



Research article

Synthetic and computational studies on CuI/ligand pair promoted activation of C(Aryl)-Cl bond in C–N coupling reactions

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ABSTRACT

Cu/ligand-mediated coupling reactions have been widely investigated in the recent past. However, activation of cheaper aryl chlorides is still a great limitation of these reactions. During the course of present investigations efforts have been made to develop a normal and facile CuI/ligand pair protocol for arylation of phthalimide using aryl chlorides. The protocol has also been extended for arylation of amines. On the basis of experimental and theoretical results, a catalytic cycle has also been proposed and it has been established that these reactions follow oxidative addition-reductive elimination (OA-RE) pathway. These studies have indicated that tetracoordinated $[\text{Cu}(\text{L}1)(\text{L}2)]^+$ complex is active catalytic species in these reactions.

1. Introduction

More than a century ago, coupling reaction was introduced by Ullmann [1] but limited substrate scope, the requirement of high temperature ($>200^\circ\text{C}$ temperature) and higher loading of copper restricted its synthetic use. In the 1990s, Buchwald-Hartwig reaction [2, 3] and modern Ullmann reaction (Cu/ligand system) [4, 5, 6, 7] proved to be important methods for coupling reactions. Use of N,N/N,O/O,O ligand significantly improved the efficiency of Cu mediated reactions. Usually, Pd-mediated reactions [8] are more efficient than Cu-mediated reactions and have a wider substrate scope (ArX, X = Cl, Br and I). Aryl iodides and aryl bromides are good substrates in Cu-mediated C-heteroatom arylation reactions [9, 10, 11, 12, 13, 14, 15, 16] but reactions are not much successful in activation of commercially cheaper aryl chlorides (ArCl) [17] which are easily activated in presence of expensive Pd/ligand and CuI/oxamide ligand system [18]. As compared to Buchwald-Hartwig reaction (Pd-mediated reactions) modern Ullmann reaction has many advantages like simplicity of the ligands, low toxicity of copper and overall low cost of the process. A large number of experimental and computational studies are reported on modern Ullmann reaction but most of the studies are focused on C-heteroatom coupling reactions involving more reactive arylating agents (aryl iodides and aryl bromides) [5, 7, 14, 19, 20, 21, 22, 23, 24, 25, 26, 27]

Efforts have also been made to activate aryl chlorides using the copper-ligand system. Buchwald group [28, 29] reported that when aryl

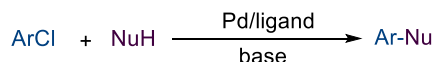
chlorides are used as a substrate as well as solvent arylation is observed. Xia and Taillefer [30] reported $[\text{Cu}(\text{L}8)_2]/\text{L}9(0.9 \text{ equivalent})/\text{DMF}$ (135°C) system for activation of aryl chlorides in the C–O bond formation but higher loading of the ligand is required in this system.

Very recently CuI/oxalamides/DMSO (120°C) protocol has also been reported by Ma's group for C–Cl bond activation [18, 31, 32, 33, 34, 35, 36, 37, 38]. However, the requirement of a highly polar solvent, hydrolysis of oxalamides during the course of the reaction and overall poor atom economy (because of greater molecular weight of ligands) are disadvantages of the protocol [18]. In view of the above and role of N-aryl imides and amines as intermediates in the synthesis of a large number of bioactive molecules [38,39]. A CuI/ligand pair protocol has been developed for N-arylation of phthalimide and aromatic amines using commercially cheaper aryl chlorides (21 examples of N-arylation) (Scheme 1). Ligand pair has been constituted using commercially available and previously used [4, 5, 6, 7] cheaper diamine ligands (L) (Figure 1, a) and the present ligand pair has significantly improved the arylation of phthalimide amines using aryl chloride (Figure 2). These reactions [38,39] and N-arylphthalimides [34,40–44] have wider industrial and pharmaceutical applications. Interesting experimental results prompted us to focus on DFT studies about the role of second ligand and probable mechanism of the process. Extensive DFT studies have been performed considering the cross-coupling of chlorobenzene and phthalimide and plausible mechanistic pathways have been investigated for a meaningful comparison.

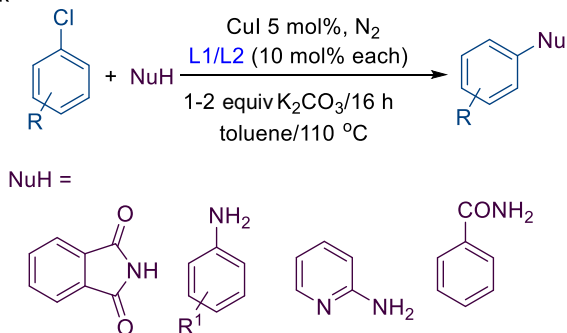
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Buchwald Hartwig reaction



This work



Scheme 1. Pd and Cu-mediated C–N coupling reactions.

2. Results and discussion

2.1. Synthetic studies

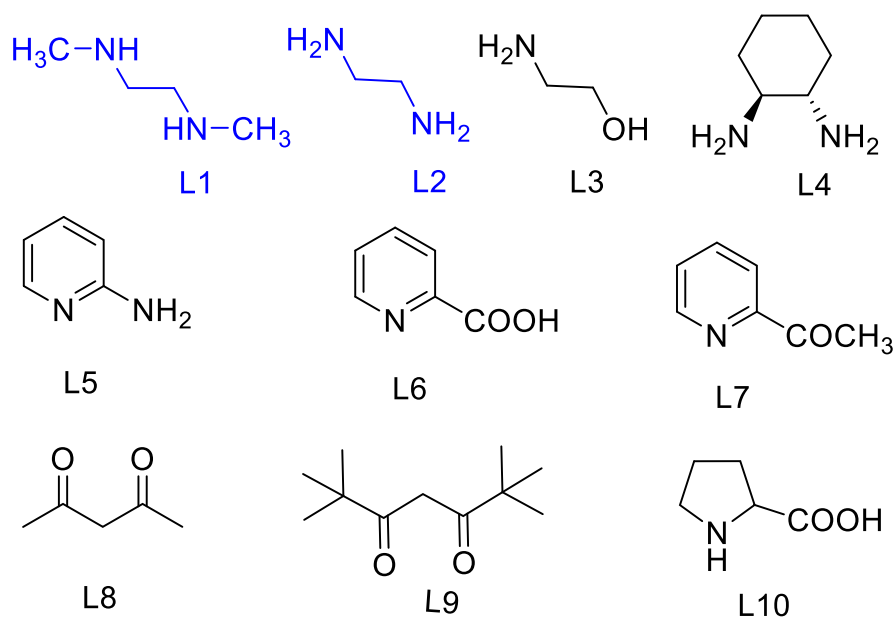
In our earlier published study on the role of the base in cross-coupling reaction, it was emphasised that the introduction of the second ligand in the process can facilitate activation of C–Cl bond [26].

For further investigations on the role of the second ligand in coupling reactions, different set of reactions were studied.

The cross-coupling reaction of PhCl and phthalimide in CuI/single ligand system having 10–25 mol% ligand does not yield the corresponding product (Figure 2).

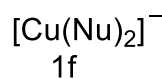
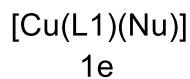
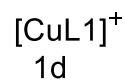
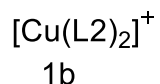
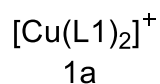
In another set of reaction ligand pairs were framed using 10 mol% each from the 10 readily available ligands (Figure 1, a), Chlorobenzene and phthalimide were used as model substrates. It has been observed that protocol developed using CuI (5 mol%)/ligand pair activates aryl chloride relatively at low temperature (110 °C) and even in less polar solvent toluene. Protocol efficiently works in the coupling reactions of different ArCl (1.5 equiv) with phthalimide in the presence of K₂CO₃ (1–2 equiv) and gives moderate to excellent yield in 16 h (Scheme 2).

a. Ligands



b. Possible copper catalytic species (CCS)

In presence of single ligand (L1 or L2)



Additional CCS in presence of two ligands (L1 and L2)

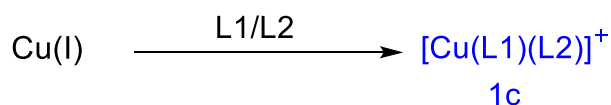


Figure 1. a. List of investigated ligands. b. Possible catalytic species in the presence of L1 or L2 ligand and in presence of ligand pair (L1 and L2).

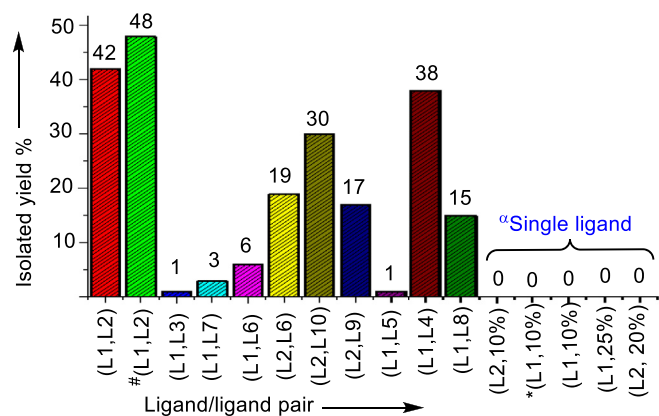


Figure 2. Screening of ligand pairs. Reaction conditions- PhCl (2.5 equiv, 12.5 mmol), phthalimide (1 equiv, 5 mmol), 10 mol% each ligand in ligand pair, CuI (5 mol%) and K_2CO_3 (1 equiv) in toluene (6 mL) heated to reflux for 16 h under N_2 at 110 °C. *Base K_3PO_4 (2 equiv), # K_2CO_3 (2 equiv). ^aSingle ligand concentration (mol %) is shown in the bracket.

These observations indicate that the copper catalytic species (CCS) possible in presence of CuI/single ligand, **1a**, **1b** and **1d-1f** are not able to activate C–Cl bond in the reaction (Figure 1, b).

During the screening of ligand for CuI/ligand pair protocol, it was observed that the nature of members of the ligand pair significantly affects the efficiency of the catalytic cycle (Figure 2). The ligand pairs comprising ligand L1 with the ligands L3, L5, L6 and L7 have poor performance in the catalytic cycle. Ligand pairs comprising L2 with L6, L9 and L10 are moderate performers in C–N bond formation (Figure 2). The performance of ligand pair L2/L10 is better than the ligand pairs L2/L6 and L2/L9. In general, the ligand pairs L1/L2 and L1/L4 are found most efficient. These results indicate that good electron donor ligands having no bond strain during structural reorganisation (flexible ligand) and able to form 5 membered chelate complex perform better in the catalytic cycle. It is also evident from the observation that L5 (4 membered chelate ring) and L6 (non-flexible ligand) are poor performers than L10. Experimental results also indicate that good combination of the ligands in the ligand pair is that in which one ligand is less sterically hindered (L2 and L4) and another one is efficient electron donor (L1, L6, L9 and L10).

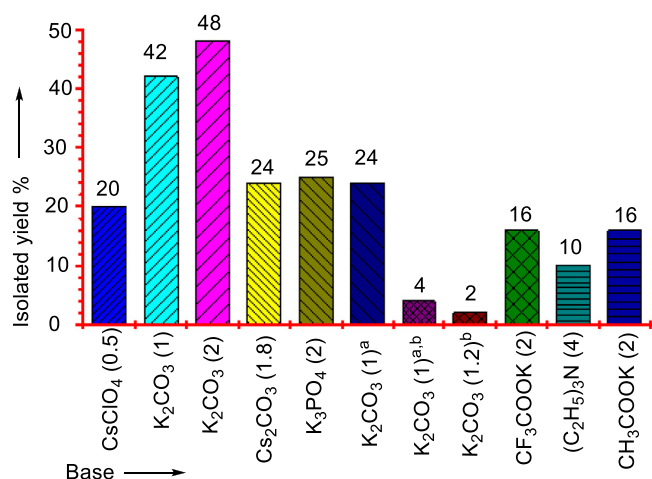


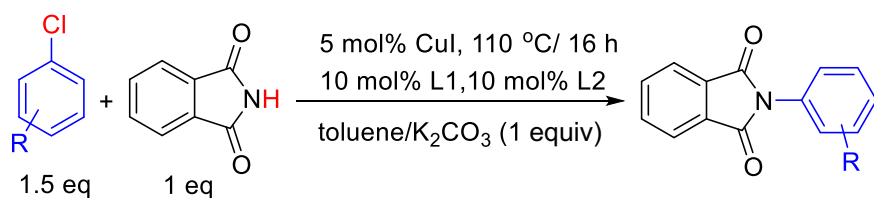
Figure 3. Screening of bases (equivalents are shown in brackets). Reaction conditions- PhCl (2.5 equiv, 12.5 mmol), phthalimide (1 equiv, 5 mmol), L1 and L2 (10 mol% each), CuI (5 mol%) in toluene (6 mL) heated to reflux for 16 h under N_2 at 110 °C. ^amolecular sieves (4 Å), ^b50 °C and 72 h. The yield was declined with 2.5 and 3 equivalents of K_2CO_3 (yield, 39% and 24% respectively).

As discussed above that yield depends on the nature of both the members of ligand pair and combination of L1 and L2 is an efficient ligand pair. Therefore, **1c** can be considered as active CCS in the present case. Its formation in the solution of CuI, L1 and L2 is also favourable on the basis of entropy (Figure 4).

The base plays an important role in the catalytic cycle. Initially, cost-effective K_2CO_3 (1–2 equiv) was used as a base. 42% yield was observed with 1 equiv K_2CO_3 , which was noticed slightly higher (48%) with 2 equiv K_2CO_3 (Figure 3). Improvement in yield was not noticed in the presence of an excess base and even slightly decline was observed in the presence of 2.5–3 equiv base. Compared to K_2CO_3 , the yield was found to be reduced in Cs_2CO_3 and K_3PO_4 bases.

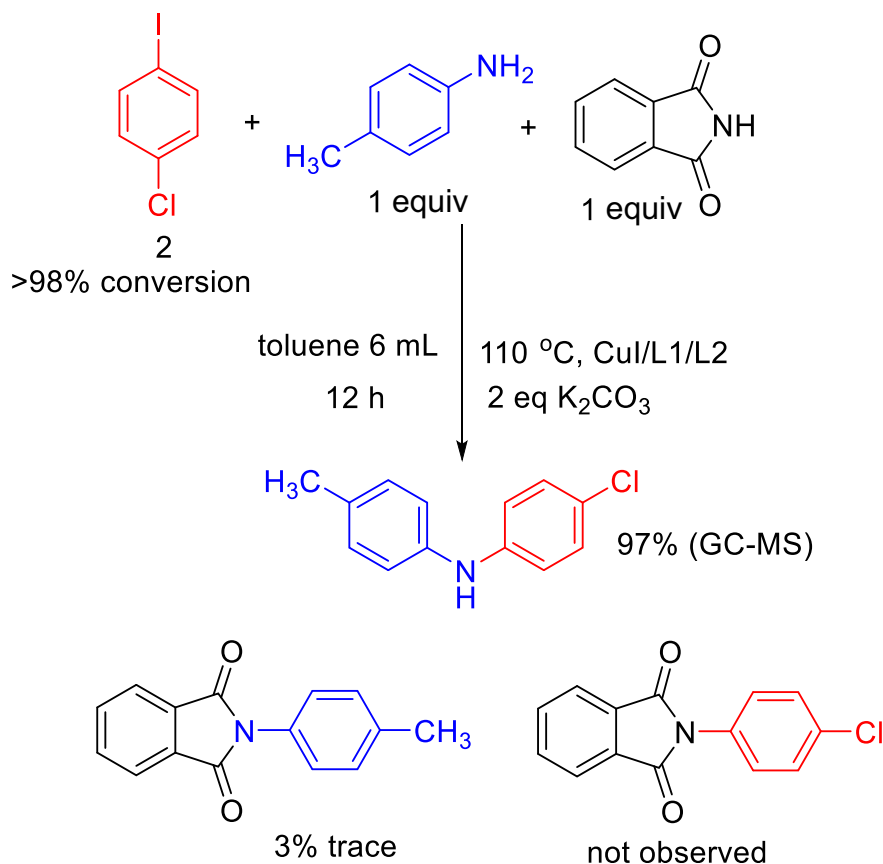
It was also observed that weaker bases CF_3COOK and $CsClO_4$ work better than the more soluble and stronger base triethylamine.

As per literature reports, excess base generates the inert copper species like **1f** and halt the reaction cycle. Recently, Davies and Nguyen groups [27,45,46] also highlighted the adverse role of bases in coupling



Entry	R	Isolated yield%	Entry	R	Isolated yield%
1.	H	48 (96) ^{a,c} (20) [*]	8.	<i>o</i> -Me	15 (19) ^{c,d}
2.	<i>p</i> -NO ₂	82 (Blank test-0) ^b	9.	<i>o</i> -COCH ₃	22
3.	<i>o</i> -NO ₂	0	10.	<i>p</i> -Me	16 (36) ^{c,d}
4.	<i>m</i> -NO ₂	96	11.	<i>p</i> -Cl	60 (89) ^a
5.	<i>p</i> -OH	42	12.	<i>p</i> -NH ₂	92
6.	<i>p</i> -CHO	48	13.	<i>p</i> -COOH	86 ^c
7.	<i>o</i> -CHO	35 (75) ^a	14.	<i>o</i> -COOH	99 ^c

Scheme 2. Arylation of phthalimide using different aryl chlorides. *Yield% with fluorebenzene, [a] phthalimide conversion (%), estimated on the basis of the isolated and unreacted amount of phthalimide after 16 h [b] In absence of CuI and Ligands, [c] 2 equiv K_2CO_3 , [d] reaction time 40 h.



Scheme 3. The competitive reaction between nucleophiles as well as between -Cl and -I.

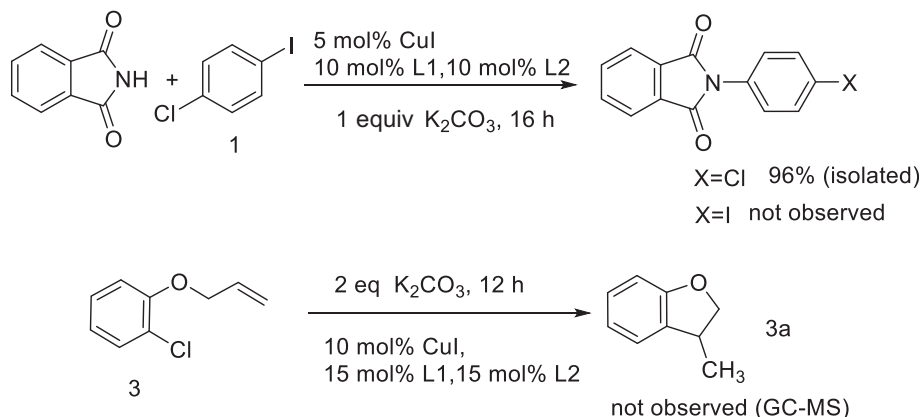
reactions [47]. Similar results were also obtained in our previous studies and we reported that the efficiency of the catalytic cycle depends on competitive ligation of carbonate ion and diamine ligand/nucleophile to copper [26,48]. Considering the role of the base in current and previous studies that its excess amount adversely affects the activity of the catalyst, the amount of base was carefully fixed to 1–2 equivalent (K₂CO₃) for further investigations. Optimization of other reaction parameters excess PhCl (2.5 equiv) was used. In other cases, it was used 1.5 equiv.

After optimization of reaction conditions and screening of ligand pairs and bases, the present investigation was extended for other aryl chlorides (Scheme 2). The present protocol gives variable yield with electron-poor (-COOH, -CHO, -NO₂, -Cl) and electron-rich (-Me, -OH, -NH₂) aryl chlorides. *o*-NO₂ and *o*-Me phenyl chlorides are found to be extremely poor substrates (Scheme 2, entry 3 and 8). In previous studies, zero yield was reported even with *o*-methyliodobenzene [27]. The *p*-Me

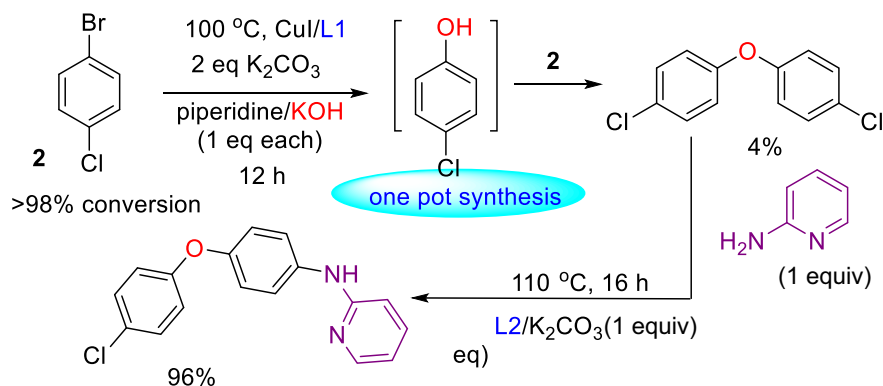
derivative requires more reaction time (40 h, Scheme 2, entry 10) to reach an acceptable yield (36%).

Reported studies show that electron-deficient aryl halides are good substrates [5]. However, in the present case 2-nitrochlorobenzene (yield 0%) was found poor substrate than 4-nitrochlorobenzene (yield 82%) (Scheme 2, entry 2 and 3). Moreover, the reactivity of 3-nitrochlorobenzene (yield 96%) was found more. These observations clearly indicate that steric factor predominant in these transformations. Thus, the presence of -NO₂ and -CH₃ groups at ortho-position adversely affect the conversion.

In view of the above, we focused on the mechanistic aspects of the reaction. Literature reports indicate that electron-deficient aryl chlorides undergo to transformation in alkaline conditions through S_NAr pathway [30]. In the present case, the *p*-NO₂ derivative could not turn up into the desired product in the blank test (without CuI/Ligand) through S_NAr



Scheme 4. Competitive reaction between -Cl and -I. Radical clock test to probe the free radical pathway.

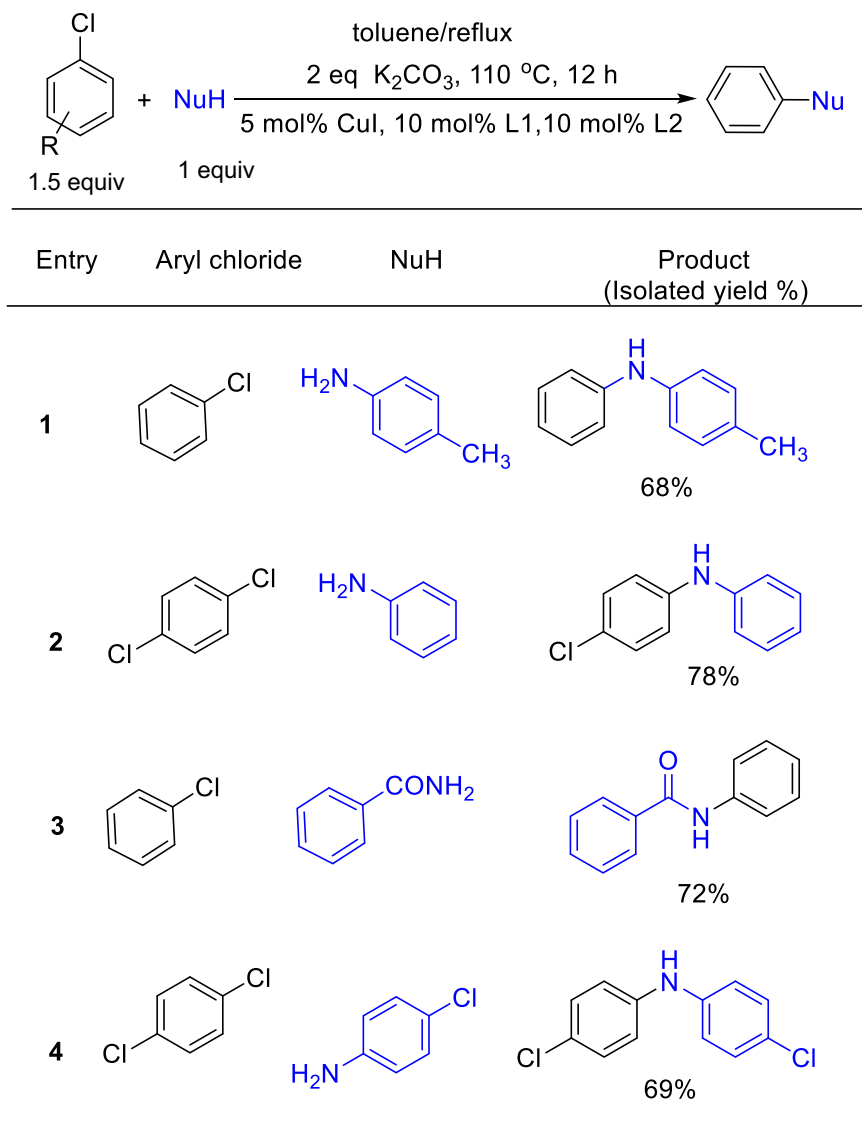


pathway (Scheme 2, entry 2). A possible reason is poor solubility of carbonate base in toluene. Electron-deficient aryl fluoride also shows relatively poor conversion.

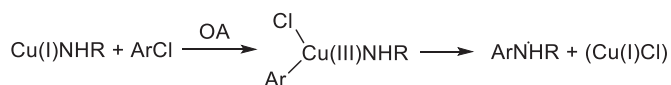
To explore the possibility of SET mechanism reactivity of –I and –Br in the same substrate was investigated and substrates **1** and **2** were used for the purpose (Schemes 3, 4, and 5). These substrates exclusively turned in to the corresponding products through C–I/C–Br bond activation. No reactivity was observed in C–Cl bond over C–I/C–Br bond, even

though ArCl has greater potential for reduction than the ArI/ArBr. This observation indicates that radical anion (through SET mechanism) is not involved in the reactions. In recent past, o-allyl aryl chlorides (**3**) have been used to investigate radical reactions (Scheme 4) and thus, a similar experiment was performed to trace out radical species [27, 31, 38,49]. However, these studies discarded the radical pathway.

As discussed above Cu/ligand pair is able to activate C–Cl bond and there is a difference in reactivity of C–Cl and C–Br. Therefore, we



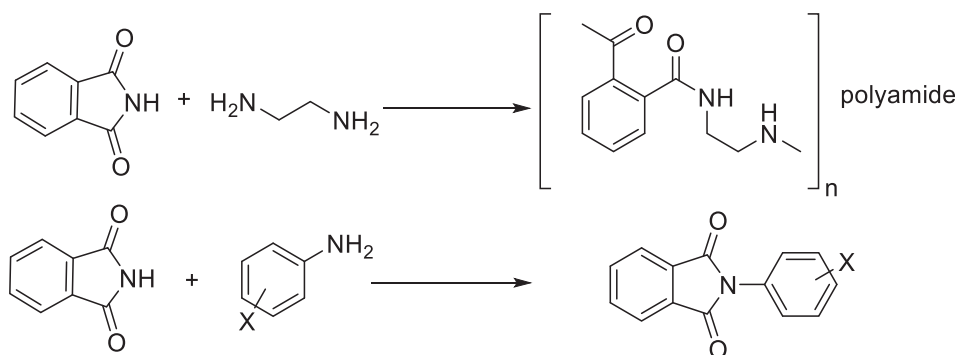
Scheme 6. Arylation of arylamines and benzamide.



Scheme 7. Oxiadtive addition-reductive elimination pathway.

investigated a new synthetic approach to install two different nucleophiles on the substrate. In the first step, a nucleophile (hydroxide ion) and Cu/L1 were introduced and diaryl ether was produced through intermediate phenol. In the second step, L2 and desired nucleophile (2-aminopyridine) were introduced in the same reaction flask and arylation of 2-aminopyridine was observed through C–Cl bond activation. It is worthwhile to mention that the aforesaid synthetic approach has been

successful in installing two different nucleophiles by sequential activation of C–Br and C–Cl bonds in **2** (Scheme 5). The proposed synthetic approach can be further explored for the synthesis of important pharmaceutical molecules, e.g. imatinib and acetaminophen [49]. This is also important to mention that in the first step, two nucleophiles (piperidine and KOH) were present in the flask, but only C–O coupling was observed and diaryl ether was the main product. These results are in agreement with the studies of the Buchwald group about C–N and C–O selectivity [11,50]. This is also supported by the studies of Taillefer and Jutand group [51] that if both KOH/K₂CO₃ bases are present in the system, ethers are main products instead of phenols. Activation of C–Cl bond in the above-mentioned sequence of reactions clearly indicates that only



Scheme 8. Side reactions, (2–3%), transamidation of phthalimide with L2 and halo anilines were observed. See supplementary content for more detail.

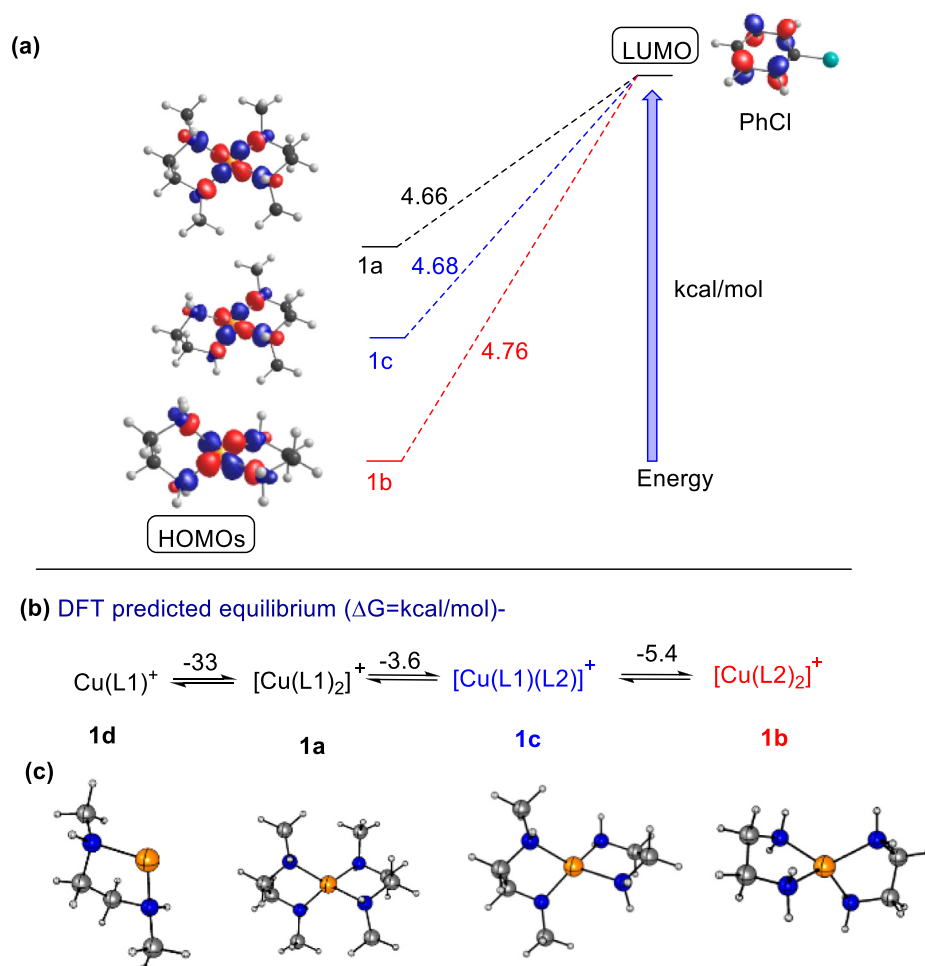


Figure 4. FMO analysis of CCS (**1a**, **1b** and **1c**), the energy gap of HOMO–LUMO is in kcal/mol (a) and DFT predicted equilibrium (b) and optimized geometries of **1a–1d** species (c).

Cu/ligand pair protocol is able to activate it and it is in support of the earlier discussed results and assumption of the active CCS in the process.

To compare the nucleophilicity of aromatic amines and amides competitive reaction presented in Scheme 3 was investigated and it has been observed that aromatic amines are better nucleophile than imides. In view of the above, we prompted to extend the protocol for arylation of readily available N-nucleophile (Scheme 6) and it has been observed that protocol is successful for amines also. The yield was observed 68–78% in the arylation of aromatic amines and aniline is found to be better nucleophile than benzamide with a yield of 78% and 72% respectively (Scheme 6).

2.2. Mechanistic studies

In view of the interesting experimental results, DFT studies were also performed to investigate the mechanistic aspects of these reactions. Mostly, three mechanistic pathways [7] are under debate for Cu-mediated cross-coupling reactions; (i) oxidative addition-reductive elimination (OA-RE) via Cu(III) complexes [21,52] (ii) free radical single electron transfer (SET) pathway via Cu(II) complexes [50,53] and (iii) halogen atom transfer (HAT) pathways via Cu(II) complexes [54].

Remarkable studies have been performed by various groups to determine the mechanism of Cu-mediated coupling reactions. Most of these studies suggest that coupling reactions follow OA-RE pathway (Scheme 7) [5, 7]. Free radical pathways were discarded many times on the basis of radical clock experiments [23, 24,55]. However, these mechanistic studies are confined to coupling reactions of aryl bromides or aryl iodides and studies have not been extended for aryl chlorides.

Most of the mechanistic studies suggest that [LCuNu] (L = neutral diamine ligand) and [LCu] (L = anionic ligand) type species (1e) are active catalytic species in OA-RE pathway involving ArBr/ArI. However, it has not been determined that coupling reactions involving aryl chlorides follow the same pathway or not. However, more recently, Ahmed and Roy [56] proposed OA-RE pathway.

Guo and co-workers [25] have reported that copper complex 1f is inert species in OA-RE path due to its repulsion with anionic nucleophiles and 1d species have very poor solubility because of higher charge density and thus these have no significant contribution in the catalytic cycle. Species 1e has been accepted as active species in the reactions of ArI/ArBr. In view of the above, we have performed DFT calculations to find out the appropriate CCS and catalytic cycle. DFT predicted equilibrium (Figure 4) indicates that 1c species are more stable ($\Delta G = -33$ kcal/mol) than 1d. Therefore, 1d species are present in a little fraction and they do not play a key role in the catalytic cycle. However, in the present study, we have considered both the species 1d and 1f as possible CCS for comparison purpose. In the present case, 1c appears as a new species in Cu(I)/ligand pair system. In summary, all the complexes 1a-1f have been considered as CCS for comparison and just to find out appropriate catalytic cycle (Figures 5, 6, 7, 8, 9, 10, and 11).

2.2.1. Free radical single electron transfer mechanism



ArCl has greater potential for reduction and expected to be more reactive in a SET path. In the present case, firstly SET (outer-sphere

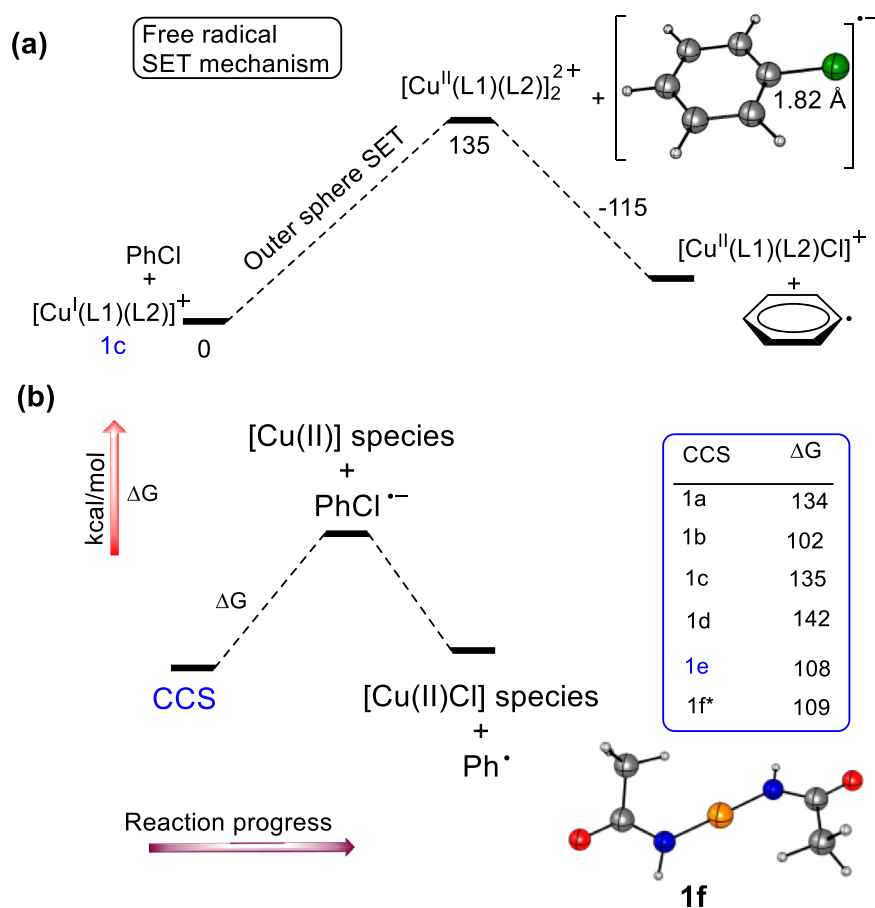


Figure 5. DFT calculated free energy (ΔG) profile for SET pathways for 1c species (a) and other CCS (b). * ΔG calculated for $[\text{Cu}(\text{NHAc})_2]$. Bond lengths are shown in (Å).

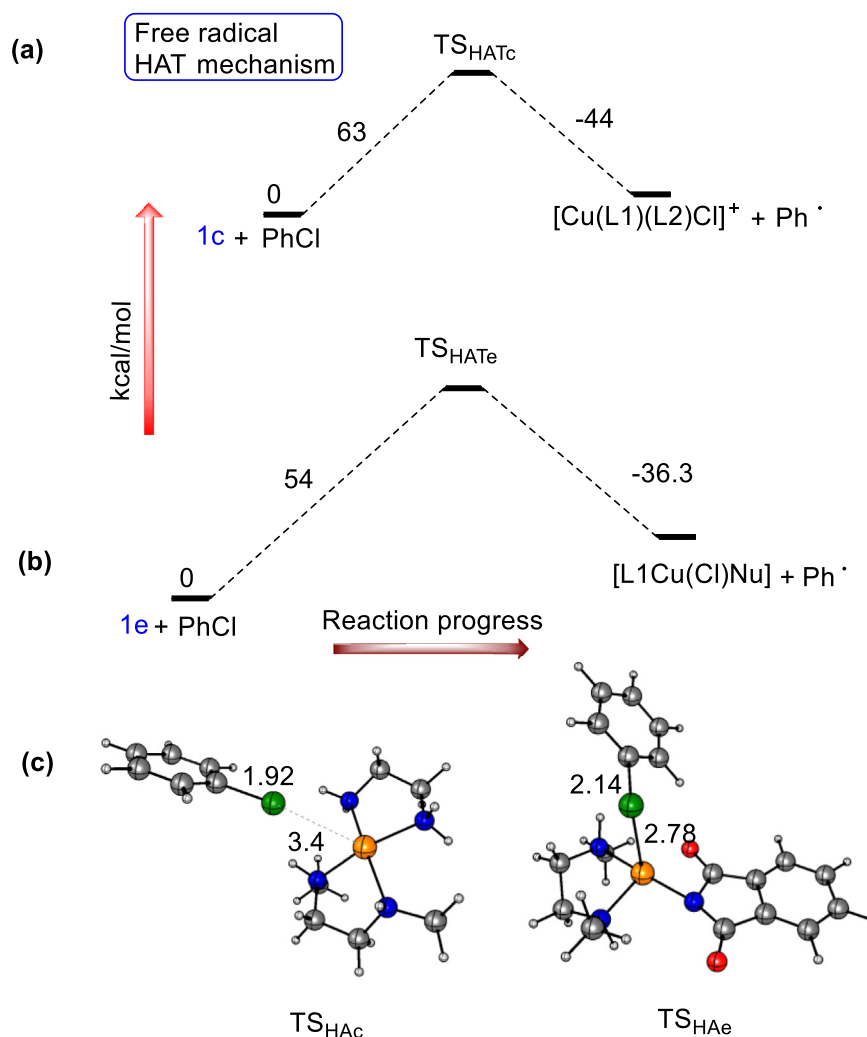
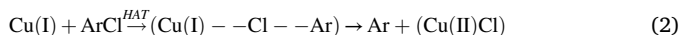


Figure 6. DFT calculated free energy profile for HAT pathways for **1c** (a) and **1e** (b). Optimized geometries (c) of transition states (important bond lengths are shown in Å).

electron transfer) mechanism that delivers anion free radical $[\text{PhCl}]^-$ and Cu(II) has been considered (Figure 5) for DFT studies and it was revealed that formation of $[\text{PhCl}]^-$ and Cu(II) species through SET has very high free energy barrier ($\Delta G = 102\text{--}142$ kcal/mol) for **1a-1f** species. Higher ΔG for SET pathways is attributed to charge separation during the course of reaction and formation of Cu(II) in non-polar solvent toluene.

2.2.2. Free radical halogen atom transfer mechanism



DFT calculations corresponding to halogen atom transfer (HAT) path considering the **1a-1f** species (Figure 6 and Figure 7), indicates that species **1c** (63 kcal/mol) has higher free energy barrier than that of **1e** (54 kcal/mol). HAT path for **1a** and **1b** species has 64 and 61.7 kcal/mol free energy barrier respectively. The higher energy barrier for **1a** and **1f** species is attributed to greater steric hindrance and electronic repulsion respectively. It is in agreement with the earlier reports indicating **1f** as inactive CCS in coupling reactions [22]. However, Copper species **1d** has the lowest ΔG barrier. Nonetheless, **1d** species has a poor presence in the system [25]. HAT paths are relatively more favourable than SET mechanism.

In view of the above, experimental studies were also conducted to ensure that the free radical mechanism is not operative. No side arylation of **L1** and **L2** was observed in the GC-MS analysis of the crude products (see supplementary content, Figures S14 and S17). 4-iodochlorobenzene (**1**) delivered only a single product corresponding to C-I bond activation (reactivity order in the free radical path, C-Cl > C-I) [55]. More reactivity of C-I bond than C-Cl bond is not in favour of free radical mechanism. Furthermore, cyclic ether **3a** was not observed in the coupling reaction of radical clock 1-(allyloxy)-2-chlorobenzene (**3**) (Scheme 4). These results indicate that the coupling reaction does not proceed through a radical pathway.

2.2.3. Oxidative addition -reductive elimination mechanism

Considering **1a-1e** complexes, DFT studies were performed for OA step (Figures 8, 9, and 10 and Table 1). Earlier studies indicate that OA step is rate-determining step in coupling reactions [5, 7]. OA path of arylation reactions proceeds through $^2\eta$ species (Figure 8) and they are key intermediates [25].

DFT studies reveal that species **1e** $[\text{LCuNu}]$ has a very weak interaction with PhCl . Several attempts were made to optimize $^2\eta$ species for **1e** but whatever the input geometry, PhCl pushed away from **1e** (see supplementary content for more detail). It means **1e** species is not able to form $^2\eta$ complex. The free energy barrier for

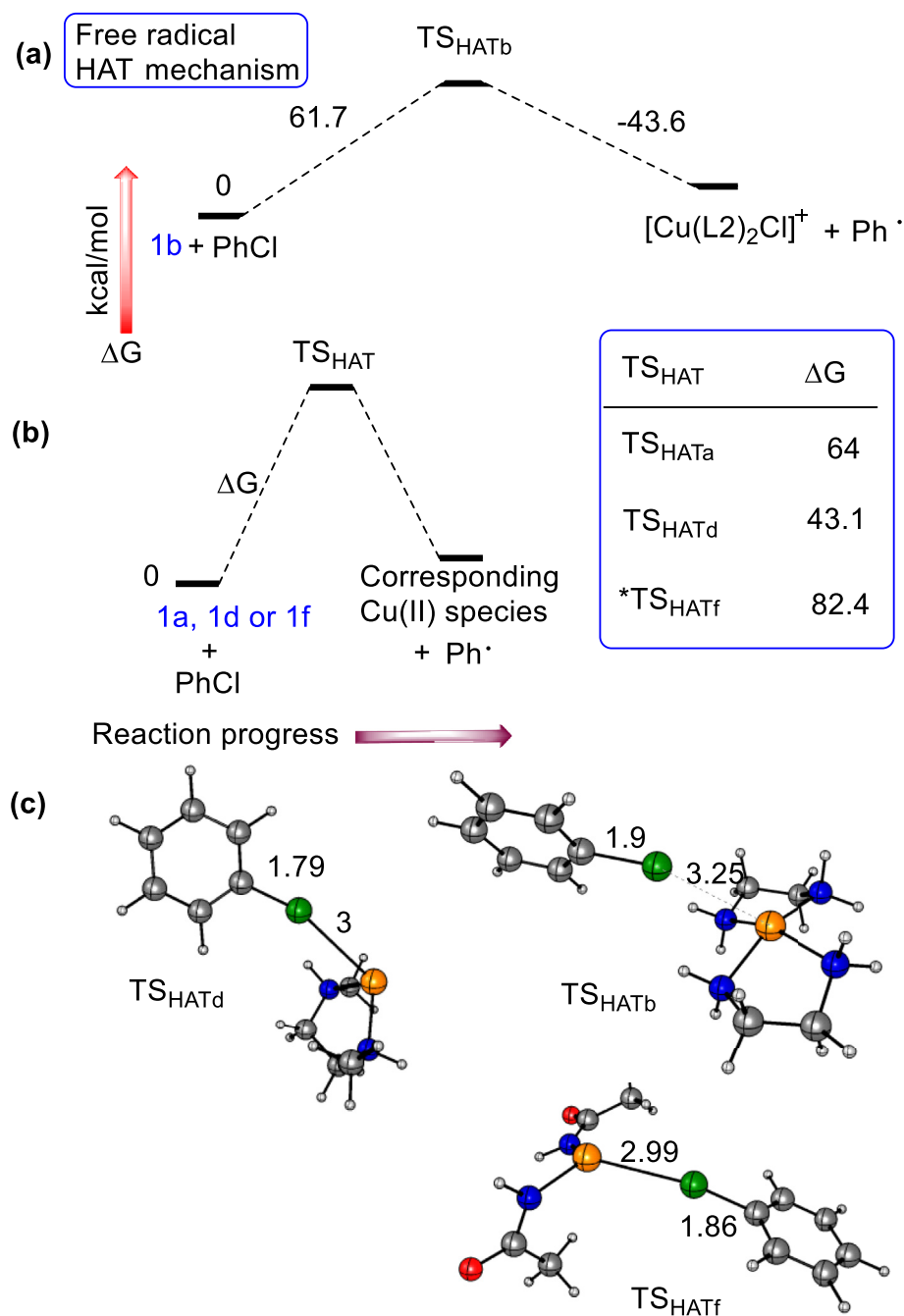


Figure 7. DFT calculated free energy profile for HAT pathways for **1b** (a) **1a**, **1d** and **1f** (b). Optimized geometries (c) of transition states (important bond lengths are shown in Å). *ΔG was calculated for $[\text{Cu}(\text{NHAc})_2]^+$ and PhCl.

TS_{OAe} was found 54.3 kcal/mol (Figure 9). Buchwald and co-workers have suggested that aryl chlorides are less reactive because of poor interaction with copper species and the suggestion seems applicable to **1e** species [50].

Copper complex, **1a**, **1b** and **1e** have higher free energy barrier than **1c** (Table 1) for the formation of respective $^2\eta$ complexes (**1d** has a poor presence in the active system). A careful comparison of ΔG for OA indicates that **1c** is the most suitable species for OA of PhCl (49 kcal/mol). It is the minimum energy barrier amongst the all considered CCS. A comparison of calculated free energies and frontier molecular orbital (FMO) analysis of **1a**, **1b** and **1c** indicates that higher energy barriers for **1a** and **1b** may be due to steric hindrance and electron deficiency

respectively (Figure 4). The **1c** species has balancing of these factors and thus it appears as more appropriate active species. Presence of two diamine ligands (L1 and L2) in the complex, also ensures better solubility and availability of these tetra-coordinated species in the solvent system. It is also evident about the active role of two ligands in the present protocol.

In view of the above, the full catalytic cycle was established by considering the **1c** species (Figure 11). Intermediate $^2\eta$ complex **2c** undergoes OA (ΔG = 4 kcal/mol) by the migration of Cu from C₂ (ortho) to C₁ (ipso). The bond length in **2c** indicates that ortho-position (C2) remains in strong interaction with Cu. TS_{OAe} delivers **3c** species (ΔG = -27 kcal/mol) and it subsequently turns into **4c** (ΔG = -34 kcal/mol) through

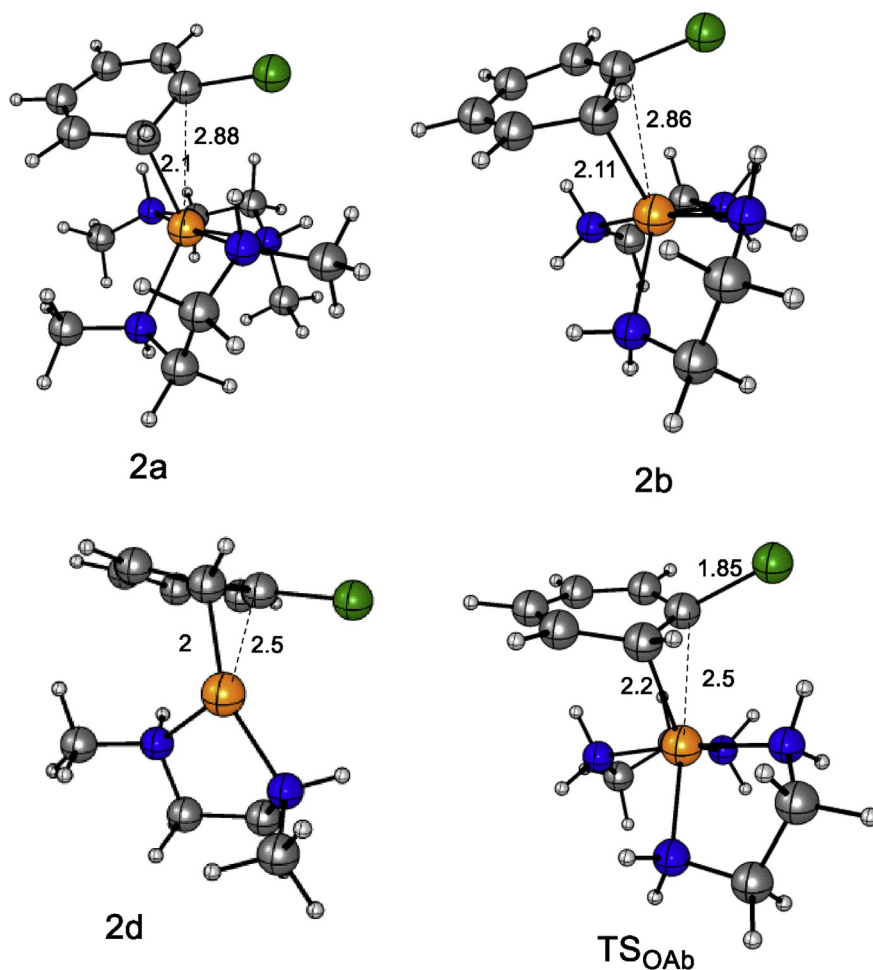


Figure 8. Optimized geometries of 2η complexes and TS_{OAb} . Important bond lengths are shown in (Å).

the displacement of chloride with a nucleophile (Nu^-). Species **4c** undergoes to RE with a free energy barrier for TS_{RE} 16 kcal/mol. Energy

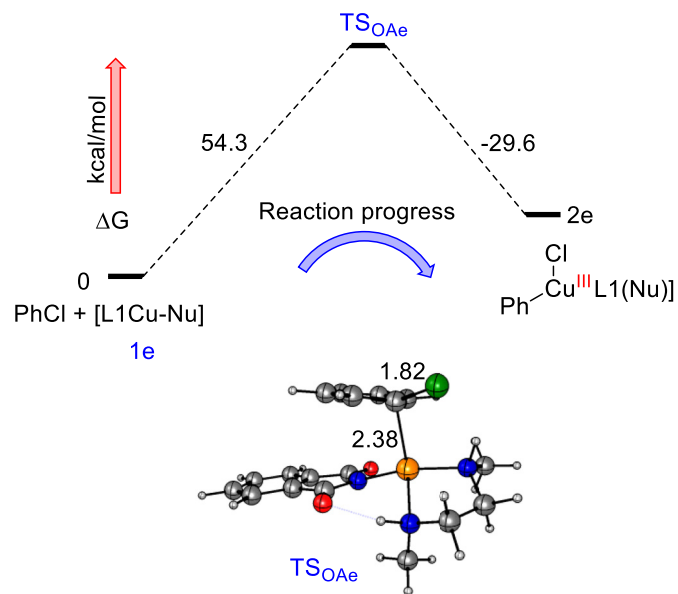


Figure 9. DFT calculated free energy profile for OA of PhCl to **1e** species. Optimized geometry of transition state (important bond lengths are shown in Å).

changes indicate that formation of product through TS_{RE} is energetically highly favourable process ($\Delta G = -53$ kcal/mol).

Notably, SN_2 ionic mechanism of OA was found unfavourable. Total free energy of $[PhCu^{III}(L1)(L2)]^{2+}$ was found more than that of TS_{OAc} . $[PhCu^{III}(L1)(L2)]^{2+}$ was found much higher in free energy (65.68 kcal/mol) compared to **3c**.

Studies indicate that OA is rate-determining step and reaction proceeds through Cu(III) intermediate species. The ΔG values for TS_{OAc} were also calculated with other basis sets and found in good agreement (See supplementary content, Table S01). These results are also supported by

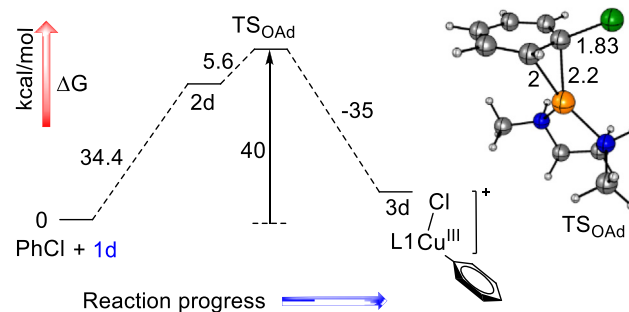


Figure 10. DFT calculated free energy profile for OA of PhCl to **1d** species. Optimized geometry of transition state (important bond lengths are shown in Å).

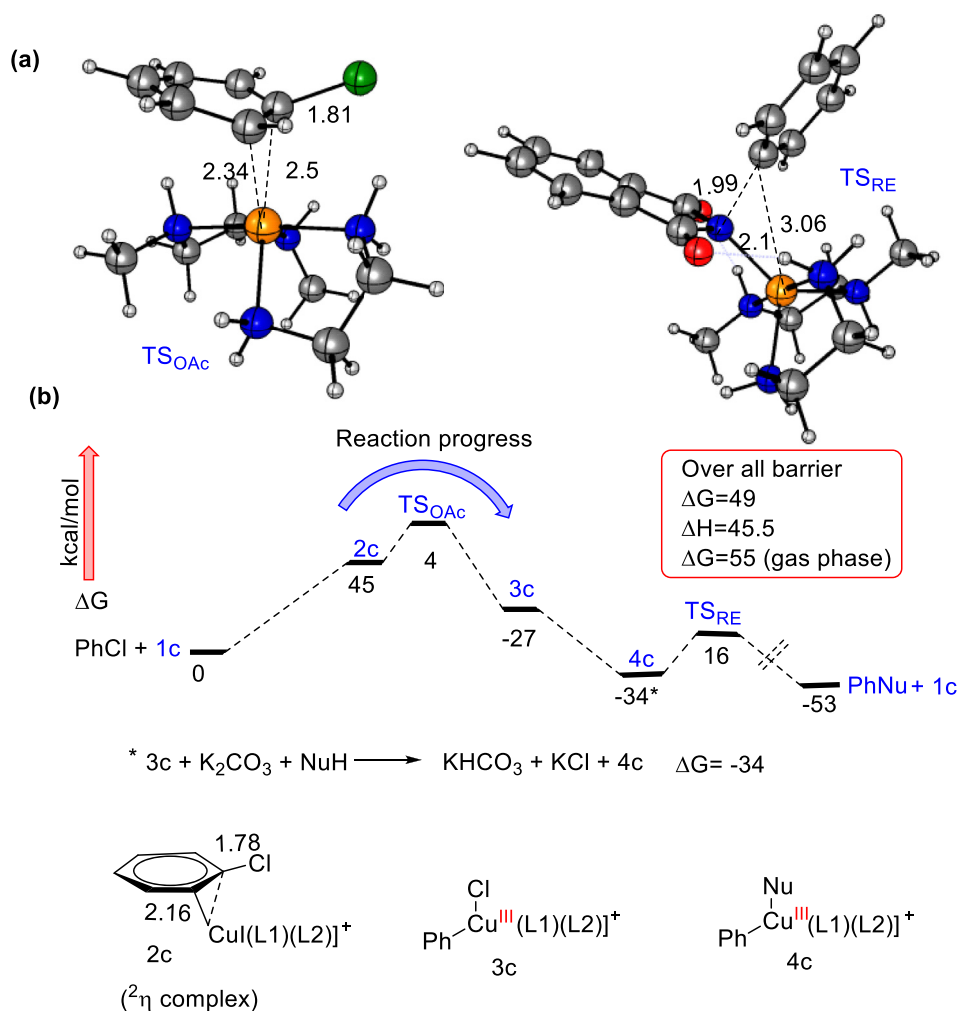


Figure 11. Optimized geometries of transition states (a). DFT calculated free energy profile for OA of PhCl to 1c species (b). For more clarity free energy of incoming and outgoing species are adjusted in every step. The proposed catalytic path for arylation of NuH (phthalimide). Important bond lengths are shown in Å.

Table 1. DFT calculated free energy (ΔG) barrier for oxidative addition.

CCS	ΔG for η^2 complex	ΔG for TS	Overall ΔG for TS
1b	52.2 (2b)	4.2 (TS _{OAb})	56.4
1c	45 (2c)	4 (TS _{OAc})	49
1d ^a	34.4 (2d)	5.6 (TS _{OAd})	40 (73) ^b
1e	Not stabilize	54.3 (TS _{OAc})	54.3
1a	58.1 (2a)	Not calculated	>58.1
1f	Reported as inert catalytic species in OA path (ref. 28 and 31)		

^a 1d species carry +1 charge and have poor solubility. Therefore, it plays little or no role in OA (ref.31). Predicted solubility order- $1e > 1a > 1c > 1b > 1d$. Free energy barrier for OA, $1d > 1a > 1b > 1e > 1c$.

^b ΔG from 1c.

the DFT studies on CuI/oxalic diamide mediated reaction [56] indicating that aryl chlorides follow OA pathway.

In situ and under N_2 atmosphere recorded an electronic spectrum of the reaction solution (supplementary content, Figure S31) also indicates

the appearance of Cu(III) species and absence of Cu(II) ($\lambda_{max} = 500-600$ nm) species [26,57-59].

On the basis of experimental and theoretical results, the possible catalytic cycle has been proposed for coupling reaction of PhCl and

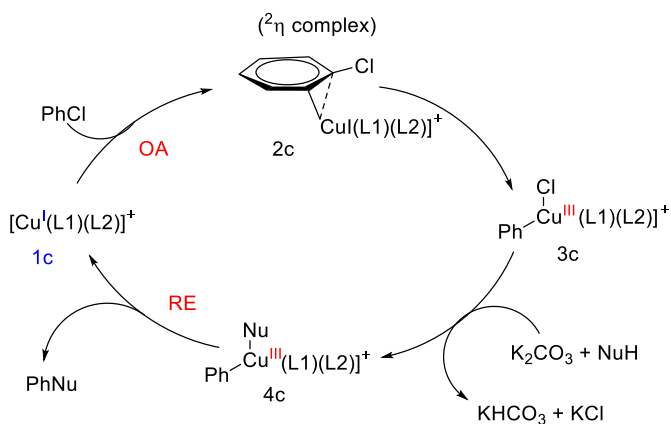


Figure 12. Proposed catalytic cycle.

phthalimide (Figure 12). Transamidation as side reaction was also observed (Scheme 8).

3. Conclusion

As discussed above a simple CuI/ligand pair protocol has been developed for C–N coupling reactions of aryl chlorides and phthalimide. The protocol has also been extended for coupling reactions of arylamines and it gives satisfactory results. Low cost of CuI and commercial availability of the diamine ligands used in the protocol is expected to make the method attractive for industries and academia. On the basis of experimental and theoretical results catalytic cycle has been proposed and it has been suggested that coupling reactions involving aryl chlorides and imides follow OA-RE pathway. The proposed catalytic cycle will further contribute to the studies on mechanistic aspects of these reactions. Since protocol has also been successful in installing two distinct nucleophiles on the substrate by successive C–Br and C–Cl bond activation, therefore, it can be further investigated for the synthesis of molecules of industrial importance.

4. Experimental and computational section

Gaussian 09 package [60] was used for calculations. Hybrid DFT (20% HF exchange) B3LYP (reported reliable for copper) [25,61] using 6–31g (d, p) basis set [62], calculations were performed (at 298 K, in toluene) and solvation model C-PCM with universal force field was employed for solvent toluene (dielectric constant 2.374). Accordingly, geometries were fully optimized without any constraint and single-point energy calculations were performed. Zero-point and thermal corrections to Gibb's free energy were adjusted from harmonic vibrational frequency calculations at 298 K. Berny algorithm was used for Transition state optimization. Transition states were confirmed by single imaginary frequency corresponding to involved atoms. Further, backward and forward direction IRC were performed on transition states. Exclusively, effective core potential (ECP)/LANL2DZ basis set was used for K₂CO₃, KHCO₃, iodine and KI. Orca package 4.0 was also used for a few calculations [63].

Unless and until not specified, all the reactions were performed in toluene and heated to reflux for 16 h under N₂ at 110 °C. Aryl chloride (7.5–12.5 mmol), phthalimide (5 mmol), CuI 5 mol% and base (2.5–20 mmol) were used in reactions. Products were analysed by H-1/C-13 NMR/Mass spectroscopy. (See supplementary content for more experimental and computational details).

Declarations

Author contribution statement

Kamlesh K Gurjar: Conceived and designed the experiments; Performed the experiments.

Rajendra K Sharma: Analyzed and interpreted the data; Wrote the paper.

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The authors declare no conflict of interest.

Additional information

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