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Supporting Information

for

Palladium-Catalyzed, Unsymmetrical Homocoupling of Thiophenes *via* carbon–sulfur Bond Activation: a New Avenue to Homocoupling Reaction

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General information:

Melting points measured on an Electrothermal 9100 apparatus. IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer. ¹H NMR (300 and 500 MHz) and ¹³C NMR (75 and 100 MHz) spectra were obtained using Bruker DRX-300 AVANCE and Bruker DRX-500 AVANCE spectrometers. All NMR spectra at room temperature were recorded in CDCl₃ and DMSO- d_6 . Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Elemental analyses for C, H and N performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. All chemicals were purchased from Merck or Aldrich and were

used without further purification. Due to very low solubility of the products 9h, no ¹³C NMR data were obtained for this product.

Optimization of Reaction Conditions for Synthesis 9:

Screening the various solvents revealed that only DMF and DMSO at heat condition afforded the desired product in moderate yield (Table S1, entries 1 and 2) under aerobic condition. Other solvents such as MeOH, THF, MeCN, and dioxane were completely ineffective (results not shown). Running the reaction under oxygen atmosphere did not improve the isolated yield relative to air atmosphere (entry 3). Next, it was found that under aerobic condition, among the range of the Cu^I and Cu^{II} salts (entries 1-9), only Cu(OAc)₂, CuSO₄.H₂O, and CuI could proceed the reaction to give **9a** in moderate yield within 10 h (entries 1, 6, and 9). Using Cu(OAc)₂ under argon atmosphere led to 21% yield, while CuI showed completely to be unreactive (entries 10 and 11). The reactivity was improved by lowering the loading amount of Cu(OAc)₂ from 50 mol % to 10 mol % under air (entries 12-14). However, further decrease in the loading amount of the catalyst was undesirable (entry 15). Raising temperature to 100 °C deteriorated the reaction (entry 16). Significant improvement achieved by increasing the phenylboronic acid from 1 to 2 equiv (entry 17). As a result of this modification, the reaction time decreased to 1h. Interestingly, using scrupulously dried DMF caused dramatic decrease in yield (35 %, entry 18).

Table S1.	Optimization	of the	reaction	conditions
	-			-

NC.	NH ₂ B(OH) ₂	NC	
MeS		u salts MeS	S S
Entry	Cu salt (mol %)	Condition	Yield ^b (%)
1	$Cu(OAc)_2$ (100)	air/70 °C	52
2°	Cu(OAc) ₂ (100)	air/70 °C	50
3	Cu(OAc) ₂ (100)	O ₂ /70 °C	52
4	Cu(acac) ₂ (100)	air/70 °C	_
5	Cu(OTf) ₂ (100)	air/70 °C	_
6	CuSO ₄ .H ₂ O (100)	air/70 °C	43
7	CuCl (100)	air/70 °C	_
8	CuBr (100)	air/70 °C	_
9	CuI (100)	air/70 °C	48
10	Cu(OAc) ₂ (100)	Ar/70 °C	21
11	CuI (100)	Ar/70 °C	_
12	Cu(OAc) ₂ (50)	air/70 °C	60
13	Cu(OAc) ₂ (20)	air/70 °C	72

15 $Cu(OAc)_2(5)$ $air/70 \ ^{\circ}C$ 63 16 $Cu(OAc)_2(10)$ $air/100 \ ^{\circ}C$ 22 17^d $Cu(OAc)_2(10)$ $air/70 \ ^{\circ}C$ 93 18^e $Cu(OAc)_2(10)$ $air/70 \ ^{\circ}C$ 35 19^f $Cu(OAc)_2(10)$ $air/70 \ ^{\circ}C$ 80 Unless otherwise stated, reaction conditions: a thiophene (0.1 mmol), phenylboronic acid (0.1 mmol), 1 ml of DMF, 10 h. b Isolated yield. c DMSO used as solvent. d 2 equiv phenylboronic acid used, 1h. c DME used f. One pot condition: after the set of th	14	$Cu(OAc)_2$ (10)	air/70 °C	78
16 $Cu(OAc)_2(10)$ $air/100 ^\circ C$ 22 17^d $Cu(OAc)_2(10)$ $air/70 ^\circ C$ 93 18^e $Cu(OAc)_2(10)$ $air/70 ^\circ C$ 35 19^f $Cu(OAc)_2(10)$ $air/70 ^\circ C$ 80 Unless otherwise stated, reaction conditions: <i>a</i> thiophene (0.1 mmol), phenylboronic acid (0.1 mmol), 1 ml of DMF, 10 h. <i>b</i> Isolated yield. <i>c</i> DMSO used as solvent. <i>d</i> 2 equiv phenylboronic acid used, 1h <i>c</i> Dried DME used <i>f</i> One pot condition: after	15	$Cu(OAc)_2(5)$	air/70 °C	63
17^{d} Cu(OAc)_2 (10)air/70 °C93 18^{e} Cu(OAc)_2 (10)air/70 °C35 19^{f} Cu(OAc)_2 (10)air/70 °C80Unless otherwise stated, reaction conditions: a thiophene (0.1 mmol), phenylboronic acid (0.1 mmol), 1 ml of DMF, 10 h. b Isolated yield. c DMSO used as solvent. d 2 equiv phenylboronic acid used, the s Dried DME used f. One not condition: after	16	$Cu(OAc)_2$ (10)	air/100 °C	22
18^{e} Cu(OAc)_2 (10)air/70 °C35 19^{f} Cu(OAc)_2 (10)air/70 °C80Unless otherwise stated, reaction conditions: a thiophene (0.1 mmol), phenylboronic acid (0.1 mmol), 1 ml of DMF, 10 h. b Isolated yield. c DMSO used as solvent. d 2 equiv phenylboronic acid used, 1 h. c Dried DME used f. One pot condition: after	17 ^d	$Cu(OAc)_2$ (10)	air/70 °C	93
19fCu(OAc)2 (10)air/70 °C80Unless otherwise stated, reaction conditions:athiophene (0.1 mmol), phenylboronic acid (0.1 mmol), 1 ml of DMF, 10 h. b Isolated yield. c DMSOused as solvent.d 2 equiv phenylboronic acid used,1h s DriedDME used f One pot condition:	18 ^e	$Cu(OAc)_2$ (10)	air/70 °C	35
Unless otherwise stated, reaction conditions: ^{<i>a</i>} thiophene (0.1 mmol), phenylboronic acid (0.1 mmol), 1 ml of DMF, 10 h. ^{<i>b</i>} Isolated yield. ^{<i>c</i>} DMSO used as solvent. ^{<i>d</i>} 2 equiv phenylboronic acid used, 1h. ^{<i>s</i>} Dried DME used (One not condition: after	19 ^f	$Cu(OAc)_2$ (10)	air/70 °C	80
	Unless thioph mmol) used a	s otherwise stated ene (0.1 mmol), , 1 ml of DMF, 10 as solvent. ^d 2 equiv	, reaction c phenylboroni h. ^b Isolated y y phenylboron	conditions: ^a c acid (0.1 ield. ^c DMSO ic acid used, adition: after

Gratefully, the reaction showed good compatibility with multi-component reaction by affordeding 9a in 80% yield (Scheme S1 and Table S1, entry19). Therefore, due to the advantages of the multicomponent reactions, the 10 mol % Cu(OAc)₂ in the presence of 2 equivalent phenylboronic acid at 70 °C under air atmosphere was selected for the synthesis of **9a** (Table S1, entry19). It is notable the EtOH is nessesery for the reaction and a mixture of DMF-EtOH was selected as best solvent [1].

execution the required condition for synthesis thiophen (as for 4a in Table 1): ArB(OH)₂ (2 eq) and Cu(OAc)₂ (10 mol %) at 70 °C under air for 1 h.



Scheme S1. One-pot synthesis of 9a

Characterization of Cu-thiophene Complex (E):

First, considering the general remarks about the reactivity of Cu^I and Cu^{II} salts under air (Table S1, entries 1, 6, and 9), low reactivity of Cu^{II} and lacking the reactivity of Cu^I under argon (Table S1, entries 10 and 11), following the progress of the reactions drawn our attention (Figure 1). As shown in Figure 1, the starting mixture containing CuI, aminothiophene, and PhB(OH)₂ readily involved complexation right after stirring under aerobic and heat condition (Figure 1, entry 1B). Then, upon elapsing time, the insoluble yellow participants gradually changed to a brownish-red solution within 1 h (entry 1C). In contrast, the reaction mixture remained intact under argon atmosphere, and no complexation observed (Figure 1, entry 2). TLC examination of this reaction did not show the presence of the desired adduct 9a even after prolonging the reaction time to 24 h (Table S1, entry 11). No complexation could account for the inefficiency of CuI (Cu^I) under inert condition

(Table S1, entry 11). Using $Cu(OAc)_2$ under air led to the same sequence as CuI, involving rapid complexation and gradually dissolution of the complex (Figure 1, entry 3). Unlike CuI, using $Cu(OAc)_2$ under argon atmosphere led to Cu-complexion and following dissolution of the corresponding Cu-complex (Figure 1, entry 4). Finally, to gain knowledge on the structure of complex, a reaction containing $Cu(OAc)_2$ /thiophene/air and without the presence of PhB(OH)_2 was performed (Figure 1, entry 4). The experiment showed that the readily formed Cu-complex remained intact even after a prolonged time. Therefore, we conclude that PhB(OH)_2 did not involve in the Cu-complex.



Figure 1. Following the progress of the reaction mixture under different conditions: A) before stirring; B) heating after 1 min; C) heating after 1 h.

Further experiments revealed that Cu-complexion as an intermediate can take place for Cu^{II} under both air and argon atmospheres. However, Cu-complexion for Cu^I is only possible under air atmosphere. Also, it was found that the complexation reaction can occur in a wide range of solvents (MeOH, THF, MeCN, and dioxane) without the need of heat. However, conversion from intermediate (Cu-complex) to the target molecule is only possible by DMF or DMSO under heat condition. The experiments revealed that trying the reaction at room temperature is completely unfruitful. At this juncture, we recognized through this study that the suitable choice of the solvent, presence of heat and oxygen are critical for this transformation. We envisioned that characterization of the readily formed complex may give an important clue for mechanism elucidation. Therefore, we analyzed the in situ generated Cu-complex obtained from the three different conditions i) the mixture of CuI, aminothiophene and PhB(OH)₂ at heat condition in DMF under air atmosphere (Figure 1, entry 1B); ii) the mixture of Cu(OAc)₂, aminothiophene and PhB(OH)₂ at heat condition in DMF under argon atmosphere (Figure 1, entry 4B), and iii) the mixture of Cu(OAc)₂ and thiophene at heat condition in DMF under air atmosphere, and in the absence of PhB(OH)₂ (Figure 1, entry 5B). Upon formation the complex, the insoluble yellow particles were collected by filtration and washed thoroughly with water and DMF. The dried powder was then analyzed by powder x-ray diffraction (XRD; Figure 2). Interestingly, all of the three complexes showed exactly the same XRD patterns.



Figure 2. XRD pattern of the complex from: a) CuI under air; b) $Cu(OAc)_2$ under argon; and c) $Cu(OAc)_2$ and thiophene without PhB(OH)₂ under air

The results of XRD patterns were further confirmed by elemental analysis as all of the three complexes showed identical element contents. The obtained data demonstrated the presence of Cu and thiophene in 1:2 ratio (Table 4).

Table S2. Elemental analysis data of Cu complexes

Cu complexes	Cu [%]	C [%]	H [%]	N [%]
CuI/O ₂	10.28	51.05	2.79	9.02
Cu(OAc) ₂ /Ar	10.19	51.13	2.92	8.93
$Cu(OAc)_2/O_2$	10.24	51.16	2.84	9.05

The IR spectroscopy results showed that two bands in 3289 cm⁻¹ and 3400 cm⁻¹ in free aminothiophene were replaced by one band in 3340 cm⁻¹ in Cu-complexes, indicating the conversion of NH_2 to NH as a result of complexation (Figure 2). More to the point, shifting the carbonyl vibrational frequency from 1590 cm⁻¹ in free aminothiophene to 1553 cm⁻¹ in Cu complexes implies that the bidentate coordination is in place.



Figure 2. Comparison between the IR spectrum of free thiophene (up) and thiophene Cu-complex (down) Having clarified that common intermediate involves in different conditions, to get further insight about the mechanism of the reaction we investigated the coupling reaction of 1 equivalent of the Cu-complex afforded by aminothiophene and $Cu(OAc)_2$ with 4 equivalent of PhB(OH)₂ (corresponding to 1/2 ratio of aminothiophene and PhB(OH)₂ found as an optimal condition in Table S1, entry 17 and considering that 1 equivalent of Cu-complex delivers 2 equivalents of thiophene) under air and argon atmosphere.

Table	S3. Reaction	on of Cu-
comple	ex with PhB(O	$H)_2^a$
Entry	Atmosphere	Yield ^b (%)
1	argon	19
2	air	44
^{<i>a</i>} Reaction conditions: Cu complex (1		
mmol, I equivalent), $PhB(OH)_2$ (4 mmol 4 equivalent) in DME (8 mI) at		
$70 ^{\circ}\text{C}$ for 24 h. ^b Isolated yield.		

According to our experiment, the reaction afforded 19 % yield based on the equivalents of the thiophene in Cu complex under argon atmosphere. However, the yield increased to 44 % under air atmosphere.

From these experiments, we can conclude these deductions: 1) demonstrating that starting from Cu^I and Cu^{II} salts leads to pass the reaction from a common intermediate, having reactivity under

Cu^I/O₂, Cu^{II}/Ar conditions, lacking the formation of any complex under Cu^I/Ar, and more importantly lacking the reactivity under Cu^I/Ar implies that dimeric thiophene Cu(II) complex is the active catalytically species during the reaction cycle. It is believed that furnishing the moderate yield under Cu^I/O₂ condition is due to the primary oxidation of Cu^I (thiophene) complex to Cu^{II} (thiophene)₂ complex through an oxidative copper amination reaction [2]; 2) crucial importance of solvent and heat for progressing from Cu^{II} (thiophene) complex to next step, indicates that transmetallation with PhB(OH)₂ may be the rate-determining step in the reaction cycle; 3) the reaction proceed through disproportionation of Cu^{II} (thiophene)₂ to Cu^{III} (thiophene)₂(phenyl) and Cu^I (thiophene) without the need of oxygen (Table S1, entry 10). Then, the monomeric Cu(I) species is re-oxidized by oxidative copper amination reaction in the presence of air, forming back the starting dimeric Cu(II) species. Otherwise, if the alternative Cu(I)/Cu(II)/Cu(0) or Cu(II)/Cu(0) involved in the catalytic cycle which in the absence of oxidizing agent could sustainably generate Cu(II) species, theoretically, the yield of **9a** under Cu^{II}/Ar would be higher than 25% (Table S3, entry 1). [3]

Crystal data and structure refinement for 4a

Identification code	d:\determination\solution\c1099\khc1099
Empirical formula	C25 H16 N4 O2 S3
Formula weight	500.63
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system, space grou	p Triiclinic, P-1
Unit cell dimensions	a = 6.4503(16) A alpha = $80.068(19) deg.$
	b = 12.709(3) A beta = 88.626(19) deg.
	c = 16.510(4) A gamma = $82.085(19) deg.$
Volume 1	320.4(5) A^3
Z, Calculated density	2, 1.259 Mg/m^3
Absorption coefficient	0.309 mm^-1
F(000) 51	6
Crystal size 0	.50 x 0.10 x 0.09 mm
Theta range for data collec	tion 2.50 to 27.00 deg.
Limiting indices	-8<=h<=7, -16<=k<=14, -21<=l<=21
Reflections collected / unic	[12119 / 5763 [R(int) = 0.2332]]
Completeness to theta $= 27$	<i>'.</i> 00 99.7 %
Absorption correction	Numerical
Max. and min. transmission	n 0.9821 and 0.9650
Refinement method	Full-matrix least-squares on F ²
Data / restraints / paramete	rs 5763 / 0 / 308
Goodness-of-fit on F ²	0.969
Final R indices [I>2sigma(I)] $R1 = 0.1350, wR2 = 0.2636$
R indices (all data)	R1 = 0.3047, wR2 = 0.3210
Largest diff. peak and hole	0.769 and -0.358 e.A^-3



Ortep Diagram of Compound 4a

Crystal data and structure refinement for 10a

Ide	entification code	f:\solution\c1203\khc1203
	Empirical formula	C31 H20 N4 O2 S3
	Formula weight	576.72
	Temperature	298(2) K
	Wavelength	0.71073 A
	Crystal system, space g	roup Monoclinic, P12/n
	Unit cell dimensions	a = 12.844(4) A alpha = 90 deg.
		b = 13.059(3) A beta = 109.17(3) deg.
		c = 17.671(6) A gamma = 90 deg.
	Volume	2799.6(14) A^3
	Z, Calculated density	4, 1.368 Mg/m^3
	Absorption coefficient	0.301 mm^-1
	F(000)	1192
	Crystal size	0.50 x 0.35 x 0.20 mm

Theta range for data collection 1.72 to 27.00 deg.
Limiting indices -16<=h<=16, -16<=k<=16, -22<=l<=22
Reflections collected / unique $25275 / 6110 [R(int) = 0.2040]$
Completeness to theta = $27.00 100.0 \%$
Absorption correction Numerical
Max. and min. transmission 0.8985 and 0.8542
Refinement method Full-matrix least-squares on F ²
Data / restraints / parameters 6110 / 0 / 370
Goodness-of-fit on F^2 0.939
Final R indices $[I>2sigma(I)]$ R1 = 0.0907, wR2 = 0.1091
R indices (all data) $R1 = 0.2212, wR2 = 0.1378$
Largest diff. peak and hole 0.261 and -0.224 e.A^-3



Ortep Diagram of Compound 10a

Experimental Procedures for Synthesis Starting Materials 11, 12 and 13:

General Procedure for Synthesis 11:

A solution of the desired ketene dithioacetal including 2-di(methylsulfanyl)methylene malononitrile, methyl 2-cyano-3,3-di(methylsulfanyl)acrylate, ethyl 2-cyano-3,3-di(methylsulfanyl)acrylate or 2,2-di(methylsulfanyl)-1-phenylvinyl cyanide (0.25 mmol) and phenylhydrazine (0.027 g, 0.25 mmol) in 1 mL of MeOH was refluxed for 3 h. After evaporation of the solvent, the residue was recrystallized by MeOH to give pyrazole **11** [4].

General Procedure for Synthesis 12:

Ethyl 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate (8) (0.242 g, 1 mmol) was stirred in H_2SO_4 (95-98 %, 0.5 mL) at room temperature for 5h. Then, the reaction mixture was poured into cool water and the precipitates were filtered. The afforded solid was recrystallized by EtOH to give Yellow powder 12 (m.p: 184-185 °C, 0.211 g, yield: 81 %) [5].

General Procedure for Synthesis 13:

Sodium hydride (0.024 g, 1 mmol,) is added portionwise to a solution of 4-amino-5-benzoyl-2methylsulfanyl-3-thienyl cyanide (0.274 g, 1 mmol) in 3 mL of DMF whilst stirring at room temperature. Stirring continued until the formation of gas has stopped. Then, methyl iodide (0.142 g, 1 mmol,) was added dropwise, and the reaction mixture is stirred for 12 hours at room temperature. For work-up, the reaction mixture was poured into water, and the resulting mixture was extracted by EtOAc. After drying the organic phase over sodium sulphate, the solvent is distilled off under reduced pressure to afford pale yellow solid **13** (m.p: 98-99 °C, 0.210 g, yield: 73 %) [6].

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 1 H NMR of **4b**





S18



¹³C NMR of 4c







S21









 1 H NMR of **4**f



 13 C NMR of **4f**



S26



¹³C NMR of **4g**







 13 C NMR of **4h**





S31







¹H NMR of 4k



S35



 1 H NMR of **4**l














 1 H NMR of **9b**











S46









¹³C NMR of **9e**



¹H NMR of **9** \mathbf{f}

















¹³C NMR of **9i**









¹H NMR of 9k





 1 H NMR of **9**l











¹H NMR of **9n**











 1 H NMR of **10a**





¹H NMR of **10b**




 1 H NMR of **10c**











¹³C NMR of **10d**



¹H NMR of **10e**





 1 H NMR of **10f**



S80



 1 H NMR of **10g**



S82







