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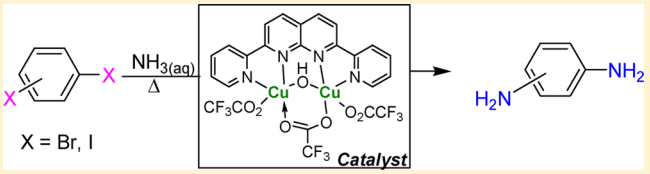
Diamination of Phenylene Dihalides Catalyzed by a Dicopper Complex

Bei-Sih Liao and Shiuh-Tzung Liu*

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan

Supporting Information

ABSTRACT: Diamination of phenylene dihalides with aqueous ammonia to give the corresponding phenylenediamines can be achieved by using a dicopper complex $[Cu_2(bpnp)(OH)(CF_3COO)_3]$ (**1**) (bpnp = 2,7-bis(pyridine-2-yl)-l,8-naphthyridine) as the catalyst in the presence of Bu_4NBr and Cs_2CO_3 in high yields. In addition, 1,3,5-tribromobenzene was converted into benzenetriamine quantitatively under the same conditions. This method offers a new opportunity, particularly simplifying steps and increasing yields, for the preparation of aryl diamines.



Phenylenediamines are important intermediates in the manufacture of polymers, dyes, pharmaceuticals, and other industrial products. In addition, phenylenediamine derivatives are an important class of chelating ligands for coordination chemistry. Hence, the development of an easier and less expensive method for the preparation of these diamines continues to be an interesting research subject. Preparation of these diamines almost always starts with aromatic nitration followed by reduction.[1]

In the past decade, transition-metal (such as palladium and copper)-catalyzed C−N formation reactions have emerged as a powerful tool for the production of anilines.[2,3] Thus, the direct coupling reaction of aryl halide with ammonia under mild reaction conditions has made a substantial improvement in the preparation of aniline. Quite a number of palladium- and copper-catalyzed methods have been reported with excellent yields.[4−6] However, little work has been done on the direct diamination of dihaloarenes to produce phenylenediamines presumably due to the highly reactive nature of the resulting products. Hartwig and co-workers reported a palladium-catalyzed method to convert phenylene dibromide into the parent anilines using lithium bis(trimethylsilyl)amide followed by the hydrolysis.[5b] To date, efficient transition-metal-catalyzed coupling protocols of direct diamination of phenylene dihalides with ammonia in an aqueous system are not known. Here, we report that a dicopper complex **1**, $[Cu_2(bpnp)(OH)(CF_3COO)_3]$ (bpnp = 2,7-bis(pyridine-2-yl)-l,8-naphthyridine), efficiently catalyzes the diamination of aryl dihalides with aqueous ammonia, leading to the corresponding phenylenediamine derivatives.

To obtain information on the catalytic systems, we examined the amination reactions of dibromobenzene with ammonia (eq 1) catalyzed by a series of copper complexes (Table 1). Copper(I) iodide and its related complexes are frequently used as precatalysts for C−N bond formation.[2−4] However, we found that the copper complexes associated with various bidentates were effective for the amination of bromobenzenes

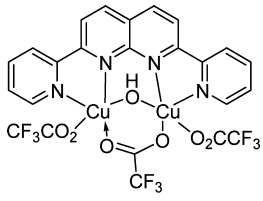


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Table 1. Diamination of *o*-$C_6H_4Br_2$ Catalyzed by Various Complexes[a]

catalytic system	**2** (%)	**3** (%)
CuI[b]	54	19
$Cu(CF_3COO)_2$[b]	52	22
CuI[b] + $Me_2N(CH_2)_2NMe_2$	35	45
CuI[b] + $Ph_2P(CH_2)PPh_2$	40	45
$Cu(OAc)_2$[b] + $Me_2N(CH_2)_2NMe_2$	38	39
complex **1**[c]	0	100

[a]Reaction conditions: *o*-$C_6H_4Br_2$ (0.25 mmol), catalyst, water (0.5 mL), Cs_2CO_3(1 mmol), NH_3(aq) (0.5 mL), and Bu_4NBr (0.25 mmol) at 140 °C (bath temperature) for 16 h. [b]2 mol %. [c]1 mol %.

but not diamination as compared to **1** (Table 1). In all instances, both mono- and diamination products were obtained with the use of a mononuclear copper catalyst. From this screening, it clearly shows complex **1** to be the promising catalyst for diamination of *o*-dibromobenzene with ammonia.

$$o\text{-}C_6H_4Br_2 \xrightarrow[Cs_2CO_3]{NH_{3(aq)}} \underset{\mathbf{2}}{o\text{-}C_6H_4Br(NH_2)} + \underset{\mathbf{3}}{o\text{-}C_6H_4(NH_2)_2} \quad (1)$$

To determine the optimal reaction conditions, different parameters such as temperature, amount of catalyst, base, and solvents were then screened on the diamination of *p*-$C_6H_4I_2$

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with ammonia (Table 2). In a typical experiment, a mixture of *p*-$C_6H_4I_2$ (0.25 mmol), Cs_2CO_3 (1 mmol), concd $NH_{3(aq)}$ (0.5 mL), and 1 mol % of the copper catalyst (based on the iodo compound) in water was heated at 110 °C for 16 h. These results show that the dicopper complex **1** gives little or no coupled product at low temperatures (entries 1 and 2) but provides the desired product *p*-phenylenediamine **4** in a quantitative yield at 110 °C (entry 3). It is noticed that solvents affect the selectivity of product dramatically (Table 2, entries 3−5), and water appears to be the best one for this diamination. A lower catalyst loading decelerated the reaction rate, resulting a lower conversion (Table 2, entry 11). In addition, the presence of Bu_4NBr (TBAB) is essential for the catalysis, presumably acting as a phase transfer agent (Table 2, entry 7).

Table 2. Diamination of *p*-$C_6H_4I_2$ Catalyzed by 1[a]

entry	solvent	base	temp	time (h)	yield **4**:**5** (%)[b]
1	H_2O	Cs_2CO_3	rt	24	
2	H_2O	Cs_2CO_3	80 °C	16	trace
3	toluene	Cs_2CO_3	110 °C	16	30:50
4	*i*-PrOH	Cs_2CO_3	110 °C	16	17:51
5	H_2O	Cs_2CO_3	110 °C	16	100:0
6	H_2O		110 °C	16	
7[c]	H_2O	Cs_2CO_3	110 °C	16	trace
8	H_2O	K_2CO_3	110 °C	16	trace
9	H_2O	Na_2CO_3	110 °C	16	59:26
10	H_2O	Cs_2CO_3	110 °C	8	45:4
11[d]	H_2O	Cs_2CO_3	110 °C	16	43:trace

[a]Reaction conditions: complex **1** (2.5×10^{-3} mmol), *p*-$C_6H_4I_2$ (0.25 mmol), solvent (0.5 mL), base (1 mmol), $NH_{3(aq)}$ (0.5 mL), and TBAB (0.25 mmol) were added in a sealed reaction tube. [b]Yield of di- versus monoamination (*p*-phenylenediamine **4**; *p*-iodoaniline **5**). [c]No TBAB. [d]0.5 mol % of catalyst.

On the basis of the results achieved with the catalyst **1**, the scope of this catalysis was investigated by subjecting various substituted dihalobenzenes to amination with ammonia. Table 3 summarizes the results of the amination. We were pleased to find that various aryl dihalides reacted smoothly with ammonia to give the desired products in good to excellent yields. Under the optimized reaction conditions, phenylene dihalides reacted with ammonia to yield the corresponding anilines except chlorides (Table 3, entries 6 and 7). The lower activity of chloro substrates toward copper catalysts has been also reported in other C−N bond formation reactions.[8] In general, the substrate scope for reactions of aryl bromide was similar to that for reactions of aryl iodides, but reactions required heating at a higher temperature (Table 3, entry 1 vs 3).

Dibromo substrates possessing electron-donating groups in the aryl ring at various positions were cross-coupled with ammonia at 140 °C (bath temperature), including examples containing methyl, hydroxymethyl, methoxy, or amino (Table 3, entries 8−14 and 23). However, this catalytic system was inactive toward the nitro-substituted substrate such as 5-nitro-1,3-dibromobenzene (entry 16). When 3,5-dibromobenzoic acid was subjected to the amination, the substrate was converted to a polymeric material presumably via the amide linkage.

It should be noted that the replacement of the solvent from water to ethylene glycol may improve the production of the desired compound. Thus, substitution of 2,5-dimethyl-1,4-phenylene dibromide with ammonia in water may provide 40% of the diamination product (Table 3, entry 12), but the yield increases up to 100% in ethylene glycol (Table 3, entry 13). Modestly hindered substrates such as dimethyl-substituted phenylene dibromides can be efficiently converted into the corresponding diamines. However, tetramethyl-*p*-phenylene dibromide gave no amination product with the substrate recovered; this is presumably due to the steric hindrance of both *ortho* substituents. Dibromopyridines, dibromobiphenyl, and 2-methoxy-1,6-dibromonaphthalene also reacted smoothly, producing the corresponding diamines with excellent yields (Table 3, entries 19−22).

Finally, this novel dicopper catalyst was tested in the triamination of tribromides. This class of compounds is not easily obtained from the traditional method.[1] To our surprise, 1,3,5-tribromobenzene can be converted at 140 °C to give the corresponding triamines in a quantitative yield (Table 3, entry 24), but it requires carrying out the reaction by using ethylene glycol as the solvent. However, amination of 2,4,6-tribromophenol led to polymeric materials.

In order to gain more insight about the dicopper system, the product distribution of diamination of *o*-$C_6H_4Br_2$ catalyzed by complex **1** was monitored during the reaction, and the results are summarized in Figure 1. It clearly shows that the monoamination product remains in a very low percentage during the reaction, indicating that the second amination *via* the dicopper system is a fast step. We believe that the copper ions bound in close proximity of **1** could be one of the key factors for the efficient double amination. Possibly, the coordination of the first amination intermediate might facilitate the activation of the second reaction site, which makes the second amination faster.

In summary, currently available data do not allow us to explain clearly the effectiveness of the bimetallic complex for the diamination, but the results of this work have demonstrated that the preparation of phenylenediamines from dihalides can be conducted with high selectivity and in high yields when using dicopper complex **1** as the catalyst. The easy use of ammonia, the use of water as solvent, and simplifying steps of this protocol are great advantages in terms of green chemistry, which makes it a practical and attractive methodology for organic synthesis.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out in a sealed high-pressure tube. Chemicals were purchased from the suppliers and were used without further purification, unless otherwise noted. Amines were purified by reprecipitation, crystallization, or chromatography. All compounds were characterized by ^1H and ^{13}C NMR and MS. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ or acetone-d_6. Chemical shifts are given in parts per million relative to Me_4Si for ^1H and ^{13}C NMR. Dicopper complex **1** was prepared according to the method previously reported.[7]

General Proecedure for Diamination. A mixture of substrate (0.25 mmol), complex **1** (2.5×10^{-3} mmol), Cs_2CO_3 (1 mmol), concd $NH_{3(aq)}$ (0.5 mL), and TBAB (0.25 mmol) in water (0.5 mL) was loaded in a sealed reaction tube. The reaction temperature was increased to 110−140 °C, and the reaction mixture was stirred for a period of time. After cooling to rt, the reaction mixture was poured into a saturated NaCl solution, extracted with ethyl acetate, and dried over anhydrous $MgSO_4$. After removal of solvents, the residue was chromatographed on silica gel.

Spectral Data of Diamination Products. *p-Phenylenediamine:* identical to the commercial available sample (27.0 mg, 99%); ^1H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 4 H), 3.4 (br s, 4 H); ^1H NMR (400

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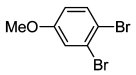
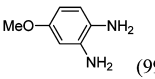
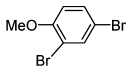
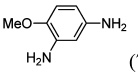
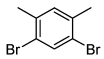
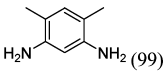
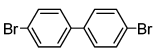
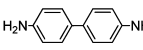
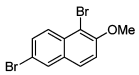
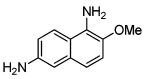
Table 3. Amination of Various Aryl Halides[a]

Entry	Substrate	Cat. Loading[b]	solvent	Product (yield)[c]
1[d]	*p*-IC_6H_4I	1 mol%	H_2O	*p*-$C_6H_4(NH_2)_2$ (99)
2	*p*-BrC_6H_4Br	1 mol%	H_2O	*p*-$C_6H_4(NH_2)_2$ (45)
3	*p*-BrC_6H_4Br	2 mol%	H_2O	*p*-$C_6H_4(NH_2)_2$ (99)
4	*o*-BrC_6H_4Br	2 mol%	H_2O	*o*-$C_6H_4(NH_2)_2$ (99)
5	*m*-BrC_6H_4Br	2 mol%	H_2O	*m*-$C_6H_4(NH_2)_2$ (99)
6	*o*-ClC_6H_4Cl	2 mol%	H_2O	No reaction
7	3-Me-1,2-$C_6H_3Cl_2$	2 mol%	ethylene glycol	No reaction
8	3,5-dibromotoluene	2 mol%	H_2O	3,5-diaminotoluene (90)
9	3,5-dibromobenzyl alcohol	2 mol%	H_2O	3,5-dibromobenzyl alcohol (99)
10		2 mol%	H_2O	 (99)
11		2 mol%	H_2O	 (79)
12		2 mol%	H_2O	 (40)
13[d)]		2 mol%	ethylene glycol	 (100)
14		2 mol%	ethylene glycol	 (99)
15		3 mol%	H_2O	No reaction
16		2 mol%	H_2O	No reaction
17	3-ClC_6H_4Br	2 mol%	H_2O	3-$ClC_6H_4NH_2$ (55)
18	3,5-$Br_2C_6H_3COOH$	1 mol%	H_2O	polymer
19	3,5-dibromopyridine	1 mol%	H_2O	3,5-diaminopyridine (96)
20	2,6-dibromopyridine	1 mol%	ethylene glycol	2,6-diaminopyridine (95)
21		3 mol%	ethylene glycol	 (100)
22		3 mol%	H_2O	 (100)
23	3,5-dibromoaniline	2 mol%	H_2O	1,3,5-triaminobenzene (100)
24	1,3,5-tribromobenzene	3 mol%	ethylene glycol	1,3,5-triaminobenzene (90)

[a]Reaction conditions: complex **1**, substrate (0.25 mmol), water (0.5 mL), Cs_2CO_3(1 mmol), NH_3(aq) (0.5 mL), and TBAB (0.25 mmol) were loaded in a sealed reaction tube, and the tube was heated at 140 °C (bath temperature) with stirring for 16 h. [b]Mol % of catalyst used. [c]Isolated yields given in parentheses. [d]At 110 °C.

MHz, DMSO-d_6) δ 6.4 (s, 4 H), 4.19 (br s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 117.2; ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.2, 115.0.

o-Phenylenediamine: identical to the commercial available sample (26.9 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75−6.69 (m, 4 H), 3.36 (br s, 4 H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.57−6.59 (m, 2 H), 6.46−6.48 (m, 2 H), 4.4 (br s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 129.8, 116.5; ^{13}C NMR (100 MHz, DMSO-d_6) δ 134.2, 117.0, 114.3.

m-Phenylenediamine: identical to the commercial available sample (26.9 mg, 99%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.65 (t, J = 8 Hz, 1 H), 5.77−5.82 (m, 3 H), 4.63 (br s, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.3, 128.5, 102.6, 99.5.

3,5-Diaminotoluene: identical to the commercial available sample (27.5 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 2 H), 5.85 (s, 1H), 3.45 (br, 4 H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 140.0, 106.8, 99.8, 21.4; ESI-MS *m*/*z* M^+ 122.13 (calcd for $C_7H_{10}N_2$ 122.08).

3,5-Diaminobenzyl Alcohol (ref 8): 34.1 mg, 99%; ^{1}H NMR (400 MHz, acetone-d_6) δ 5.90 (s, 2 H), 5.81 (s, 1 H), 4.33 (s, 2 H), 4.25 (br, 4 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 149.5, 144.4, 103.4, 100.3, 64.2; ESI-MS *m*/*z* M^+ 138.11 (calcd for $C_7H_{10}N_2O$ 138.08).

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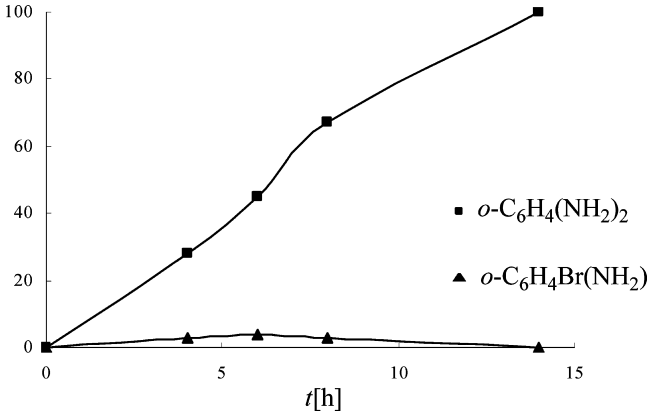

Figure 1. Product distribution during the amination of o-$C_6H_4Br_2$.

3,4-Diaminoanisole (ref 9): 34.2 mg, 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 8.4 Hz, 2 H), 6.30 (s, 1 H), 6.24 (d, J = 8.4 Hz, 1 H), 3.71 (s, 3 H), 3.20 (br, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 140.1, 136.5, 111.9, 104.6, 103.1, 56.3; ESI-MS m/z M^+ 138.16 (calcd for $C_7H_{10}N_2O$ 138.08).

2,4-Diaminoanisole (ref 10): 27.3 mg, 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, J = 9.2 Hz, 2 H), 6.12 (s, 1 H), 6.00 (d, J = 9.2 Hz, 1 H), 3.90 (br, 4 H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 140.4, 136.9, 112.1, 104.6, 103.3, 56.3; ESI-MS m/z M^+ 138.07 (calcd for $C_7H_{10}N_2O$ 138.08).

2,5-Dimethyl-1,4-benzenediamine (ref 11): 34.1 mg, 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 2 H), 3.5 (br, 4 H), 2.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 121.4, 117.6, 17.5; ESI-MS m/z M^+ 136.13 (calcd for $C_8H_{12}N_2$ 136.10).

4,6-Dimethyl-1,3-benzenediamine (ref 12): 33.7 mg, 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.7 (s, 1 H), 6.06 (s, 1 H), 3.4 (br, 4 H), 2.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 132.9, 112.3, 102.5, 16.3; ESI-MS m/z M^+ 136.21 (calcd for $C_8H_{12}N_2$ 136.10).

3-Chloroaniline: identical to the commercial available sample (17.6 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98−7.01 (m, 1 H), 6.71 (d, J = 7.6 Hz, 1 H), 6.63 (s, 1 H), 6.54 (d, J = 8 Hz, 1 H), 3.85 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 134.8, 130.4, 118.4, 115.1, 113.1.

2,6-Diaminopyridine (ref 13): 26.2 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 7.8 Hz, 1 H), 5.89 (d, J = 7.8 Hz, 2 H), 4.20 (br s, 4 H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.00 (t, J = 8 Hz, 1 H), 5.63 (d, J = 8 Hz, 2 H), 5.40 (br s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 136.3, 94.0; ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.8, 137.8, 95.0; ESI-MS m/z M^+ 109.10 (calcd for $C_5H_7N_3$ 109.06).

3,5-Diaminopyridine: identical to the commercial available sample (26.0 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 2 H), 6.35 (s, 1 H), 3.7 (br s, 4 H); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.35 (s, 2 H), 6.30 (s, 1H), 4.49 (br, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 127.9, 107.3; ^{13}C NMR (100 MHz, acetone-d_6) δ 144.8, 126.7, 105.9; ESI-MS m/z M^+ 109.17 (calcd for $C_5H_7N_3$ 109.06).

Biphenyl-4,4′-diamine (ref 4a): 46.0 mg, 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.8 Hz, 4H), 6.71 (J = 8.8 Hz, 4H), 3.4 (br, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 131.4, 126.9, 115.1; ESI-MS m/z M^+ 184.12 (calcd for $C_{12}H_{12}N_2$ 184.10).

1,6-Diamino-2-methoxynaphthalene: 47 mg, 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 10 Hz, 1 H), 7.12 (d, J = 8.8 Hz, 1 H), 7.05 (d, J = 8.8 Hz, 1 H), 6.80−6.92 (m, 2H), 3.90 (s, 3 H), 3.8 (br, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 130.7, 129.8, 121.6, 121.5, 118.5, 117.6, 116.1, 114.6, 109.3, 57.5; ESI-HRMS (TOF) m/z M^+ 188.0947 (calcd for $C_{11}H_{12}N_2O$ 188.0950).

1,3,5-Benzenetriamine (ref 14): 30.7 mg, 100%; ^{1}H NMR (400 Hz, $CDCl_3$) δ 5.52 (s, 3 H), 1.50 (br, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 93.6; ESI-MS m/z M^+ 123.21 (calcd for $C_6H_9N_3$ 123.08).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C spectra of amination products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stliu@ntu.edu.tw.

Notes

The authors declare no competing financial interest.

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