; however, the coupling reaction of ditolyldisulfane from S₈ and iodotoluene is more effective than that of ditolylsulfane frpm ditolyldisulfane and iodotoluene. Other metal carbonates and weak bases, such as CH₃COONa, did not promote the synthesis of ditolylsulfane from CuI (entries 7, 8, and 12). In contrast, all of the metal hydroxides, such as LiOH, NaOH, and KOH, broke the S-S bond by CuI and produced ditolylsulfane. This means that hydroxide is a strong base and offers more electrons to Cu in comparison with CO_3^{-} . CuOH with higher electron density is capable of facilitating the breaking of the S-S bond. All reactions can be described as shown by eq 1. In addition, the



Figure 3. ¹H NMR spectra of tracking the C–S coupling reaction of 4-iodotoluene and sulfur powder with Cs_2CO_3 (Acros) as the base: (a) 0 min; (b) 30 min; (c) 4 h; (d) 8 h; (e) 12 h.

Table 2. C–S Coupling Reaction of 4-Iodotoluene and Ditolylsulfane Catalyzed by CuI with Various Bases



$$Ar-I + S_8 \xrightarrow{pathwayA} Ar-SS-Ar \xrightarrow{Ar-I} pathwayB} Ar-S-Ar$$
 (1)

 Li^{14m} and $Srogl^{14n}$ groups showed that this reaction needs reductants, such as Fe and ascorbate, to reduce Cu intermediates, but our result showed that it worked well without reductants. This means that there is something which serves as the reductant, such as S_8 or I⁻. To figure out the real reductants, a range of S_8 amounts was tested for coupling with



Figure 4. Ratios of iodotoluene (black \blacklozenge), ditolylsulfane (blue \blacktriangle), and ditolyldisulfane (pink \blacksquare) monitored by ¹H NMR during time tracking of the C–S coupling reaction of 4-iodotoluene and sulfur powder using Cs₂CO₃ as the base.

Table 3. C–S Coupling Reaction of 4-Iodotoluene with a Range of S_8 Amounts Catalyzed by CuI and Base (LiOH-H₂O or CH₃COONa) in DMF at 100 °C for 24 h

		co			
entry	I-toluene:S	ditolyldisulfane	ditolylsulfane	I-toluene	ratio, % ^b
1^c	3:1	0	30	70	45
2^d	3:1	25	0	75	25
3 ^c	3:1.5	0	58	42	42
4^d	3:1.5	42	0	58	16
5 ^c	3:2	0	83	17	37
6^d	3:2	55	0	45	18
7^c	3:3	29	71	0	36
8^d	3:3	73	0	27	27

^{*a*}Detection from ¹H NMR spectra. ^{*b*}The ratio of S_8 was used as the reductant. ^{*c*}LiOH·H₂O. ^{*d*}CH₃COONa.

iodotoluene, shown in Table 3. In Table 3, S_8 was the limiting reagent and the quantity of S_8 was not equal to that of the

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Figure 5. DFT calculations of the reaction between CuX (X = OH, CH₃COO) and diphenyldisulfane. The values in parentheses are charges on S, Cu, and X.

coupling products. This mean that parts of S_8 may be the reductant and the ratio of S₈ used as the reductant is 36-46% using LiOH·H₂O as the base (entries 1, 3, 5, and 7) and 16-27% using CH₃COONa as the base (entries 2, 4, 6, and 8). This means that 16-27% of S₈ was the reductant in pathway A of eq 1 and 9-26% in pathway B. In addition, the concentration of S_8 is low, which made the production rate of Ar–SS–Ar (pathway A) lower than that of Ar–S–Ar (B); hence, there is no ditolyldisulfane obtained and CH₃COONa could not break the S-S bond by activating Cu to produce Ar-S-Ar. However, the results of Table 2 showed that the catalytic reaction still proceeded without S8. There must be another reductant in this reaction. Therefore, the CuI in DMF was heated at 100 °C for 5 h and I₃⁻ was detected by LC-MS. This means that I⁻ also can reduce CuI to form I₂ and Cu and then react with another I^- to become I_3^- .

To understand the influence of the base on the C–S coupling reaction of 4-iodotoluene and sulfur powder, we employed DFT calculations to investigate the different reaction behaviors of metal hydroxide and metal acetate. We propose that two equal Cu salts will interact with the S–S bond of diphenyl-disulfane to form the cyclic intermediate Ia (Figure 5). The DFT optimized geometries of intermediate Ia revealed that the S–S bond is ruptured upon coordination with the Cu salts;

the S–S distance increases from 2.12 Å in free disulfane to 3.43 and 3.25 Å in Cu complexes with hydroxide and acetate, respectively. The test of wavefunction stability indicated that the stable electronic state of Ia is a singlet biradical rather than a closed-shell singlet, reflecting the fact that the S-S bond is basically broken in these Cu complexes. In the Ia state, the Cu complex with hydroxide showed an unsymmetrical geometry with the Cu–S bond lengths being 2.22 and 2.31 Å. In contrast, the analogous complex with acetate displayed a symmetric structure with the Cu–S bond length being 2.28 Å. It is worth noting that one of the Cu-S bonds in the hydroxide-containing complex Ia (2.31 Å) is longer than that in the acetatecontaining complex Ia (2.28 Å). This difference in geometry was expected to cause the former to more easily dissociate to form the monomer Ib, which was assumed to be the active intermediate that subsequently undergoes the oxidative addition with aryl iodide, in comparison to the latter. This inference was supported by the computational results of reaction free energy $(\Delta_{rxn}G)$ for Ia \rightarrow 2Ib; the $\Delta_{rxn}G$ value for the hydroxide-containing system was calculated to be 17.1 kcal/mol, which is smaller than 19.4 kcal/mol for the acetate-containing system. The hydroxide-containing Ib might be further coordinated by a DMF solvent to form Ic; the free energy of this process was estimated to be -3.6 kcal/mol. However, the

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Figure 6. Proposed mechanism of the C-S coupling reaction of aryl halide and sulfur.

corresponding process for the acetate-containing system was energetically unfavorable, with a free energy of 2.8 kcal/mol. In addition, the charge on the Cu atom of Ib with hydroxide ion (+0.609) is less positive than that of Ib with acetate ion (+0.676). In other words, hydroxide ion donates more negative charge to Cu and makes it more electron rich in comparison with acetate ion. The Cu center with a higher electron density is expected to more effectively facilitate the oxidative addition of aryl iodide. These computational results explain why metal hydroxide is capable of producing ditolylsulfane but metal acetate is not.

Kinetic experiments were performed to reveal the reaction mechanism. The reaction can be divided into two stages: the formation of ditolyldisulfane from iodotoluene followed by the formation of ditolylsulfane from ditolyldisulfane and iodotoluene. During the C–S coupling reaction of 4-iodotoluene and sulfur powder with Na₂CO₃ as the base, the concentration of iodotoluene was monitored by ¹H NMR spectra, as shown in Table S1 and Figure S1 (Supporting Information). The linear relationship of $1/[iodotoluene] - 1/[iodotoluene]_0$ versus

reaction time indicates that rate = k_{obs} [iodotoluene].² This reveals that the rate-determining step of this reaction is the oxidative addition of aryl iodide, in which two iodotoluenes are consumed in each catalytic cycle. The C-S coupling reaction of 4-iodotoluene and ditolyldisulfane with LiOH·H₂O as the base was then performed, and the concentrations of iodotoluene and ditolyldisulfane were monitored by ¹H NMR spectra, as shown in Table S2 and Figures S2 and S3 (Supporting Information). In Figure S2, the linear relationship of [ditolyldisulfane] versus reaction time indicates that the reaction rate is irrelevant to the concentration of ditolyldisulfane. In Figure S3, the linear relationship of $\ln[iodotoluene]_0 - \ln[iodotoluene]$ versus reaction time indicates that the reaction rate is irrelevant to the concentration of ditolyldisulfane. Plots of $\ln[iodotoluene]_0$ - ln[iodotoluene] vs time are linear, indicating that the coupling reaction proceeded with a first-order dependence on the concentration of iodotoluene. The rate of the C-S coupling reaction of 4-iodotoluene and ditolyldisulfane can be written as $-d[iodotoluene]/dt = k_{obs}[ditolyl disulfane]^0[iodotoluene]^1.$

Table 4. C–S Coupling Reaction of Various A	yl Halides and Sulfur Powder	Catalyzed by CuI with Various Bases
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	R X +	$S_8 = \frac{Cul, Base, 100^{\circ}C}{DMF, N_2}$	R+ n R+ (S) _n n	= 1 or 2	
entry	ArX	base	time, h	Ar ₂ S:Ar ₂ S ₂	total conversn, %
1 ^{<i>a</i>}	2-iodotoluene	LiOH·H ₂ O	36	1:0	100
2^a		NaOAc	72	0:1	100
3 ^{<i>a</i>}	3-iodotoluene	LiOH·H ₂ O	36	1:0	100
4 ^{<i>a</i>}		NaOAc	72	0:1	100
5 ^b	4-iodotoluene	Cs ₂ CO ₃	10	9:1	100
6 ^{<i>c</i>}		NaOAc	10	0:1	75
7^d	4-nitrobromobezene	Cs_2CO_3	10	1:0	100
8^e		NaOAc	10	1:3.4	62
9 ^f	4-bromobenzonitrile	Cs_2CO_3	10	1:0	100
10^g		NaOAc	15	1:7.5	51
11^{b}	4-iodobenzotrifluoride	Cs ₂ CO ₃	10	1:0	100
12^c		NaOAc	40	1:15	96
13^d	3-iodopyridine	LiOH·H ₂ O	72	1:0	100
14^h		NaOAc	72	1:1.6	100
15	2-bromopyridine	LiOH·H ₂ O	168	3.6:1	97
16		NaOAc	168	1: 3	93
17^d	4-fluoroiodobenzene	LiOH·H ₂ O	24	1:0	100
18 ^d		NaOAc	24	1:2.3	94
19 ^d	4-chloroiodobenzene	LiOH·H ₂ O	24	15.6:1	100
20^d		NaOAc	24	0:1	92
21	4-bromoiodobenzene	LiOH·H ₂ O	24	1:0	100
22		NaOAc	24	1:1.2	82
23 ⁱ	4-iodophenol	LiOH·H ₂ O	168	8.1:1	100
24^i		NaOAc	168	0:1	100
25	4-iodoanisole	LiOH·H ₂ O	168	2.0:1	98
26		NaOAc	168	0: 1	37
27	1,3,5-trimethyliodobenzene	LiOH·H ₂ O	168	4.9:1	100
28		NaOAc	168	0:1	56

^{*a*}Detection by GC-MS; the spectrum showed only one product without the precursor. ^{*b*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15a. ^{*c*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15b. ^{*d*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15g. ^{*f*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15g. ^{*f*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15d. ^{*h*}Detection by ¹H NMR spectrum is given in ref 15d. ^{*b*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15d. ^{*h*}Detection by ¹H NMR spectrum is given in ref 15d. ^{*b*}Detection by ¹H NMR spectrum is given in ref 15f. ^{*i*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15d. ^{*b*}Detection by ¹H NMR spectrum is given in ref 15f. ^{*i*}Detection by ¹H NMR spectrum; the spectrum is given in ref 15d. ^{*b*}Detection by ¹H NMR spectrum is given in ref 15f. ^{*i*}Detection by ¹H NMR spectrum is given in ref 15f. ^{*i*}Detection by ¹H NMR spectrum is given in ref 15f. ^{*i*}Detection by ¹H NMR spectrum is given in ref 15f. ^{*i*}Detection by ¹H NMR spectrum is given in ref 15f. ^{*i*}Detection by ¹H NMR spectrum is given in ref 15f.

This reveals that the rate-determining step of this reaction is also the oxidative addition of aryl iodide; however, only one iodotoluene is consumed in every catalytic cycle. The reaction mechanism is outlined in Figure 6. Initially, sulfur powder reacted with the base to become metal sulfide. The exchange of anions between CuI and metal sulfide produced copper sulfide and metal iodide. Our kinetic study revealed that two iodotoluenes were consumed in every catalytic cycle; therefore, the two iodotoluenes caused the oxidative addition of copper sulfide to become A. Reductive elimination then occurred to form B, and ditolyldisulfane disscoiated to generate the original CuI. Ditolyldisulfane may return to associate with CuI to form B because this is a reversible reaction. The hydroxide of the base exchanged with B to become C, and Cu^I quickly reduced the S-S bond to become the Cu^{II} dimer form **D**. The dimer then transformed into a monomer form and reduced to Cu^I complex E by reductants, such as I⁻ and sulfur powder. The oxidative addition of iodotoluene occurred with complex E to become Cu^{III} complex F, another rate-determining step. Finally, a reductive elimination occurred, resulting in the production of ditolylsulfane and CuI.

To determine whether the selectivity of the base control is suitable for the C–S coupling reaction of sulfur powder with other aryl iodides, we tested a variety of aryl halides in this coupling reaction, as shown in Table 4. Most coupling products from aryl halides and sulfur powder are controlled by the base. Aryl halides with electron-withdrawing groups had greater activity than electron-donating groups. However, aryl halides with electron-withdrawing groups using a weak base, such as CH₃COONa, also produced a trace of diarylsulfane. 3-Iodopyridine and 2-bromopyridine presented poor selectivity between diaryldisulfane and diarylsulfane. It may be that the potential energy of the transition state from C to D (Figure 6) is low for aryl halides with electron-withdrawing groups because electron-withdrawing groups let Cu reduce the S–S bond easily.

This study demonstrated that the base is a key in controlling the ratio of diaryldisulfane and diarylsulfane from the C–S coupling reaction of aryl halide and sulfur powder. A weak base, such as metal carbonate or acetate, produced only diaryldisulfane.

A strong base, such as metal hydroxide, first produced diaryldisulfane, which then pushed the Cu center to catalyze diaryldisulfane and aryl halide to become diarylsulfane. This can be explained by DFT calculations which show that hydroxides form a monomer (ArS-Cu-OH) from a dimer more easily than acetate ions. Controlling the base is an effective method to obtain the single product of diaryldisulfane and diarylsulfane.

EXPERIMENTAL SECTION

2-Iodotoluene, 4-iodotoluene, 4-nitrobromobezene, cesium carbonate, and 4-iodobenzotrifluoride were purchased from Acros. 3-Iodotoluene, potassium carbonate, sodium carbonate, lithium carbonate, 4-bromobenzonitrile, and 3-iodopyridine were purchased from Alfa. Sulfur powder was purchased from Shimakyo's Pure Chemicals. Potassium hydroxide, sodium hydroxide, and lithium hydroxide were purchased from Nihon Shiyaku. Potassium phosphate, sodium acetate, copper(I) oxide, copper(II) sulfide, and copper chloride were purchased from Showa. Copper iodide, copper bromide, copper chloride, copper(I) oxide, copper(II) oxide, copper(I) sulfide, copper(II) sulfide were purchased from Aldrich. Copper bromide, copper(I) sulfide, were purchased from Strem Chemicals. Copper(II) oxide was purchased from Merck. Palladium(II) acetate was purchased from Seedchem Co. Palladium(II) chloride was purchased from Catalyst Co. ¹H and ¹³C NMR spectra were recorded on Varian Gemini 2000-200 (200 MHz for ¹H and 50 MHz for ¹³C) and Mercury plus-400 (400 MHz for $^1\!\mathrm{H}$ and 100 MHz for $^{13}\mathrm{C})$ spectrometers with chemical shifts given in ppm from internal TMS or the center line of CDCl₃.

General Procedure for Coupling Reactions of S_8 and Aryl Halide. A typical coupling reaction was exemplified by the synthesis of entry 2 (Table 1); iodotoluene (1.5 mmol), sulfur powder (1.5 mmol), CuI (0.1 mmol), and Cs_2CO_3 (3.0 mmol) were stirred at 100 °C in DMF (2 mL). After 5 h, the solution was cooled to room temperature, diluted with CH_2Cl_2 , and filtered through silica gel with copious washing (CH_2Cl_2). The yield was determined by a ¹H NMR spectrum.

General Procedure for the Kinetic Study of the C–S Coupling Reaction of 4-lodotoluene and Sulfur Powder. In a flame-dried test tube containing a magnetic stirring bar were placed CuI, Na_2CO_3 , sulfur powder, and iodotoluene in DMF under N_2 . The mixture was heated to 100 °C. At appropriate time intervals, 0.1 mL aliquots were removed and quenched with CDCl₃ (1 mL). The CDCl₃ solution was analyzed by a ¹H NMR spectrum.

Dipyridin-2-ylsulfane. ¹H NMR (CDCl₃, 400 MHz): δ 8.53 (d, 2H, *J* = 5.2 Hz), 7.62 (t, 2H, *J* = 7.6 Hz), 7.44 (d, 2H, *J* = 7.6 Hz), 7.10 (t, 2H, *J* = 6.4 Hz).

Dipyridin-2-yldisulfane. ¹H NMR (CDCl₃, 400 MHz): 8.46 (s, 2H, *J* = 4.8 Hz), 7.61 (b, 2H), 7.11 (m, 2H), 6.58 (m, 2H).

Bis(4-bromophenyl)disulfane. ¹H NMR (CDCl₃, 200 MHz): δ 7.41 (b, 4H), 7.35 (b, 4H).

Bis(4-methoxyphenyl)sulfane. ¹H NMR (CDCl₃, 400 MHz): δ 7.23 (d, 4H, J = 8.4 Hz), 6.91 (d, 4H, J = 8.4 Hz), 3.60 (s, 3H).

Bis(4-methoxyphenyl)disulfane. ¹H NMR (CDCl₃, 400 MHz): δ 7.40 (d, 4H, J = 6.0 Hz), 6.91 (d, 4H, J = 6.0 Hz), 3.60 (s, 3H).

Dimesityldisulfane. ¹H NMR (CDCl₃, 400 MHz): δ 6.83 (s, 4H), 2.24 (s, 6H), 2.20 (s, 12H).

Dimesitylsulfane. ¹H NMR (CDCl₃, 400 MHz): δ 6.82 (s, 4H), 2.42 (s, 6H), 2.20 (s, 12H).

Computational Methods. All the density functional theory (DFT) calculations were accomplished by the Gaussian 09 program.¹⁶ Geometry optimizations and vibrational frequency calculations were performed at the M06/6-31+G* level. The M06 functional was used in this work, as it has been recommended for treating chemical problems in which both main-group and transition-metal chemistries are important.¹⁷ Each optimized structure was verified by vibrational frequency analysis to ensure that it is a local minimum on the potential energy surface. The "stable=opt" keyword was applied to check the wavefunction stability as well as to locate the stable broken-symmetry wavefunction once the instability was found. The unscaled vibrational frequencies were employed for the thermal correction to Gibbs free energy at the standard conditions of 298.15 K and 1 atm. The charge

ASSOCIATED CONTENT

G Supporting Information

Tables and figures giving compound characterization data, including NMR spectra, and details of the kinetic study and DFT atom coordinates and absolute energies for all relevant computationally studied species. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Notes

analysis.

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support was obtained from the National Science Council (Grant NSC 101-2113-M-037-009) and the Fundamental Research Funds from Kaohsiung Medical University (KMU-Q100011). We thank the Center for Research Resources and Development at Kaohsiung Medical University for the instrumentation and equipment support. We also thank the National Center for High-performance Computing for computer time and facilities.

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