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Octanuclear Cu(I)-dithiophosphates: An Efficient Catalyst System for N-Arylation of Azoles, Amines, and Amides

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The formation of a C-N bond via the cross-couplings of aryl iodides with azoles, aryl amine, and amides can be successfully achieved in decent yield by the utilization of both $[Cu_8(H){S_2P(O^iPr)_2}_6]^+$ and $[Cu_8{S_2P(OEt)_2}_6]^{2+}$ as the pre-catalysts.

Keywords: Copper; S-donor ligands; N-arylation; Cross-coupling.

Catalytic C-N bond formation reactions are highly valuable in organic synthesis because the yielded products, aromatic amines/amides, are important classes of compounds as those are ubiquitous in a multitude of bioactive natural products,¹ and pharmaceuticals.² Though palladium-catalyzed N-arylation is an effective but expensive method with limited functional group tolerance,³ yet century old Ullmann-type reaction has been limited due to its harsh reaction conditions despite lower cost.⁴ Nevertheless, several efforts have been made in past decades to overcome these limitations with the use of various copper sources, additives, and bases to achieve the couplings of aryl halides with amines/amides,⁵ which have shown a high functional group tolerance.⁶ It is generally agreed that the deprotonated amine/amide acts as a nucleophile followed by the oxidative addition of aryl halide to copper, then the reductive elimination to yield the coupling products in the N-arylation reaction.⁷ The ligands used as additives might facilitate the copper salts to dissolve in common laboratory organic solvents, avoid the metal aggregation, lower the reaction energy barrier, and thus enhance the activities.⁸

Normally 5-10 mol% of copper salts and 10-20 mol% of ligands as additives are utilized in a typical catalytic N-arylation.⁹ In addition well defined copper complexes supported by N-donor ligands and exhibited a 1:1 Cu/L ratio are also effective to perform the N-arylation of 2-pyrrolidinone.¹⁰ Thus a cluster with eight Cu(I) centers held together by six ligand units, which is highly soluble in common organic solvents, must be cost effective in terms of the amount of the Cu/L ratio used. Inspired by the successful coupling reaction of aryl iodides with alcohols catalyzed by copper clusters of the type $[Cu_8(CI){S_2P(OR)_2}_6]^+$,^{11a}

accordingly the potentials of $[Cu_8 \{S_2P(OEt)_2\}_6]^{2+}$ and $[Cu_8(H) \{S_2P(O^iPr)_2\}_6]^+$ synthesized solely from our group¹² as the precatalyst for N-arylations were tested. Herein we report the structure of $[Cu_8 \{S_2P(OEt)_2\}_6-(MeCN)_2](PF_6)_2$ (**A**), and catalytic activities of both $[Cu_8(H) \{S_2P(O^iPr)_2\}_6](PF_6)$ (**B**) and (**A**) in the Ullmann-Goldberg type coupling of aryl halides with nitrogen-containing heterocycles, aryl amines, and amides. *To our knowledge, this is the first report of N-arylation by utilizing copper dithiolato clusters as the precatalyst*.

Only recently we have reported the synthesis of empty, octanuclear Cu_8^I cluster involving six dichalcophosphate ligands despite of its high tendency to incorporate an anion at the center even from solvent impurities.^{12,13} Now we could successfully grow single crystals of its sulfur analogue [$Cu_8{S_2P(OEt)_2}_6(MeCN)_2$] (PF₆)₂ (**A**), which was synthesized simply by mixing of [$Cu(MeCN)_4$](PF₆) and dithiophosphate (dtp) ligand in a 4:3 ratio in THF followed by the re-crystallization in MeCN. The avoidance of any chlorinated impurities existed in the common laboratory solvent is crucial for the isolation of the empty Cu_8 cube.

The di-cationic cluster of octanuclear Cu(I) species contains a distorted Cu₈ cubic core supported by six dtp ligands which coordinate through S atoms in a tetraconnective-tetrametallic (μ_2 , μ_2) bridging mode (Figure 1).¹⁴ The molecule contains a centre of inversion. Each of the Cu atoms is coordinated by three S atoms from three dtp units. Thus three-coordinated Cu1, Cu2, Cu4 and their symmetry-related atoms remain in trigonal planar geometry with averaged S-Cu-S angles of 119.43(9)°. In addition, both Cu3 and Cu3A are further connected to a N atom from a

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[†] Electronic Supplementary Information (ESI) available: Tables S1, S2, and spectroscopy data (¹H, ¹³C NMR) are available.

solvated MeCN and hence these two 4-coordinated Cu atoms adopt pyramidal geometry. Cu...Cu distances are irregular, $3.596(2) \sim 3.125(2)$ Å, which are at least 0.3 Å longer than those anion-encapsulated Cu₈ cubes surrounded by six dtp ligands.¹¹ Thus the structural characteristic of a copper framework contraction in the diselenophopshate ligand system,¹³ which is induced by the encapsulated halide and/or chalogenide, is nicely demonstrated in the analogous S-donor ligands. Cu-S distances are in the range of $2.222(3) \sim 2.303(3)$ Å, which are comparable to $[Cu_8(S_2PPh_2)_6]^{2+,15}$ and Cu(3)-N distance is 2.139(9) Å.

Initially the coupling reaction of tolyl iodide and pyrrole was examined by using K_2CO_3 as the base (Table S1), but only a trace amount of product was produced. Later the use of Cs_2CO_3 yielded a fair result where the reaction temperature could be kept as low as 90 °C to produce 74% yield of the N-arylated product (entry 7, Table S1). However, the optimized condition was chosen as listed in entry 4 with 83% yield at 105 °C for 24 h. Finally the optimum amount of the catalysts used was screened by using the pyrrole and iodotoluene as the protocol listed in Table S2 from which 0.8 mol % of the catalyst was chosen for all the reactions.

In a typical reaction 1 mmol of iodotoluene and 0.8 mol% of catalyst were charged in a glass tube followed by the addition of 1.5 mL of pyrrole. The reaction is then carried out at elevated temperature with stirring as mentioned in Table 1. Thus in this reaction, pyrroles acts as a solvent. Similar reactions performed on 4-bromotoluene, the use of



Fig. 1. (a) Perspective view of the cationic part in A (ethyl groups have been omitted for clarity). Cu1-S1 2.228(3), Cu1-S4 2.233(2), Cu1-S2 2.237(3), Cu2-S5 2.235(3), Cu2-S3 2.239(3), Cu2-S4 2.244(2), Cu3-S6 2.220(2), Cu3-S5 2.230(2), Cu3-S2 2.240(2), Cu4-S3 2.277(2), Cu4-S6 2.292(3), Cu4-S1 2.315(3), Cu3-N1 2.139(9), Cu...Cu 3.125(2) ~ 3.596(2), S-P 2.005(4) ~ 2.027(4). (b) Schematic diagram of the cationic part in A. Only four dtp ligands are shown in diagram for clarity.

Table 1. List of reactions using pre-catalysts (A) and (B)

	Н У + 2		at. 0.8 mol ⁹ Cs ₂ CO ₃ , 24	thr C		
Entry	azole	Aryl iodide	Cat.	Yield ^a	Temp (°C)	Solvent
a 1	NH		А	83	105	pyrrole
a2	NH		В	90	105	pyrrole
a3	NH	- Br	А	63	105	pyrrole
a4	NH	— — Br	В	75	105	pyrrole
a5	NH	- Ci	Α	Trace	120	pyrrole
a 6	NH	- Ci	В	Trace	120	pyrrole
a7	NH		A	90	105	pyrrole
a8	NH	, Ì	В	94	105	pyrrole
a9	NH	MeO-	A	92	105	pyrrole
a10	NH	MeO-	В	92	105	pyrrole
a11	NH	сі—	Α	82	105	pyrrole
a12	NH	сі——	В	88	105	pyrrole
a13			А	94	105	DMF
a14			В	96	105	DMF
a15		MeO-	А	95	105	DMF
a16		MeO-	В	98	105	DMF
a17		ci—	А	88	105	DMF
a18	NH	сі——	В	92	105	DMF
a19	NH NH		А	92	105	DMF
a20	NH NH		В	94	105	DMF

^a Isolated yields

catalyst (**A**) produced a 63% yield while catalyst (**B**) could make it up to 75% yield (entry a3, a4). However the reaction of pyrrole with 4-chlorotoluene could only result in trace amount of the coupling product even at an elevated temperature up to 120 °C (entry a5, a6). In addition, the reactions of both 3,5-dimethyliodobenzene and 4-methoxyiodobenzene with pyrrole produced the coupling products in high yield in the presence of either catalyst (entry a7a10). The electron-donating substituent on the aryl iodide is thus enhancing the catalytic activity. On the other hand, no coupling products were afforded at all between 4-nitroiodobenzene (or 4-acyliodobenzene) and pyrrole even at

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120 °C, which could be due to the electron withdrawing nitro (or acyl) group on the aryl halide. Despite the electron-withdrawing chloro substituent on the aryl iodide (entry all, al2), the coupling reaction with pyrrole did achieve in good yield presumably the resonance effects increase the negative charge of the C atom connected to iodide, which assists the subsequent oxidative addition reaction of the aryl iodide.

The coupling reaction of indole with equimolar amount of 4-iodotoluene was carried out initially in toluene in the presence of catalyst A (0.8 mol%) at 105 °C, which produced only 40% yield of the coupling product, but the same reaction could yield 94% products in DMF. Obviously the polar DMF made the aryl iodide polarizable and easier to perform the oxidative addition reaction. The reactions of indole with 4-methoxyiodobenzene proceed almost quantitatively (entry a15, a16). On the other hand, catalytic reactions of 4-nitroiodobenzene (or 4-acyliodobenzene) with indole do not yield any coupling products at all.

The change of amine from pyrrole to pyrazole having an extra N atom showed a better reactivity while coupled with 4-iodotoluene (entry a19, a20). Surprisingly the reaction of imidazole with iodotoluene did not produce any coupling products after the addition of either catalyst. It should be noted that color changes from brown to bluegreen in the reaction media were observed. In order to explore the probable reaction intermediates which failed to yield any coupling products, the reation of forty equivalents of imidazole with A was performed under a normal catalytic reaction condition. Surprisingly a Cu-imidazole complex where five N atoms of imidazoles coordinated to a copper atom in a square pyramidal fashion was isolated and characterized structurally.¹⁶ Thus the unsuccessful reaction can be foreseen by the formation of five Cu-N bonds, which block the potential coordination sites around the copper center, hence the impedance of catalytic activities, for the follow-up oxidative addition of aryl halides to produce the coupling products. On the other hand, the coupling of 4iodotoluene with aniline, a weaker nucleophile than azole, in the presence of A in DMF took place with 61% yield even at 140 °C (entry b1, Table 2), the catalyst **B** showed a better catalytic activity on this reaction (86% yield, 120 °C) (entry b2). However, no coupling reactions between diphenyl-, cyclohexyl-, and diethylamine with 4-iodotoluene were observed. Whereas the bulky phenyl groups of the diphenylamine after coordinated to copper center could poWu et al.

Table 2. List of reactions using pre-catalysts (A) and (B)

H₂N—	- X	$\frac{\text{Cat. 0.8 mo}}{\text{Cs}_2\text{CO}_3,\text{DN}}$	ol% MF, 24hr		R_3	
Entry	Amine	Aryl iodide	Catalyst	Yield ^a	Temp (°C)	
b1	H ₂ N-		Α	61	140	
b2	H ₂ N-		В	86	120	
b3	H ₂ N-		В	89	120	
b4	H ₂ N-	MeO-	В	83	120	
b5	H ₂ N-	ci-	В	71	120	
^a Isolated yields						

tentially hinder the oxidative addition reaction of iodotoluene, either diethyl- or cyclohexylamine is definitely a better nucleophile than aniline as evidenced by their K_b values.¹⁷ These reactions suggest that the nucleophilicity of amines cannot be too strong in the reaction media. Otherwise the cleavage of the Cu-N bond will not be possible to afford the reductive-elimination product.

Both clusters were also tested for their ability to catalyze the coupling of aryl halides with amides and also found positive results. For example, A facilitates the reaction of 4-iodotoluene with benzamide in 76% yield at 140 °C (86% yield at 160 °C) while **B** shows a far better activity to 89% yield just at 120 °C (entry c1-c4, Table 3). Unfortunately the same product could not be synthesized using 4bromotoluene. A similar activity trend between A and B is observed for the coupling of acetamide with 4-iodotoluene (entry c10-c13). The presence of electron-donating group on aryl halide displays a better reactivity while coupling with amide. Thus $\sim 80\%$ yield is achieved in the reaction of benzamide with both 3,5-dimethyliodobenzene and 4methoxyiodobenzene in the presence of A at 140 °C (entry c5, c7) and 90% yield at 120 °C by using B as the catalyst (entry c6, c8). A similar reactivity trend is also identified in the reaction of acetamide and 4-methoxyiodobenzene (entry c14, c15).

The di-cationic cluster **A**, which is more electropositive and thus electrophilic, does not display better catalytic activities toward N-arylations than those of **B**, a monocationic cluster. Thus the in-situ generated chloride-centered Cu₈ clusters, $[Cu_8(Cl) \{S_2P(OEt)_2\}_6]^+$, from **A** could be the factor to reduce its electrophilicity. Indeed almost the same amount of coupling products from the reaction of

Table 3. List of reactions using pre-catalysts (A) and (B)

	H N—R'	Cat	0.8 mol%	$o \rightarrow R$	
R—	+ X—	$R_3 \frac{cm}{Cs_2C}$	O ₃ ,DMF, 24hr	R'N-	$\langle \rangle_{R_3}$
Entry	Amide	Aryl iodide	Catalyst	Yield ^a	Temp (°C)
c1			А	37	120
c2	$\square H_2$		Α	76	140
c3	\square		Α	86	160
c4			В	89	120
c5			А	88	140
c6		ک ا	В	90	120
c 7		MeO-	A	82	140
c8		MeO-	В	90	120
c9			В	79	120
c10			A	39	120
c11			A	75	140
c12	-		A	89	160
c13			В	91	120
c14	-	MeO-	A	83	140
c15	\sim	MeO-	В	89	120
c16	⊩≺∽		В	83	120

^a Isolated yields

4-iodotoluene with benzamide was obtained by utilizing $[Cu_8(Cl) \{S_2P(OEt)_2\}_6]^+$ as the precatalyst. The slightly better catalytic activity of **B** over **A** could be due to the cluster stability in the reaction media, which cannot be fully rationalized in the present study.

During the reaction work-up via column chromatography, minute (or negligible) amounts of $Cu_4[S_2P(O^iPr)_2]_4$,¹⁸ which compositions were affirmed by X-ray crystallography, were isolated. This suggests the pre-catalysts, **B**, has decomposed to some extents after the cross-coupling reaction. This suggests that the catalysts are the polynuclear copper compound in nature. Presumably the slow decomposition was initiated by the partial replacement of the dithiolate ligands with nucleophiles (amine/amides).

In conclusion we have successfully demonstrated the diverse, catalytic activities of the Cu(I) clusters involving

dithiophosphates (**A**, **B**) toward N-arylations. The catalysts can work at mild conditions to couple azoles, aryl amine, and amides with aryl iodide. They have shown better performance in the case of azoles, which can also be coupled to aryl bromide. Coupling of amide requires slightly higher temperature, however. When the aryl iodide contains an electron-releasing group as the substituent, the catalysts work with high efficiency to produce ~90% yield of Narylated products. In addition, the strength of nucleophilicity to which the amine exhibits is critical to the formation of a N-C bond catalyzed by either clusters **A** or **B**. Preliminary results indicate that B is also an efficient catalyst for the Sonogashira C-C coupling reaction.

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- 14. Crystal data for **A**: $C_{28}H_{66}Cu_8F_{12}N_2O_{12}P_8S_{12}$, M = 1991.63, orthorhombic, *P*bcn, a = 14.0239(11) Å, b = 22.967(2) Å, c = 22.431(2) Å, V = 7224.6(11) Å³, Z = 4, T = 296(2) K, $\rho_{calcd} = 1.831$ g/cm³, $\mu = 2.908$ mm⁻¹, 27189 reflections collected, 6993 unique ($R_{int} = 0.1261$) which were used in all calculations. Final R_1 [$I > 2\sigma(I)$] was 0.0589 and wR₂ (for all data) was 0.1691. GooF = 0.876.
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- 16. The compound formulated as [Cu(C₃N₂H₄)₅(SO₄)] (C₃N₂H₄)(H₂O)₄ has been confirmed by X-ray diffraction. A

square-pyramidal Cu(II) is surrounded by five imidazoles and the counter anion is a sulfate. In addition there are four solvated water molecules and a free imidazole in the asymmetric unit. Crystal data for **CuN5**: $C_{18}H_{32}CuN_{12}O_8S$, M =640.16, monoclinic, P_{21}/n , a = 8.8438(7) Å, b = 21.5264(19) Å, c = 15.2063(13) Å, $\beta = 102.391(2)^\circ$, V = 2827.5(4) Å³, Z = 4, T = 296(2) K, $\rho_{calcd} = 1.504$ g/cm³, $\mu = 0.910$ mm⁻¹, 17833 reflections collected, 5731 unique ($R_{int} = 0.034$) which were used in all calculations. Final R_1 [$I > 2\sigma(I)$] was 0.0422 and wR₂ (for all data) was 0.1197. GooF = 1.003. CCDC reference numbers: 806558 for A; 806559 for **CuN5**. Copies of the data can be obtained free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 IEZ UK (Fax: +44-1-223-336033; Email: deposit@ccdc.cam.ac.uk).

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