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Journal:	*Dalton Transactions*
Manuscript ID:	DT-ART-02-2014-000582.R2
Article Type:	Paper
Date Submitted by the Author:	20-May-2014
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Journal Name RSCPublishing

ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Possible Intermediates of Cu(Phen)-catalyzed C-O cross coupling of phenol with aryl bromide by *in situ* ESI-MS and EPR studies

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The C-O coupling reaction between 2,4-dimethylphenol and 4-bromotoluene catalyzed by CuI/K_2CO_3/phen system can be inhibited by radical scavenger cumene. Complexes [Cu(I)(phen)(1-(2,4-dimethylphenoxy)-4-methylbenzene)]$^+$ (denoted as **A**), {H[Cu(I)(phen)(2,4-dimethylphenoxy)]}$^+$ and [Cu(I)(2,4-dimethylphenoxy)2]$^-$ (denoted as **B**) were observed by *in situ* electrospray ionization mass spectrometry (ESI-MS) analysis of the copper(I)-catalyzed C-O coupling reaction under the catalytic reaction condition indicating that they could be intermediates in the reaction. *In situ* EPR study of the reaction solution detected a Cu(II) specie with a fitted *g* value of 2.188. A catalytic cycle with a single electron transfer (SET) step was proposed based on these observations.

Introduction

The synthesis of aryl ester by Ullmann type reaction using Cu(I) salt as the catalyst is prevalent in biological, pharmaceutical, and materials interests due to its economic attractiveness, low toxicity, and air and moisture stability.[1] Workable catalytic systems usually consists of a ligand, a base and a copper salt.[1d,2,3] Better yields are often obtained when ligands are added, and different ligands may have different catalytic activities.[1d,1j,2c,3] Thus, Cu(I) complex containing the added ligand is generally proposed as the working intermediate of the catalytic reaction.[4] Complexes with the corresponding ArO^- ligand have been prepared, and their catalytic activities have been evaluated.[5] Mechanisms involving either the 2e oxidative addition path or the free radical path for the activation of aryl halide in the copper-catalyzed C-O cross coupling reaction have also been reported.[4b-c,5] However, the mechanism of the overall catalytic reaction so far has not been well established.

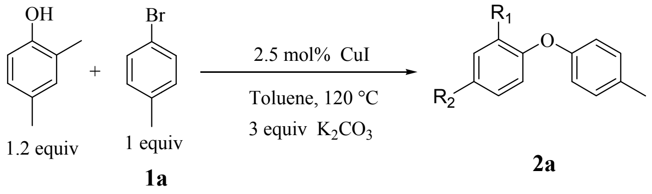
In recent studies for the Ullmann type C-S coupling reaction with the catalyst system of CuI/*t*BuOK/phen (phen = 1,10-phenanthroline), intermediates including $Cu(SPh)_2^-$, $[Cu(SPh)I]^-$ and $\{K[Cu(SPh)_2(Ph)]\}^+$ were clearly observed by *in situ* ESI-MS studies, but for the phen-containing intermediate,[6] indicating ligand may not be involved in the catalytic center. In CuI/*t*BuONa/phen catalyzed C-N coupling reaction, copper(I) complex $[Na(phen)_3][Cu(NPh_2)_2]$ was isolated from the catalytic system, and intermediates $Cu(NPh_2)_2^-$ and $\{Na[Cu(NPh_2)_2(p\text{-tolyl})]\}^+$ were observed in the ESI-MS spectra.[7] Based on these observations, mechanisms involving 2e oxidative addition of aryl halide to the corresponding phen-free Cu(I) complexes $Cu(NPh_2)_2^-$ or $Cu(SPh)_2^-$ were proposed for both reactions. It is therefore possible that Cu(I) catalyzed C-O coupling reaction may have also involved intermediates similar to that of the corresponding C-N and C-S coupling reactions.

Recently, $[(phen)Cu(OAr)(HOAr_2)_2]$ was proposed as the intermediate in the C-O cross coupling reaction between (*E*)-bromostilbene and phenol catalyzed by the CuI/K_3PO_4/phen catalytic system, and a 2e oxidative addition reaction path was proposed based on the observation of $[LCu(OAr)(HOAr_2)_2]^+$ (L is an ionically-tagged phen derivative) in the *in situ* ESI-MS measurement. However, the oxidative addition intermediate was not observed and the negative-ion mode of the ESI-MS has not been reported. The existence of $[Cu(OAr)_2]^-$ in the reaction system is still unclear.[8]

We herein report the *in situ* ESI-MS analysis[9] for the Ullmann type copper(I)-catalyzed C-O coupling reaction using K_2CO_3 as the base and phen as the ligand under the reaction conditions described. {H[Cu(I)(phen)(2,4-dimethylphenoxy)]}$^+$ and [Cu(I)(phen)(1-(2,4-dimethylphenoxy)-4-methylbenzene)]$^+$ (denoted as **A**) or [Cu(III)(phen)(2,4-dimethylphenoxy)(*p*-tolyl)]$^+$ (denoted as **A′**) were observed in the CuI/K_2CO_3/phen reaction system indicating that they are possible intermediates in the reaction. Addition of radical scavenger cumene inhibits the reaction indicating the existence of free radical pathway in the mechanism of the reaction. In addition, *in situ* EPR study of the reaction solution detected a Cu(II) specie with a fitted *g* value of 2.188. A catalytic cycle is proposed based on these observations.

Results and Discussion

In situ ESI-MS analysis. We followed the procedure reported in literatures to investigate the copper-catalyzed C-O coupling reaction between an aryl bromide and a phenol.[2c,3g,3h,10] The reason to choose toluene as the solvent is that toluene is considered as a greener solvent and easier to work up as compare to DMF or DMSO which have been frequently used.[11] A mixture of 2,4-dimethylphenol (1.2 equiv), 4-bromotoluene (**1a**, 1 equiv), K_2CO_3 (3 equiv), phen (5.0 mol%) and CuI (2.5 mol%) was allowed to stir in toluene at 120 ºC for 8 h. The result of the reaction is summarized in Scheme 1.



i) with 5 mol% phen, 8 h	i) 63%
ii) with 5 mol% phen, 20 mol% cumene, 8 h	ii) 29%
iii) with 5 mol% phen, 50 mol% cumene, 8 h	iii) 8%
iv) without phen, 8 h	iv) 0%
v) without phen, 48 h	v) 1.4%

Scheme 1. C-O coupling reaction between aryl bromide and phenol.

To gain the best representative results, *in situ* ESI-MS analysis was also carried out at 120 $^{\circ}$C in order to detect the Cu containing species which may be possible intermediates. Similar reaction mixture in toluene was stirred at 120 $^{\circ}$C for 2 h. The solution was then transferred to a GC vial in a dry box. The temperature of the solution was kept at 120 $^{\circ}$C by immersing the GC vial in a sand bed, and ESI-MS spectra of the solution were taken (Figure 1). The ESI-MS spectrum in negative-ion mode showed a peak at m/z = 305.06 which is identified as [Cu(I)(2,4-dimethylphenoxy)$_2$]$^{-}$ (denoted as **B**) according to its measured accurate mass and isotopic distribution pattern (Figure 2).[12] In the positive-ion mode, peaks at m/z = 365.07, m/z = 455.13 and m/z = 423.07 are identified as {H[Cu(I)(phen)(2,4-dimethylphenoxy)]}$^{+}$,[13] **A** or **A′** and [Cu(phen)$_2$]$^{+}$ correspondingly according to their respective measured accurate mass and isotopic distribution pattern (Figure 3).[12,13]

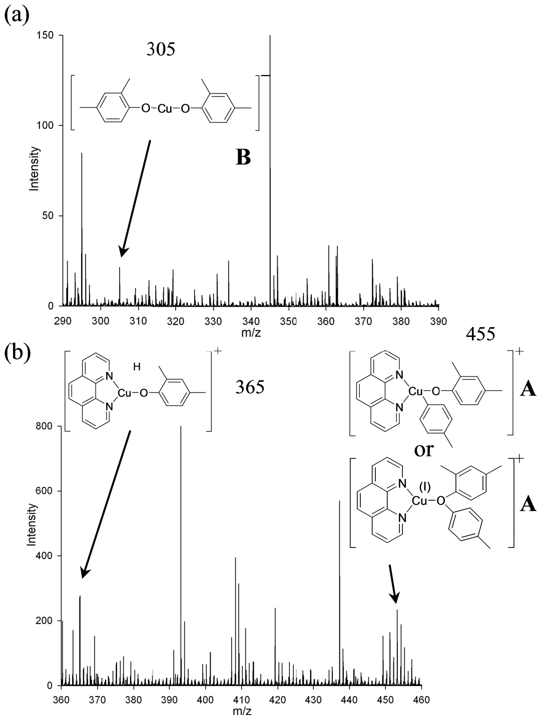


Figure 1. (a) ESI(-)-MS and (b) ESI(+)-MS from the solution taken during the reaction of 2,4-dimethyl phenol and 4-bromotoluene with K_2CO_3 in the presence of CuI and phen in toluene at 120 °C.

The presence of [Cu(phen)$_2$]$^{+}$ and **B** suggests the formation of [Cu(phen)$_2$][Cu(I)(2,4-dimethylphenoxy)$_2$] in the reaction. It has been reported that in polar solvent (DMF) at -25 $^{\circ}$C, Cu(phen)(phth) and Cu(phen)(pyrr) can form [Cu(phen)$_2$][Cu(phth)$_2$] (phth = phthalimidate) and [Cu(phen)$_2$][Cu(pyrr)$_2$] (pyrr = pyrrolidinonate) correspondingly,[14] and Cu(I)(phen)(2,4-dimethylphenoxy) (denoted as **C**) was observed as {H[Cu(I)(phen)(2,4-dimethylphenoxy)]}$^{+}$ in the ESI-MS spectrum.

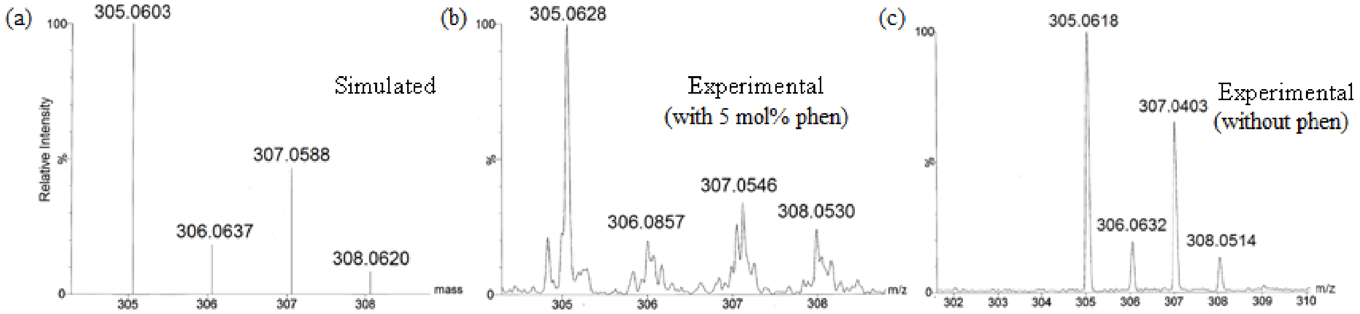


Figure 2. Simulated and experimental isotopic distribution of [Cu(I)(2,4-dimethylphenoxy)2]$^{-}$ (denoted as **B**), (a) simulated, (b) with 5 mol% phen and (c) without phen.

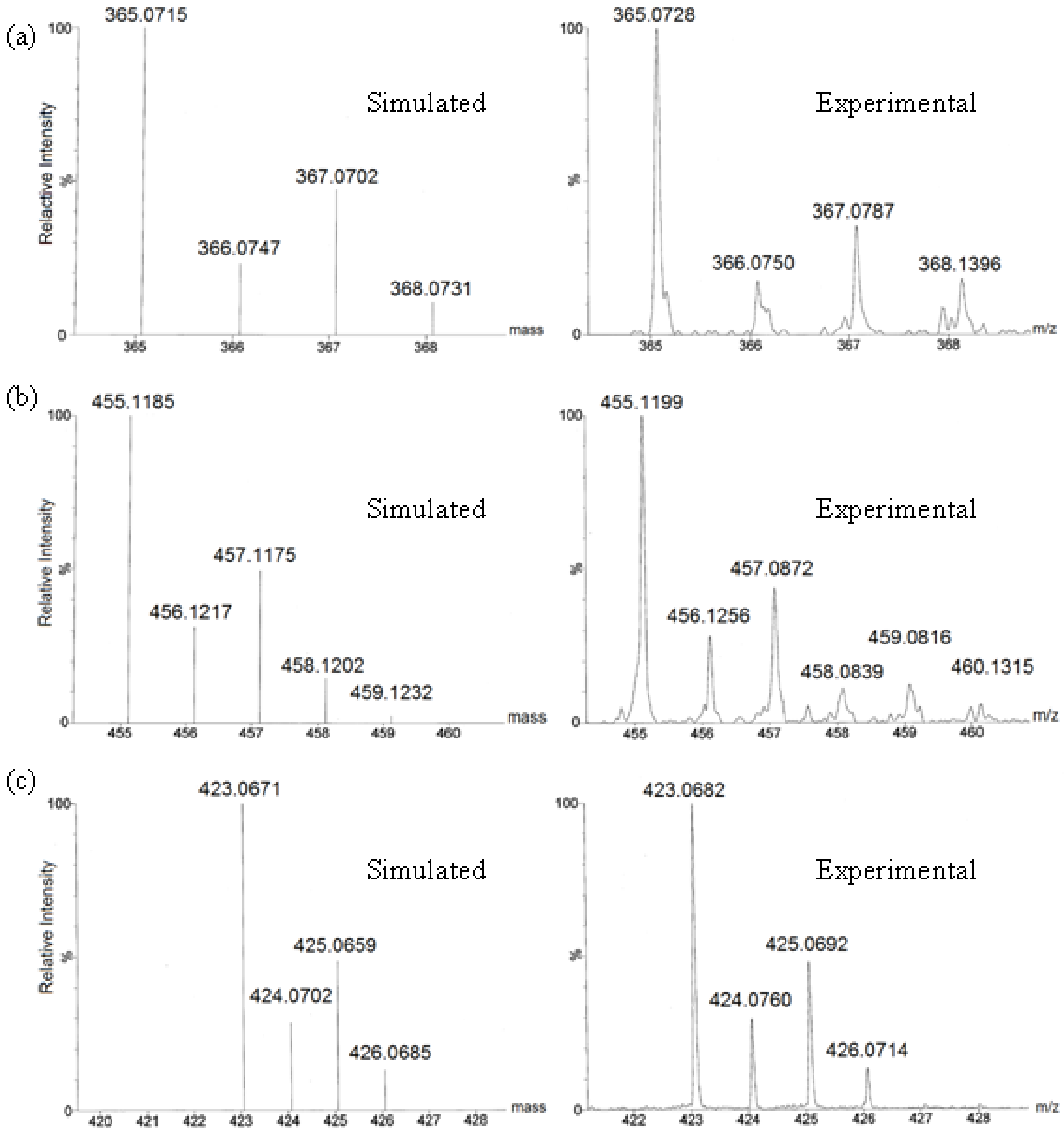
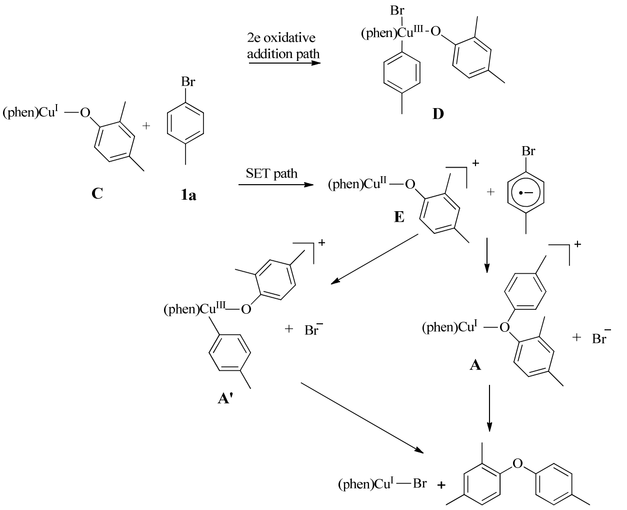


Figure 3. Isotopic distributions of (a) H[Cu(I)(phen)(2,4-dimethylphenoxy)]$^+$, (b) **A** or **A′** and (c) [Cu(phen)$_2$]$^+$.

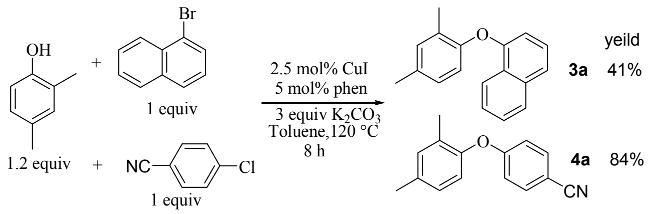
Peak at *m/z* = 455.13 observed in ESI-MS spectrum may be assigned as **A** and/or **A′** since they are isomers. 4-Bromotoluene reacts with **C**, via 2e oxidative addition reaction (Scheme 2), to form Cu(III)(phen)(2,4-dimethylphenoxy)(*p*-tolyl)Br (denoted as **D**), which may be fragmented into Br$^-$ and **A′** during the ESI-MS measurement.[4c] Formation of **A** is through single electron transfer (SET) path in which **C** transfer an electron to 4-bromotoluene to form [Cu(II)(phen)(2,4-dimethylphenoxy)]$^+$ and 4-bromotoluene free radical anion. Further recombination of these two species produces **A (**or **A′**) and Br$^-$ as suggested by DFT calculation (Scheme 2).[4b] Thus observation of peak at *m/z* = 455.13 may indicate the reaction go through the free radical path if the signal is **A**, or non-free-radical path if the signal is **A′** as both mechanisms have been proposed and supported by DFT calculations.[4b,4c] MS/MS experiments were tried in order to obtain additional information. No informative data were observed due to the very low intensity of the signal.

Effect of free radical scavenger. One effective way to elucidate the possibility of free radical path is the addition of free radical scavenger into the system. When 20 mol% of cumene was added into the reaction system, the reaction yield dropped from 65% to 29%.[15] When the amount of cumene was increased to 50 mol%, the yield dropped further to 8%. The radical scavenger inhibits the reaction indicating the existence of radical path (Scheme 1).[16]

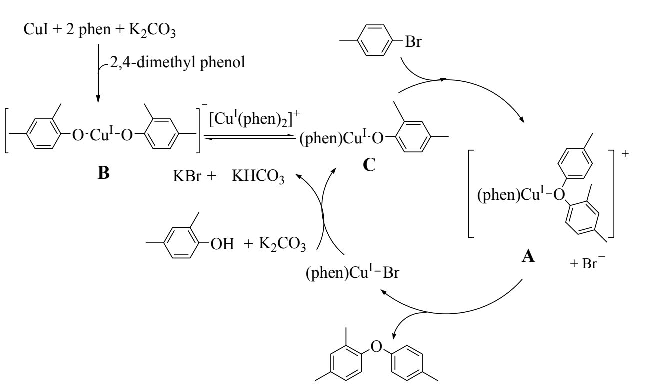


Scheme 2. Two possible reaction paths: 2e oxidative addition path and single electron transfer (SET) path.

It has been reported that 1-bromonaphthalene has a higher reactivity than 4-chlorobenzonitrile in the C-O coupling reaction if non-free-radical path dominates.[5] When the same comparison study was performed based on our catalytic system, 1-bromonaphthalene reacted to give 1-(2,4-dimethylphenoxy)naphthalene(**3a**) in 41% yield; while 4-chlorobenzonitrile gave 4-(2,4-dimethylphenoxy)benzonitrile(**4a**) in 84% yield (Scheme 3). These observations together with the reaction inhibition by cumene and the observation of prop-1-en-2-ylbenzene (product of the reaction between cumene and the tolyl radical) indicate that free radical path is present or even dominates in the reaction.[17] Such dual reaction path, i.e., both 2e oxidative addition path and free-radical path, has been observed in the C-N coupling reaction in the mixed base system.[7b,]



Scheme 3. C-O coupling reaction with 1-bromonaphthalene and 4-chlorobenzonitrile



Scheme 4. The proposed catalytic cycle with phen.

EPR Measurement In order to evaluate the existence of any Cu(II) intermediates, *in situ* EPR study was also carried out at components of g-tensor because the spectrum was taken at high 100 °C. Similar reaction mixture in toluene was stirred at 120 °C for 2 h in a sealed tube. The upper portion of the reaction solution was then transferred to an EPR tube in a dry box. The EPR spectrum was taken at 100 °C and a signal around 3200G was observed (Figure 4). We are unable to obtain all temperature. After fitting,[18] the isotropic g value is 2.188 which is in agreement with a Cu(II) signal.[19] We tentatively assign this signal to complex **E** based on the result of DFT calculation reported and our ESI-MS spectra.[4b] Although, the assignment cannot be conclusive, the presence of a Cu(II) complex further support the reaction may go through a SET mechanism. (Scheme 2).

Catalytic cycle for the Cu(I) catalyzed C-O coupling reaction between 2,4-dimethylphenol and 4-bromotoluene in the presence of phen. Two possible paths were proposed if the reaction goes through single electron transfer (SET) mechanisms when phen was used as the ligand (Scheme 2).

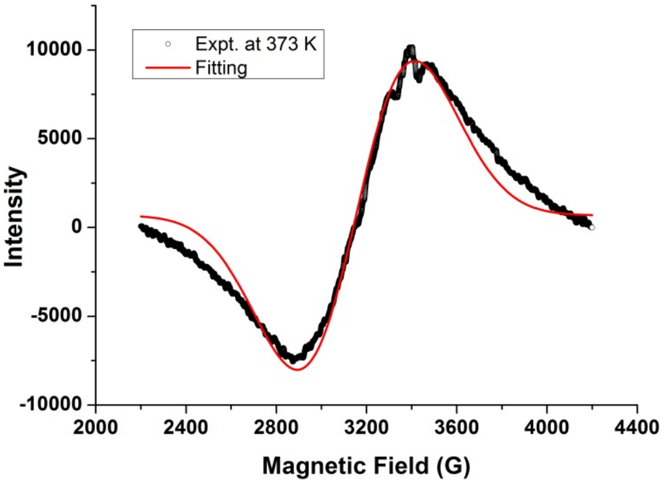


Figure 4. Experimental and simulated EPR spectra for the reaction of 2,4-dimethyl phenol and 4-bromotoluene with K_2CO_3 in the presence of CuI and phen in toluene at 373K.

Based on all above observations and the reported DFT studies, a catalytic cycle is proposed and shown in Scheme 4. Complexes **B** and $[Cu(phen)_2]^+$ are generated by the reaction among 2,4-dimethylphenol, potassium carbonate, phen and CuI. Likewise, the ligand redistribution reaction between **B** and $[Cu(phen)_2]^+$ produces complex **C** in an equilibrium fashion (**C** picks up a H^+ and was observed as $\{H[Cu(I)(phen)(2,4\text{-dimethylphenoxy})]\}^+$ in the ESI-MS

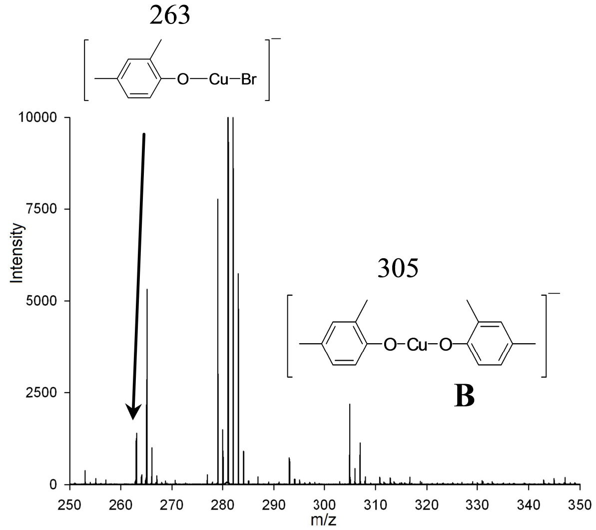


Figure 5. ESI (-)-MS from the solution taken during the reaction of 2,4-dimethyl phenol and 4-bromotoluene with K_2CO_3 in the presence of CuI in toluene at 120 °C.

measurement).[13,14] 4-bromotoluene then reacts with **C** to form **A** and Br^- through SET oxidative addition process. Substitution of the ligand, 1-(2,4-dimethylphenoxy)-4-methylbenzene (**2a**), on **A** by Br^- produces Cu(I)(phen)Br, which further reacts with 2,4-dimethylphenoxy anion to produce **C** and completes the catalytic cycle.[4b]

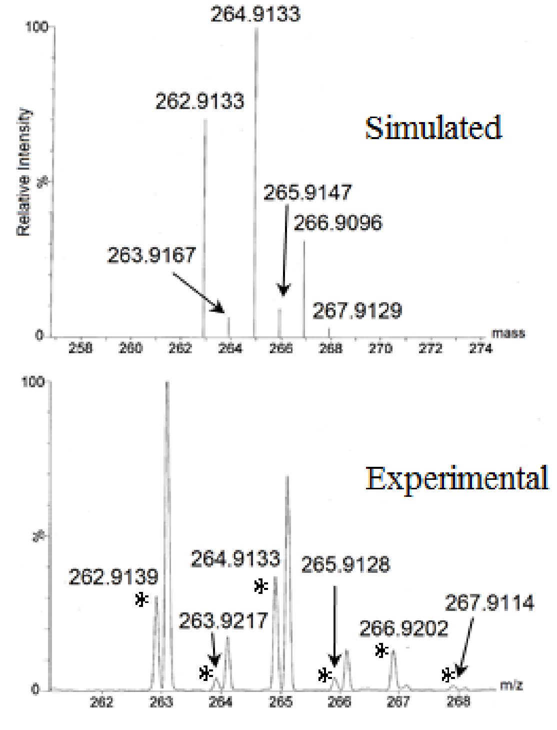
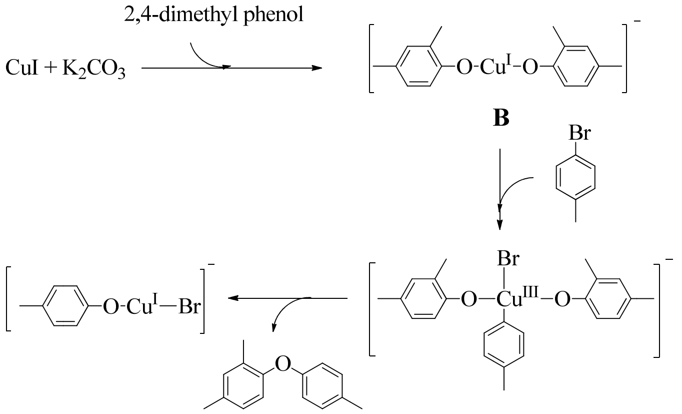


Figure 6. Isotopic distributions of $[Cu(I)(2,4\text{-dimethylphenoxy})Br]^-$.



Scheme 5. The proposed reaction path of the stoichiometric C-O coupling reaction.

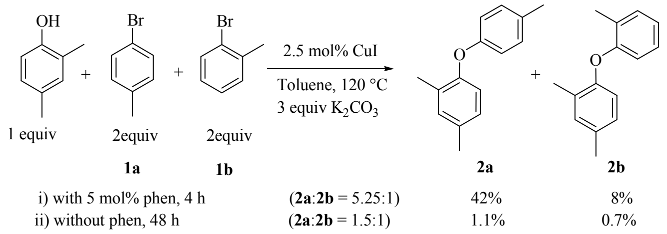
The role of **B** in the reaction is still unclear. It may act as a precursor of **C** by reacting with $[Cu(phen)_2]^+$, a species also observed in the ESI-MS spectra, to generate **C.**[5,14] It may also act as a catalytic active species to react with aryl bromide forming the ether through oxidative addition and reductive elimination cycle.[6,7] One way to evaluate the reactivity of **B** is to generate **B** in-situ and evaluate its reactivity toward aryl bromide in the absence of phen.[6,7] In order to generate **B** as the sole intermediate, only CuI/K_2CO_3 was used as the catalyst to repeat the above reaction. The yield of the ligand-free reaction reduced to zero under the same reaction condition and it was still as low as 1.4% even when much longer reaction time (48 h) was applied (Scheme 1).

C-O coupling reaction between 2,4-dimethylphenol and 4-bromotoluene without phen. In situ ESI-MS analysis was carried out at 120 ºC in order to confirm the presence of **B** in the reaction (Figure 5). Similar experimental procedures were carried out with similar amount of reagents except the reaction time was 14 h. The ESI-MS spectrum in negative-ion mode showed two peaks at m/z = 305.06 and m/z = 262.91, which are identified as **B** and $[Cu(I)(2,4\text{-dimethylphenoxy})Br]^-$ respectively, according to their measured accurate mass and isotopic distribution pattern (Figure 2c and Figure 6).[12]

Based on these observed Cu species of the stoichiometric reaction (the turnover number of the reaction is less than one) and the reported catalytic cycles in C-S and C-N coupling reaction with similar intermediates, $[Cu(NPh_2)_2]^-$ and $[Cu(SPh)_2]^-$,[6,7] a 2e oxidative addition path is proposed as showed in Scheme 5. Although **B** can go through oxidative addition followed by reductive elimination to generate ether, the contribution of this reaction path in the phen added catalytic system should be very limited because the yield of the reaction was zero in the ligand free reaction system under similar reaction condition (reaction time 8 h).

In addition, when a mixture of **1a** (2 equiv), 2-bromotoluene (**1b**, 2 equiv), 2,4-dimethylphenol (1 equiv), K_2CO_3 (3 equiv), phen (5 mol%) and CuI (2.5 mol%) were allowed to react in toluene at 120 ºC for 4 h (Scheme 6), the yield of **2a** and 1-(2,4-dimethylbenzyl)-2-methylbenzene (**2b**) were 42% and 8%

respectively, with the **2a**/**2b** ratio of 5.25. But, when similar reaction was carried out without phen for 48 h (cf. longer reaction time was needed to obtain a measurable yield), the yield of **2a** and **2b** were 1.1% and 0.7% respectively, with the **2a**/**2b** ratio of 1.5. The higher selectivity (higher **2a**/**2b** ratio) in the CuI/K_2CO_3/phen system is consistent with the observations in ESI-MS analysis that the reaction mainly goes through **C**, which would show a greater steric effect because of the presence of the bulky phen ligand.[5]



Scheme 6. Comparison of selectivities in the C-O coupling reactions.

Conclusions

Phen can enhance the reactivity of the Cu(I)/K_2CO_3 catalyzed C-O coupling reaction by forming a possible intermediate **C** which reacts with **1a** to form **A** as the intermediate via free radical path, and steric selectivity can be introduced because of the bulky phen ligand in **C**. It is worth to noted that in the reaction between $[L_2Cu][Cu(OPh)_2]$ (L = trans-N,N'-dimethyl-1,2-cyclohexanediamine) and a mixture of 1-bromonaphthalene and 4-chlorobenzonitrile in DMSO, 1-bromonaphthalene has higher reactivity than 4-chlorobenzonitrile, and non-free radical path was proposed.[5] This report together with our present study indicate that the reaction mechanism depends on the substrate, the base and even the solvent of the reaction.

Experimental Section

All reagents were purchased from commercial sources and used without further purification. Copper(I) iodide (fine grey powder), 2,4-dimethylphenol, 4-bromotoluene, 1,10-phenanthroline, 1,4-di-*tert*-butylbenzene were purchased from ACROS. K_2CO_3 was purchased from Alfa Aesar. Toluene (dried, seccoSolv®) was purchased from Merck and purged with argon for 15 min before use. Reagents were transferred to the reaction vessel (Pyrex tube with a Teflon screw cap) in a glove box. GC experiments were performed on an Agilent 6890N gas chromatograph equipped with a 30 m X 0.53 mm X 3.0 m HP-1 capillary column and a FID detector. 1,4-di-*tert*-butylbenzene was used as the internal standard in the quantitative GC analyses.

Typical procedure of copper-catalyzed C-O coupling reaction.

2,4-Dimethylphenol (0.147 ml, 1.2 mmol), 4-bromotoluene (0.123 ml, 1.0 mmol) were added to a Pyrex tube with a septum. The tube was evacuated and backfilled with nitrogen through needle for 3 cycles, then capped with parafilm before it was put into dry box. CuI (4.8 mg, 0.025 mmol, 2.5 mol%), 1,10-phenanthroline (9.0 mg, 0.050 mmol, 5.0 mol%), 1,4-di-*tert*-butylbenzene (19.0 mg, 0.1 mmol), K_2CO_3 (414.0 mg, 3.0 mmol) and toluene (2 ml) were added to the tube in dry box at RT, and capped with a Teflon screwcap. The reaction mixture was stirred at 120 °C for 8 h. GC yield of **2a**: 63% (1,4-di-*tert*-butylbenzene was used as the internal standard, response factor for **2a**: 1.1325).

Typical procedure of copper-catalyzed C-O coupling reaction with radical scavenger.

2,4-Dimethylphenol (0.147 ml, 1.2 mmol), 4-bromotoluene (0.123 ml, 1.0 mmol) were added to a Pyrex tube with a septum. The tube was evacuated and backfilled with nitrogen through needle for 3 cycles, then capped with parafilm before it was put into dry box. CuI (4.8 mg, 0.025 mmol, 2.5 mol%), 1,10-phenanthroline (9.0 mg, 0.050 mmol, 5.0 mol%), 1,4-di-*tert*-butylbenzene (19.0 mg, 0.1 mmol), K_2CO_3 (414.0 mg, 3.0 mmol), cumene (5 mol%, 0.069ml; 20 mol%, 0.276 ml; 50 mol% 0.690 ml) and toluene (2 ml) were added to the tube in dry box at RT, and capped with a Teflon screwcap. The reaction mixture was stirred at 120 °C for 8 h. GC yield of **2a**: 64%; 29%; 8% (1,4-di-*tert*-butylbenzene was used as the internal standard, response factor for **2a**: 1.1325).

Copper-catalyzed C-O coupling reaction of 2,4-dimethylphenol with 1-bromonaphthalene.

2,4-Dimethylphenol (0.147 ml, 1.2 mmol), 1-bromonaphthalene (0.140 ml, 1.0 mmol) were added to a Pyrex tube with a septum. The tube was evacuated and backfilled with nitrogen through needle for 3 cycles, then capped with parafilm before it was put into dry box. CuI (4.8 mg, 0.025 mmol, 2.5 mol%), 1,10-phenanthroline (9.0 mg, 0.050 mmol, 5.0 mol%), 1,4-di-*tert*-butylbenzene (19.0 mg, 0.1 mmol), K_2CO_3 (414.0 mg, 3.0 mmol) and toluene (2 ml) were added to the tube in dry box at RT, and capped with a Teflon screwcap. The reaction mixture was stirred at 120 °C for 8 h. GC yield of **3a**: 41% (1,4-di-*tert*-butylbenzene was used as the internal standard, correction factor for **3a**: 1.0758).

Copper-catalyzed C-O coupling reaction of 2,4-dimethylphenol with 4-chlorobenzonitrile.

2,4-Dimethylphenol (0.147 ml, 1.2 mmol), 4-chlorobenzonitrile (0.138 g , 1.0 mmol) were added to a Pyrex tube with a septum. The tube was evacuated and backfilled with nitrogen through needle for 3 cycles, then capped with parafilm before it was put into dry box. CuI (4.8 mg, 0.025 mmol, 2.5 mol%), 1,10-phenanthroline (9.0 mg, 0.050 mmol, 5.0 mol%), 1,4-di-*tert*-butyl benzene (19.0 mg, 0.1 mmol), K_2CO_3 (414.0 mg, 3.0 mmol) and toluene (2 ml) were added to the tube in dry box at RT, and capped with a Teflon screwcap. The reaction mixture was stirred at 120 °C for 8 h. GC yield of **4a**: 84% (1,4-di-*tert*-butylbenzene was used as the internal standard, response factor for **4a**: 1.0714).

Selectivity

2,4-dimethyl phenol (0.123 ml, 1.0 mmol), 4-bromotoluene (**1a**) (0.246 ml, 2.0 mmol), 2-bromotoluene (**1b**) (0.240 ml, 2.0 mmol) were added to a Pyrex tube with a septum. The tube was evacuated and backfilled with nitrogen through needle for 3 cycles, then capped with parafilm before it was put into dry box. CuI (4.8 mg, 0.025 mmol, 2.5 mol%), 1,10-phenanthroline (9.0 mg, 0.050 mmol, 5 mol%), 1,4-di-*tert*-butylbenzene (19.0 mg, 0.1 mmol), K_2CO_3 (414.0 mg, 3.0 mmol) and toluene (2 ml) were added to the tube in dry box at RT, and capped with a Teflon screwcap. The reaction mixture was stirred at 120 °C for 4 h. GC yield: **2a** 42%, **2b** 8% (1,4-di-*tert*-butylbenzene was used as the internal standard, response factor for **2a** and **2b**: 1.1325).

ESI-MS analysis

High-resolution ESI-MS were measured with a Waters LCT Premier XE with a Z-spray atmospheric pressure ionization source for ESI in the Mass Spectrometry Facility in the Institute of Chemistry, Academia Sinica. Leucine Enkephalin m/z 556.277 $[M+H]^+$ was used as a reference standard. Samples were injected 10 μL using a model Agilent 1100 autosampler system with flow injection analysis (FIA). The mobile phase was 100% acetonitrile at a flow rate of 50 μL/min.

EPR Measurement. EPR measurements were performed at the X-band using a Bruker E580 spectrometer equipped with a Bruker ELEXSYS super-high-sensitivity cavity in National Tsing Hua University. X-band EPR spectra of toluene reaction solution in a 4 mm EPR tube at 373K were obtained with a microwave power of 15.000 mW, frequency at 9.6589 GHz, ADC conversion time of 20.39 ms, receiver gain of 30, and modulation amplitude of 0.16 G at 100 kHz with phase of 0.0 deg. EPR spectra were examined by the program WINEPR. Simulations were carried by the EasySpin toolbox in Matlab.[16]

Acknowledgements

We are grateful to the National Science Council, Republic of China, and Academia Sinica for financial support of this work.

Notes and references

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Electronic Supplementary Information (ESI) available: GC data and ESI and EPR spectra. See DOI: 10.1039/b000000x/

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Possible Intermediates of Cu(Phen)-catalyzed C-O cross coupling of phenol with aryl bromide by in situ ESI-MS and EPR studies

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Cu(I) complexes with phen, 2,4-dimethylphenoxide and (1-(2,4-dimethylphenoxy)-4-methylbenzene) as ligands were observed in the copper(I)-catalyzed C-O coupling reaction using K_2CO_3 as the base and phen as the ligand under the catalytic reaction condition by *in situ* electrospray ionization mass spectrometry (ESI-MS) and EPR analysis.