ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 6686–6688

www.rsc.org/chemcomm

COMMUNICATION

A copper(II) complex as an intermediate of copper(I)-catalyzed C–N cross coupling of *N*-phenylaniline with aryl halide by *in situ* ESI-MS study†

Chia-Kai Tseng,[ab] Mei-Chun Tseng,[a] Chien-Chung Han*[b] and Shin-Guang Shyu*[a]

Received 4th April 2011, Accepted 19th April 2011
DOI: 10.1039/c1cc11906k

Complexes [Cu(NPh$_2$)$_2$]$^-$, [Cu(NPh$_2$)I]$^-$ and K[Cu(phen)(NPh$_2$)(*p*-tolyl)]$^+$ were observed by *in situ* electrospray ionization mass spectrometry (ESI-MS) analysis of the copper(I)-catalyzed C–N coupling reaction under the catalytic reaction condition indicating that they are intermediates in the reaction. A catalytic cycle composed of a free radical path and a 2e oxidative addition path is proposed based on these observations.

Catalytic C–N coupling reactions using a Cu-catalyzed process have been intensively studied due to its economic attractiveness, low toxicity, and air and moisture stability.[1] Copper(I)-catalyzed C–N cross coupling reaction usually consists of a ligand, a base and a copper salt.[2] In addition, Cu complexes with various ligands were synthesized, which served as the catalytic center in the catalytic system.[3] In general, a better yield of the reaction can be obtained when a ligand is present, and different ligands may have different catalytic activities.[4] Thus, Cu(I) complex with the additive ligand is generally proposed as the intermediate of the catalytic reaction.[5] During the copper-catalyzed C–N coupling reaction, the proton of the amide may be removed by the base to generate an amido anion, which may then replace the counter anion of the copper source and produce a copper complex with the amido ligand Cu(I)L(NR$_2$).[2a,b,5a] Oxidative addition of the aryl halide (ArI) to the complex produces Cu(III)LArI(NR$_2$) which regenerates the Cu(I)LI and the desired product ArNR$_2$ through reductive elimination.[6] Complexes with the corresponding amido ligand have been prepared, and their catalytic activities have been evaluated.[7] A free radical path has also been proposed based on the theoretical study,[8] however, DFT calculations also support the 2e oxidative addition path.[9] Recently, copper(I) complex [Na(phen)$_3$][Cu(NPh$_2$)$_2$] was isolated from the catalytic system, and an *in situ* ESI-MS study revealed that [Cu(NPh$_2$)$_2$]$^-$ is the active species for the reaction. Oxidative addition intermediates [Cu(NPh$_2$)I]$^-$ and Na[Cu(NPh$_2$)$_2$(*p*-tolyl)]$^+$ were observed in the spectra, and a 2e oxidative mechanism was proposed.[10] Among all these studies, the role of the ligand is still unclear, and the influence of base is seldom addressed. We herein report a mixed base (*t*BuONa/K$_2$CO$_3$) copper(I)-catalyzed C–N coupling reaction which has a higher than double catalytic reactivity than that of using only *t*BuONa as the base. *In situ* ESI-MS analysis of the catalytic system under the catalytic reaction conditions reveals the presence of [Cu(NPh$_2$)$_2$]$^-$, [Cu(NPh$_2$)I]$^-$ and K[Cu(phen)(NPh$_2$)(*p*-tolyl)]$^+$ in the reaction system indicating that they are intermediates in the reaction. Based on these observations, a reaction mechanism composed of a free radical path and a 2e oxidative addition path is proposed.

We followed the procedure reported in the literature[11] to investigate the copper-catalyzed C–N coupling reaction between aryl iodide and amine (*N*-phenylaniline). A mixture of *N*-phenylaniline (1.2 equiv.), 4-iodotoluene (1 equiv.), base (3 equiv.), CuI (10 mol%) and phen (30 mol%) was allowed to stir in toluene at 120 °C for 6 h. The results of the reactions are summarized in Table 1.

Accidentally, we discovered that by adding 1 equiv. of K$_2$CO$_3$ into the CuI-phen-*t*BuONa catalytic system, the yield and the selectivity of the reaction can be enhanced up to over 140% and 15%, respectively, as compared with the case of using *t*BuONa as the sole base. This enhancement may be due to the cation exchange between K$_2$CO$_3$ and *t*BuONa such that *t*BuOK was generated *in situ* in the reaction system. In order to verify this possibility, reaction using 3 equiv. of *t*BuOK was carried out under similar reaction conditions. Although the yield (product yield 75%) is better than that of the pure *t*BuONa system, both the yield and selectivity (75%) are inferior to that of the mixed base system (2 equiv. *t*BuONa/1 equiv. K$_2$CO$_3$). The differences in reactivity and selectivity may imply that the mechanisms of the reactions in different base systems are different. In order to evaluate this possibility, *in situ* ESI-MS analyses were carried out in order to trap the intermediates in the catalytic reaction.

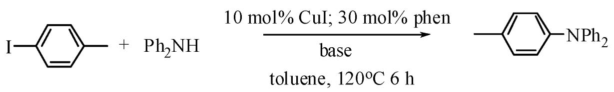
Since the catalytic reactions were carried out at 120 °C, *in situ* ESI-MS analyses were carried out at 120 °C in order to detect the intermediates (Fig. 1). Similar reaction mixture in toluene was stirred at 120 °C for 2 h. The solution was then transferred to a GC vial in a dry box. The temperature of the

---

[a] *Institute of Chemistry, Academia Sinica, Taipei 115, Taiwan, Republic of China. E-mail: sgshyu@chem.sinica.edu.tw; Fax: +886-2-2783-1237; Tel: +886-2-2789-8593*
[b] *Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, Republic of China. E-mail: cchan@mx.nthu.edu.tw; Fax: +886-3-5711082; Tel: +886-3-5724998*

† Electronic supplementary information (ESI) available: Experimental data, *in situ* ESI-MS spectra and isotope distribution of the intermediates. See DOI: 10.1039/c1cc11906k

Table 1 Cu(I) catalyzed C–N coupling reaction with different base systems^{a}



Entry	Radical scavenger^{b}	*t*BuONa^{c}	*t*BuONa/K$_2$CO$_3$^{d}	*t*BuONa/K$_2$CO$_3$^{e}
1	—	46^{f}/38^{g}(83%)^{h}	95/93(98%)	17/17(100%)
2	20 mol%	50/38(76%)	88/85(97%)	23/16(70%)
3	100 mol%	53/35(66%)	80/64(80%)	42/18(43%)

[a] 1.0 mmol 4-iodotoluene, 1.2 mmol *N*-phenylaniline, 4 mL toluene, 0.1 mmol CuI, 0.3 mmol phen. [b] TEMPO. [c] 3 mmol *t*BuONa. [d] *t*BuONa/K$_2$CO$_3$ (2 mmol/1 mmol). [e] Without phen. [f] Conversion yield based on aryl iodide. [g] GC yields based on aryl iodide. [h] Selectivity.

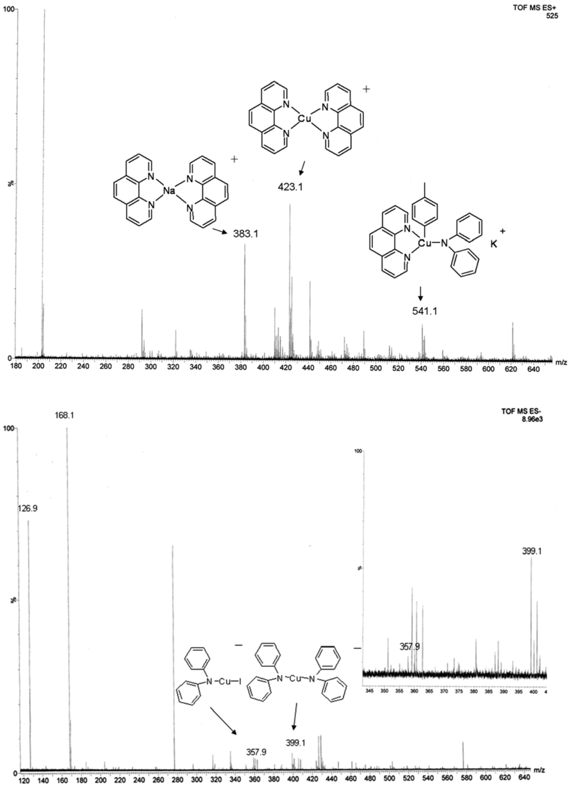


Fig. 1 ESI(+)(−)-MS from the reaction solution taken during the reaction of 4-iodotoluene, *N*-phenylaniline with *t*BuONa/K$_2$CO$_3$ in the presence of CuI and phen in toluene at 120 °C.

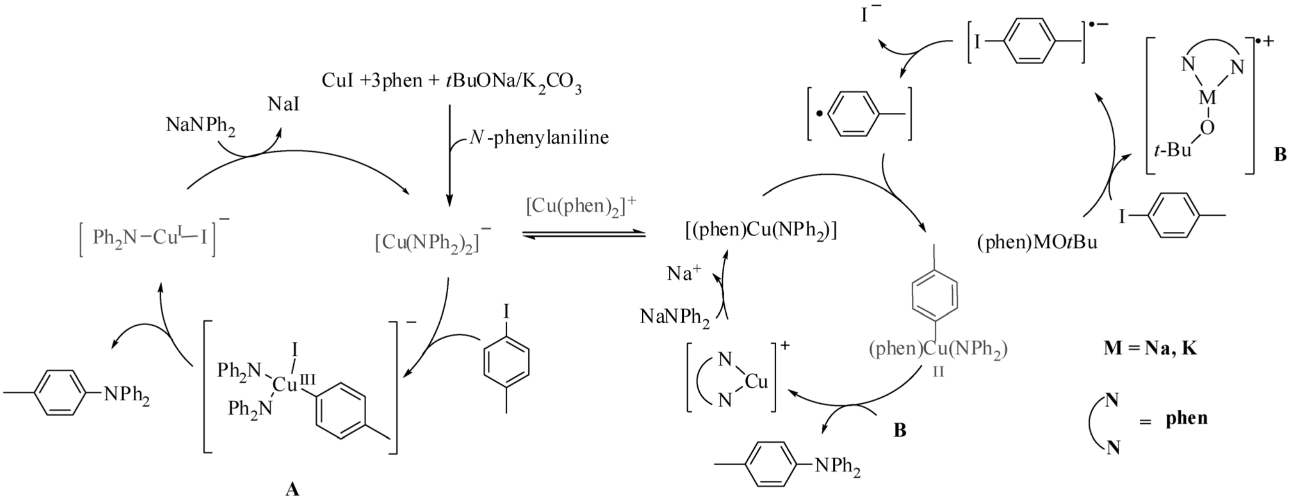
solution was kept at 120 °C by immersing the GC vial in a sand bed, and ESI-MS spectra of the solution were taken. The ESI-MS in negative-ion mode showed two peaks at m/z = 399.1 and m/z = 357.9 which are identified as $[Cu(NPh_2)_2]^-$ and $[Cu(NPh_2)I]^-$ correspondingly according to their isotope distributions.†

Peaks at m/z = 423.1 and m/z = 383.1 corresponding to $[Cu(phen)_2]^+$ and $[Na(phen)_2]^+$, respectively, were also observed in the positive-ion mode of ESI-MS indicating that ligand redistribution had occurred under the catalytic reaction condition. In addition, we observed a peak at m/z = 541.1 corresponding to K[Cu(phen)(NPh$_2$)(*p*-tolyl)]$^+$, and its isotope distribution is consistent with the assignment.†

The formation of the Cu(II) complex [Cu(phen)(NPh$_2$)(*p*-tolyl)], a portion of K[Cu(phen)(NPh$_2$)(*p*-tolyl)]$^+$, implies that a radical path is involved in the reaction mechanism. A *p*-tolyl free radical $[CH_3C_6H_4]^\bullet$ may be formed by the transformation from the radical anions $[CH_3C_6H_4I]^{\bullet-}$ upon reaction between 4-iodotoluene and the single electron donor, sodium *tert*-butoxide, because metal *tert*-butoxide was reported to act as a single electron donor toward alkyl iodide.[12] In addition, the presence of $[Cu(phen)_2]^+$ and $[Cu(NPh_2)_2]^-$ indicates the formation of $[Cu(phen)_2]$-$[Cu(NPh_2)_2]$ in the reaction. This Cu(I) complex may form two equiv. of Cu(phen)(NPh$_2$) in the reaction because it has been reported that in polar solvent (DMF) at −25 °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. Thus, the *p*-tolyl free radical $[CH_3C_6H_4]^\bullet$ reacts with the Cu(phen)(NPh$_2$) to form [Cu(phen)(NPh$_2$)(*p*-tolyl)].[7a]

Based on these observations, a catalytic cycle composed of two catalytic paths is proposed and shown in Scheme 1. Although we did not observe the intermediate Na[Cu(NPh$_2$)$_2$-(*p*-tolyl)]$^+$ or [Cu(NPh$_2$)$_2$(*p*-tolyl)I]$^-$, the presence of $[Cu(NPh_2)I]^-$ implies that the 2e oxidative addition path may involve in the reaction mechanism.[10] Complex $[Cu(NPh_2)_2]^-$ was generated by the reaction among 4-iodotoluene, metal (sodium or potassium) *tert*-butoxide and CuI. 4-Iodotoluene then reacts with $[Cu(NPh_2)_2]^-$ to form **A** through oxidative addition reaction. Reductive elimination of 4-methyl-*N*,*N*-diphenylaniline produces $[Cu(NPh_2)I]^-$. It further reacts with NPh_2^- to produce $[Cu(NPh_2)_2]^-$ and completes the 2e oxidative addition catalytic cycle. During the reaction, redistribution of phen among metal cations occurred as indicated by the observation of $[Cu(phen)_2]^+$ and $[Na(phen)_2]^+$ in the spectra. Likewise, the ligand redistribution reaction between $[Cu(NPh_2)_2]^-$ and $[Cu(phen)_2]^+$ produces complex Cu(phen)(NPh$_2$), possibly in an equilibrium fashion. Addition of the *p*-tolyl free radical to the complex generates a Cu(II) complex [Cu(phen)(NPh$_2$)(*p*-tolyl)]. After reductive elimination and reaction with the $[t\text{BuONa(phen)}]^{\bullet+}$, 4-methyl-*N*,*N*-diphenylaniline is produced, and the [Cu(I)phen]$^+$ reacts with NPh_2^- to form Cu(phen)(NPh$_2$) and completes the catalytic cycle.

In order to confirm the existence of the free radical path and to evaluate which reaction path dominates the reaction, a free radical scavenger was applied to the reaction. When 20 mol% of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction system, the yield of the reaction reduced from 93% to 85%; if 100 mol% of scavenger was added, the yield reduced to 64% (Table 1). These observations further support



Scheme 1 The proposed catalytic cycle.

the existence of the free radical path. In addition, the 32% yield reduction (as compared to the yield without TEMPO) after adding TEMPO may indicate that the free radical path contributes one third of the whole catalytic reaction. When TEMPO was added to the catalytic system with pure *t*BuONa as the base, no yield reduction was observed for the 20 mol% addition, and only 7% yield reduction was observed for 100 mol% TEMPO addition. This indicates that a free radical path contributes only a very small fraction of the catalytic reaction in the pure *t*BuONa system.

When phen is absent in the mixed base system, the yield of the reaction reduced to 18% (Table 1). When TEMPO was added into the system, the yield remains similar, indicating the absence of a free radical path in the system. The reason for the absence of a free radical path is quite understandable because Cu(phen)(NPh_2) cannot be produced without the phen.

These observations indicate that a ligand and a base can influence the mechanism of copper(I)-catalyzed C–N cross coupling reaction, and a dual path mechanism can be present in the system.

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

Notes and references

1 (*a*) R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315–4317; (*b*) R. Gujadhur, D. Venkataraman and J. T. Kintigh, *Tetrahedron Lett.*, 2001, **42**, 4791–4793; (*c*) Y. Hirai and Y. Uozumi, *Chem.–Asian J.*, 2010, **5**, 1788–1795; (*d*) S. Jammi, S. Sakthivel, L. Rout, T. Mukherjee, S. Mandal, R. Mitra, P. Saha and T. Punniyamurthy, *J. Org. Chem.*, 2009, **74**, 1971–1976; (*e*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131; (*f*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337–2364; (*g*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449.

2 (*a*) A. Klapars, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 7421–7428; (*b*) M. Periasamy, P. Vairprakash and M. Dalai, *Organometallics*, 2008, **27**, 1963–1966; (*c*) S. U. Son, I. K. Park, J. Park and T. Hyeon, *Chem. Commun.*, 2004, 778–779; (*d*) Z. Xi, F. Liu, Y. Zhou and W. Chen, *Tetrahedron*, 2008, **64**, 4254–4259; (*e*) H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164–5173; (*f*) N. Xia and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 337–339.

3 (*a*) Y.-M. Pu, Y.-Y. Ku, T. Grieme, R. Henry and A. V. Bhatia, *Tetrahedron Lett.*, 2006, **47**, 149–153; (*b*) T. Jerphagnon, G. P. M. van Klink, J. G. de Vries and G. van Koten, *Org. Lett.*, 2005, **7**, 5241–5244; (*c*) M. L. Kantam, T. Ramani and L. Chakrapani, *Synth. Commun.*, 2008, **38**, 626–636; (*d*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450–1460; (*e*) K. Moriwaki, K. Satoh, M. Takada, Y. Ishino and T. Ohno, *Tetrahedron Lett.*, 2005, **46**, 7559–7562; (*f*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2008, **47**, 3096–3099.

4 (*a*) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13–31; (*b*) J. C. Antilla, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 11684–11688; (*c*) Y.-H. Liu, C. Chen and L.-M. Yang, *Tetrahedron Lett.*, 2006, **47**, 9275–9278; (*d*) Y.-S. Feng, Q.-S. Man, P. Pan, Z.-Q. Pan and H.-J. Xu, *Tetrahedron Lett.*, 2009, **50**, 2585–2588; (*e*) J. Haider, K. Kunz and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 717–722.

5 (*a*) E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4120–4121; (*b*) A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl and X. Ribas, *Chem. Sci.*, 2010, **1**, 326–330; (*c*) H. Kaddouri, V. Vicente, A. Ouali, F. Ouazzani and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 333–336.

6 S.-L. Zhang, L. Liu, Y. Fu and Q.-X. Guo, *Organometallics*, 2007, **26**, 4546–4554.

7 (*a*) J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 9971–9983; (*b*) E. R. Strieter, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 78–88.

8 G. O. Jones, P. Liu, K. N. Houk and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 6205–6213.

9 (*a*) H.-Z. Yu, Y.-Y. Jiang, Y. Fu and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 18078–18091; (*b*) S. A. Delp, L. A. Goj, M. J. Pouy, C. Munro-Leighton, J. P. Lee, T. B. Gunnoe, T. R. Cundari and J. L. Petersen, *Organometallics*, 2011, **30**, 55–57.

10 C.-K. Tseng, C.-R. Lee, C.-C. Han and S.-G. Shyu, *Chem.–Eur. J.*, 2011, **17**, 2716–2723.

11 H. B. Goodbrand and N.-X. Hu, *J. Org. Chem.*, 1999, **64**, 670–674.

12 (*a*) E. Shirakawa, K. Itoh, T. Higashino and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 15537–15539; (*b*) J. Fossey, D. Lefort and J. Sorba, *Free Radicals in Organic Chemistry*, John Wiley and Sons, Chichester, 1995, ch. 15, pp. 181–189; (*c*) J. F. Bunnett, *Acc. Chem. Res.*, 1978, **11**, 413–420.