



Theoretical Investigations on Deactivation of Copper Catalytic Species in Ullmann Cross Coupling Reactions

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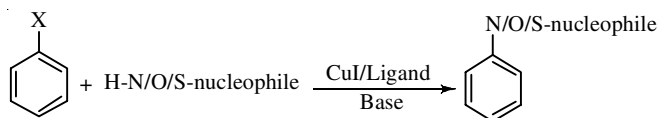
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Copper mediated reactions require higher loading of copper salt and ligand. After few hours, copper active species becomes inactive and further loading of copper salt requires. Various hypothesis proposed in literature, were investigated. DFT studies were performed on more than 20 intermediate species. In present computational studies, it was found that ligation of carbonate base to active copper species is actual reason for deactivation. Carbonate and nucleophile are competitive ligand in these reactions.

Keywords: Cross-coupling, Copper, Carbonate, Homogeneous catalysis, Density functional calculation.

INTRODUCTION

Modern Ullmann coupling reactions [1-4] (Scheme-I) are widely used in organic synthesis and C-hetero atom bond formation [5]. These reactions are essential tool in modern laboratories and industries for the synthesis of bio-active drugs, agro-chemicals and polymers [5,6-8]. Copper mediated reactions have many advantages over palladium mediated reactions, like overall low cost, simple ligands and eco-friendly process [9]. Classical Ullmann coupling reactions had certain limitations, reaction conditions could be revitalized by introduction of N,N/O,O ligands and inorganic bases [10]. However, these reactions could not be fully explored like Buchwald-Hartwig reaction [11] due deactivation of copper catalyst. It has been reported that higher loading of metal salt or more equivalents of ligand are required to sustain it in active form. Higher concentration of base also has adverse effect on catalytic activity [12-14]. Efforts have been made to find out reason of deactivation of catalyst but it could not be well understood [15].



Scheme-I: Modern Ullmann carbon-hetero atom coupling reactions

Recent studies [12,13,15,16] are focused on investigation on the possible reasons of deactivation of copper catalyst and few reports are available in the literature. Following possible

reasons of deactivation of copper catalyst have been discussed in the literature, (i) generation of nucleophile ligated inert $[\text{Cu}(\text{Nu})_2]$ species, (ii) base or ligand promoted disproportionation of Cu(I), (iii) oxidation of Cu(I) in to Cu(II) through aryl free radical formation and (iv) formation of carbonate ligated inert species (Fig. 1). However, any concrete evidence in the support of these claims is not available in the literature. In recent studies base has been considered responsible for deactivation of copper because excess base plays negative role in the catalytic cycle. In view of the above, DFT studies have been carried out to find out possible reasons of deactivation. All the possible deactivation pathways of Cu(I) active species in to inactive species have been considered and theoretical studies have been performed on various possible species to find out the appropriate species which is responsible for deactivation. Moreover, solvent effect on these species has also been addressed.

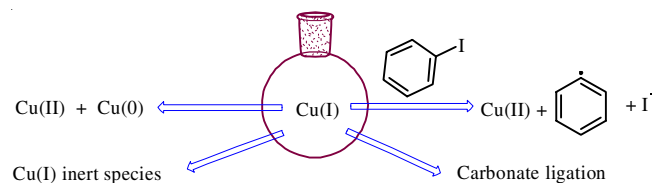


Fig. 1. Possible deactivation pathways of Cu(I) catalyst

COMPUTATIONAL METHODS

Gaussian 09 package was used for calculations [17]. Hybrid DFT (20 % HF exchange), using popular B3LYP/6-311G+(d,p)

level calculations were performed and solvation model CPCM (DMSO solvent) was implemented. Exclusively, effective core potential (ECP)/LANL2DZ basis set was used for copper and iodine and other atom were treated with 6-311G+(d,p). 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.

RESULTS AND DISCUSSION

All the four hypothesis discussed in literature, have been considered for studies. Acetamide as a model nucleophile, ethylene diamine as model ligand, K_2CO_3 as model base and DMSO as model solvent have been selected.

Generation of nucleophile ligated inert $[Cu(Nu)_2]^+$ species: Hartwig and co-workers [18] have demonstrated that species **A** do not participate in reactions. It was proposed that species **A** are inert off cycle species and responsible for deactivation of copper and high demand of Cu/ligand system. Our DFT studies indicate that these inactive species can easily turn into active species **14** (Scheme-II) and these species might not be fully responsible for deactivation of copper catalyst. It is important to mention, species **14** is considered as active species in Ullmann reactions.

Base or ligand promoted disproportionation of Cu(I): Most of the research groups have suggested that disproportionation of Cu(I) into Cu(II) and Cu(0) is possible reason of deactivation

[10,19]. To investigate this hypothesis, species **1-17** (Fig. 2) were considered for studies. It was found that Gibb's free energies required for disproportionation of these species are very high (Fig. 3) and deactivation through this path might not be possible. Generally, coupling reactions of aryl iodides occurs at 25-60 °C and present studies indicates that deactivation path requires higher energy and thus deactivation cannot operate at this temperature. However, species **6** and **7** have lowest energy barriers for disproportionation. Species **7** is highly charged (-3) and presence in system is doubtful, specially in non-polar solvent like toluene. Species **6** is found vulnerable for deactivation ($\Delta G = 68$ kcal/mol).

In view of interesting results, studies were extended for other similar species considering other ligands, those are used in Ullmann reaction (Fig. 4a). Species **6c** ($\Delta G = 75.4$ kcal/mol) is found more sensitive out of **6a-6d** for disproportionation. Study of disproportionation of carbonate ligated Cu(I) species (**6a-6d**) indicates that **6c** has lowest free energy barrier while **6b** has highest. Studies have also been carried out to find the effect of solvent on carbonate ligated these species (Fig. 4b). Interestingly, DMSO is found best choice of solvent to prevent disproportionation of **6**. It has good agreement with reported studies [10]. On the basis of these studies, we can screen the better ligands and solvents. However, free energies are higher for these carbonated ligated species and cannot explain fully the deactivation of copper. Possibly, these do not contribute significantly in deactivation.

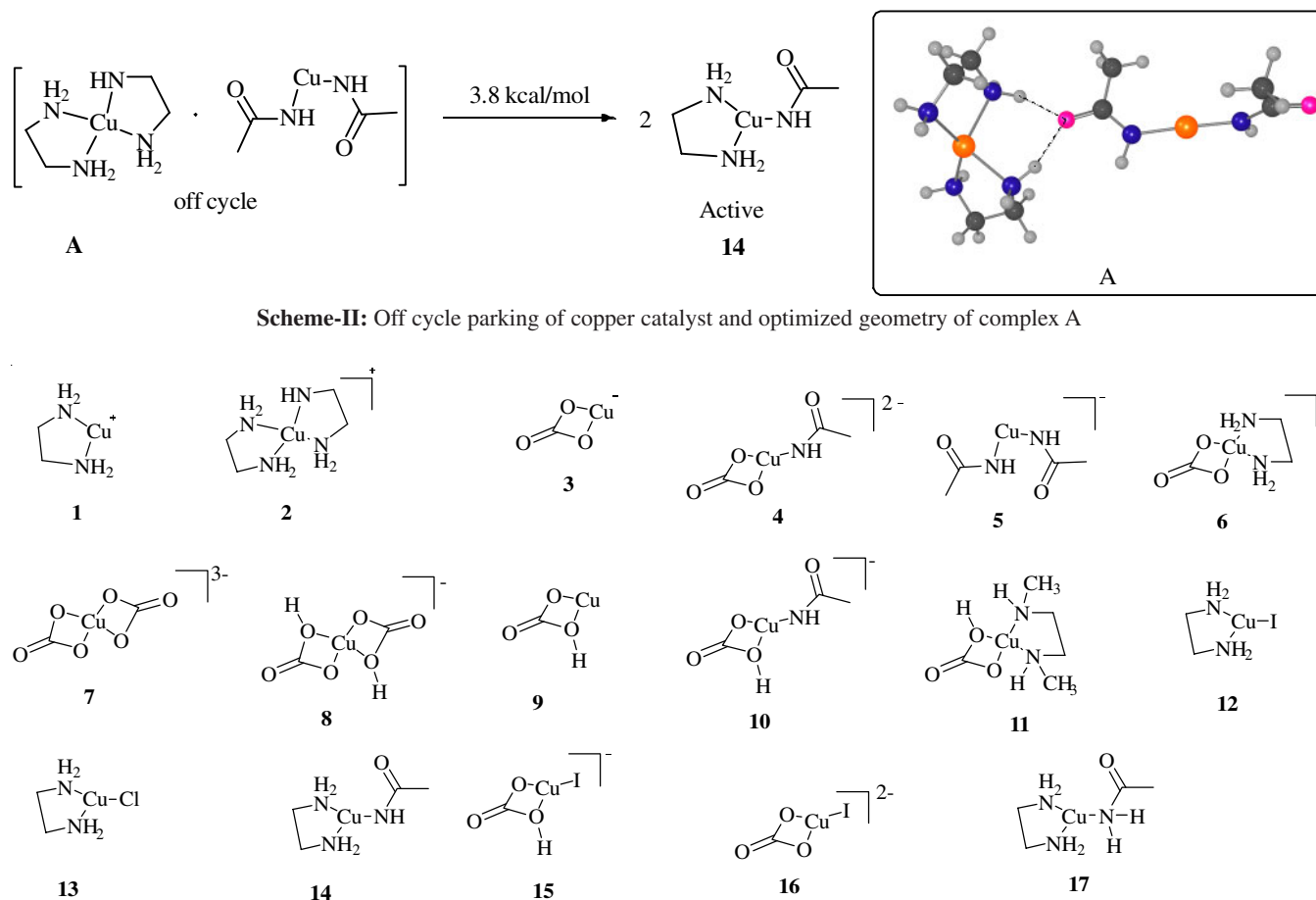


Fig. 2. List of various possible Cu(I) species in cross coupling reactions

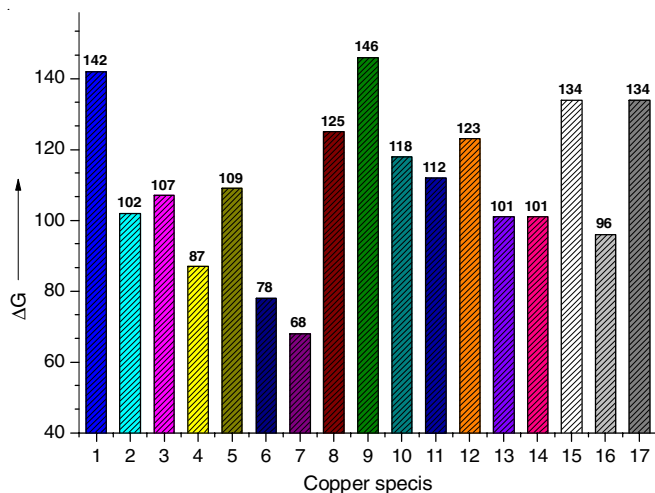


Fig. 3. Computed free energy (kcal/mol) for oxidation of Cu(I) species into the corresponding Cu(II) species

Oxidation of Cu(I) in to Cu(II) through aryl free radical formation: It is reported [14] that benzene is side product in coupling reactions of PhI. It was proposed that benzene forms through trapping of hydrogen from solvent or ligand by phenyl free radical. Cu(II) species can form through free aryl radical formation *via* outer sphere electron transfer (Fig. 5) [20]. How-

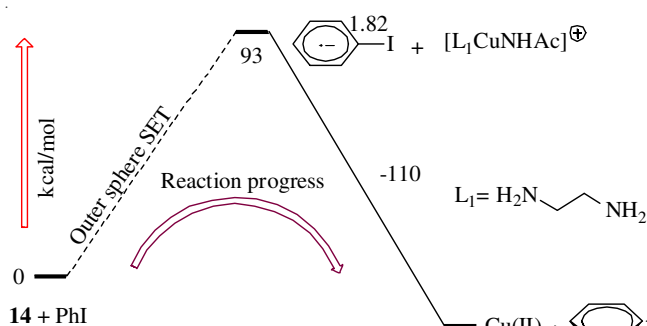


Fig. 5. DFT calculated free energy barrier for free radical SET pathway

ever, these reactions operate through oxidative addition-reductive elimination pathway [12,21]. Calculated free energy barriers for free radical formation are very high (93 kcal/mol). It is much higher than energy barrier reported for OA pathway [18]. Calculated free energy indicates that the oxidation of Cu(I) through free radical pathway is not possible.

Formation of carbonate ligated inert species: Species **14** are active catalytic species in oxidative addition of aryl halides. For the formation of **14**, L_1Cu^+ (**1**) is selected as initial species, it reacts with AcNH_2 and CO_3^{2-} and can turn in to **14** and **6** respectively (**Scheme-III**). Formation of **14** is favoured by -41.29 kcal/mol free energy. Interestingly, the ligation of

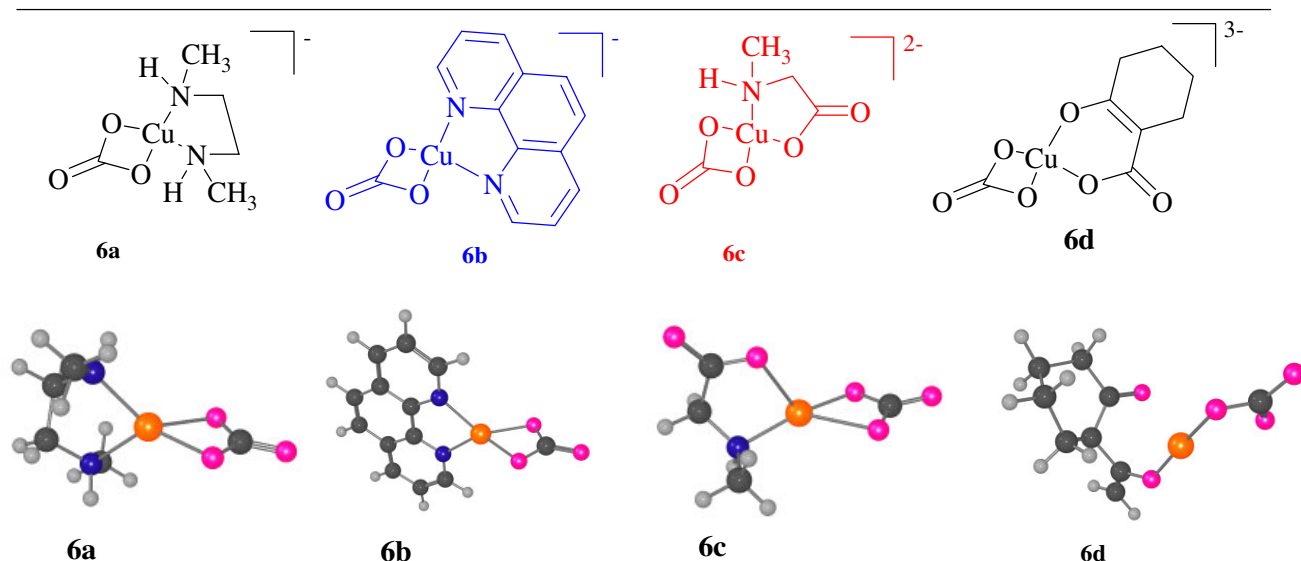
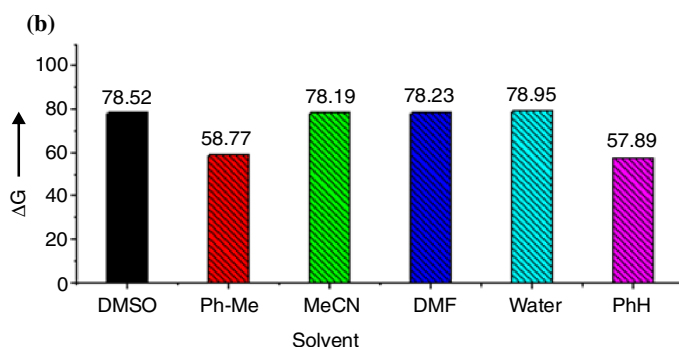
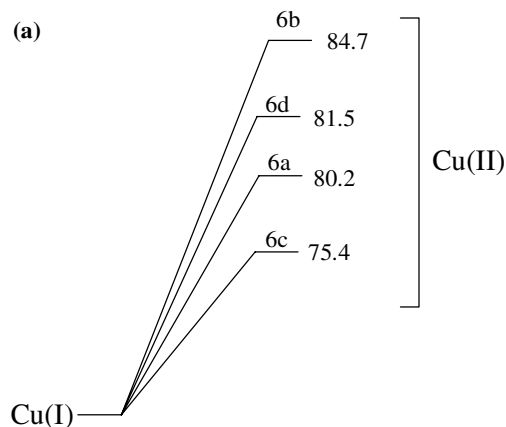
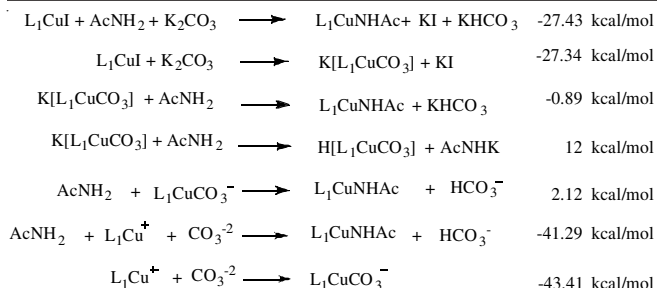


Fig. 4. (a) Free energy (kcal/mol) for oxidation of carbonato ligated Cu(I) species into the corresponding Cu(II) species, (b) Free energy changes in oxidation of **6** in to Cu(II) in different solvents. Optimized geometries of Cu(I) complexes (**6a-6d**)



Scheme-III: Role of carbonate in deactivation of Cu(I), computed free energy for various possible paths

CO_3^{2-} to **1** is more favoured ($\Delta G = -43.41$ kcal/mol) than ligation of AcNH ($\Delta G = -41.29$ kcal/mol). Actually, carbonate and nucleophile (AcNH^-) are competitor ligands. Formation of active catalytic species **14** is slightly unfavoured over formation of inert species **6** ($\Delta G = 2.12$ kcal/mol). This indicates that preferred ligation of carbonate is actual reason of deactivation. Excess carbonate prevent the formation of active species **14**. It has good agreement with our previous studies [12]. Recently, it is also reported that deactivation of catalyst is more significant in fine powdered K_2CO_3 [15]. Activity of catalyst decreases with time. Thus factors like particle size and reaction time, those increase the solubility of K_2CO_3 , deactivate catalyst more effectively.

Conclusion

Herein, we have reported the possible reasons of deactivation of copper catalyst. Carbonate base plays a negative role in process and offers direct competitive ligation to nucleophile. Presence of excess carbonate in system deactivate the catalyst. Ligation of carbonate with $\text{L}_1\text{Cu(I)}$ species is actual reason of deactivation of copper catalyst. These studies provides better understanding of modern Ullmann reaction and open the scope for further experimental studies in this direction.

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