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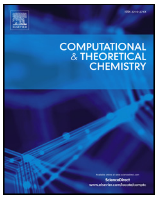

Theoretical investigations on copper catalyzed C—N cross-coupling reaction between aryl chlorides and amines

Khalil Ahmad[a,b,*], Bilal Ahmad Khan[b,c], Bilal Akram[d], Jahanzeb Khan[d], Rashid Mahmood[b], Soumendra K. Roy[e,*]

[a] Department of Chemistry, Mirpur University of Science and Technology (MUST), Mirpur 10250, AJK, Pakistan
[b] Department of Chemistry, University of Azad Jammu and Kashmir, Muzaffarabad 13100, Pakistan
[c] Fachbereich Chemie-Theoretische Chemie, Technische Universität Kaiserslautern, Kaiserslautern 67663, Germany
[d] Department of Chemistry and Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Tsinghua University, Beijing 100084, PR China
[e] Institute of Theoretical and Computational Chemistry, Shaanxi key Laboratory of Catalysis, School of Chemical & Environmental Science, Shaanxi University of Technology, Hanzhong, Shaanxi 723001, PR China

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ABSTRACT

The mechanism of CuI/oxalic diamide catalyzed arylation of amines with chlorobenzene was investigated computationally. CuI/N,N′-bis(2,4,6-trimethoxyphenyl)-oxalamide (BTMPO) system was selected as model catalytic system. On the basis of relative Gibbs free energy, five different possible intermediate Cu^1 complexes were selected for mechanistic studies. Intermediate complexes **Int1–Int3** have a BTMPO ligand deprotonated at one or both NH groups and a benzylamine or benzylamide group coordinated to Cu^1. Intermediate **Int4** has a mono deprotonated BTMPO and an η^2-coordinated chlorobenzene ligand. **Int5** is anionic analogue of **Int4** in which both NH groups of the BTMPO ligand are deprotonated. DFT calculations were carried out for oxidative addition/reductive elimination and single electron transfer mechanisms. **Int2** shows the lowest activation energy barrier (23.5 kcal/mol) for oxidative addition/reductive elimination mechanism. All the intermediates show higher activation energy for single electron transfer mechanism than oxidative addition/reductive elimination mechanism of **Int2**.

1. Introduction

Transition metal catalyzed C—N cross-coupling is a highly useful reaction in synthetic chemistry. Products acquired through this reaction find substantial applications in life sciences, agrochemicals and polymers [1–7]. The pioneering work on C—N cross-coupling was reported by Ullmann and Goldberg in the beginning of 20th century [8–11]. Traditional Ullmann reaction requires stoichiometric amounts of copper and takes place under very harsh conditions such as high temperature and use of strong bases and polar solvents. The shortcomings of traditional Ullmann C—N coupling were overcome by Hartwig [12–14] and Buchwald [15,16] by using palladium salts in combination with chelating ligands. Palladium catalyzed C—N coupling reactions provide excellent yields and are tolerant to different functional groups but they are toxic as well as expensive. Later on Buchwald [17,18] and Taillefer [19,20] were able to successfully employ chelating ligands in copper catalyzed C—N coupling reactions. Copper catalyzed C—N coupling reactions proceed well with aryl iodides and bromides but give poor results with very cheap aryl chlorides [17–23]. Recently Zhou et al. [24] have reported CuI/oxalic diamide catalyst system for the C—N coupling reaction of aryl chlorides with amines. The reaction proceeds under mild conditions, provides good yields and shows excellent tolerance to different functional groups at both aryl chloride and amine moieties. We have carried out computational studies of this reaction which aims to understand the reaction mechanism and hence further improvement in the reaction.

2. Computational details

The density-functional theory (DFT) calculations were performed with the Gaussian 09 suite of programs [25] using B3LYP functional [26–28]. All the geometries were optimized employing 6-31G* basis sets for H, C, N, O and Cl. Cu atom was described with Stuttgart RSC 1997 ECP basis set with 10 core electrons. The transition states were optimized by Berny algorithm [29]. All the ground and transition states were verified by the vibrational frequency analysis. To analyze the

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* Corresponding authors at: Department of Chemistry, Mirpur University of Science and Technology (MUST), Mirpur 10250, AJK, Pakistan (K. Ahmad).
E-mail addresses: khalilahmad77@gmail.com (K. Ahmad), soumya029@yahoo.in (S.K. Roy).

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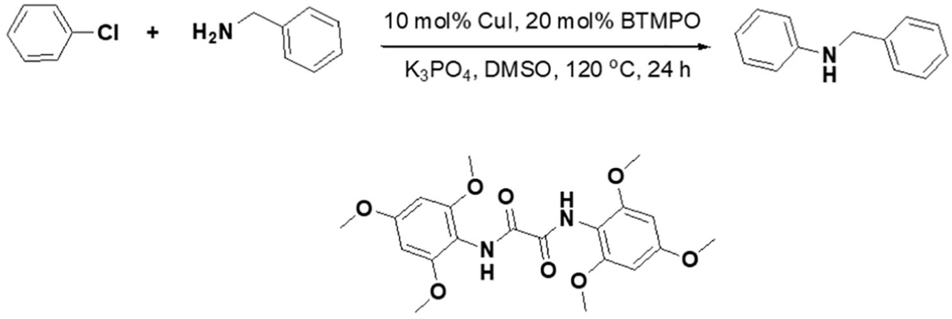

N,N′-bis(2,4,6-trimethoxyphenyl)-oxalamide (BTMPO)

Scheme 1. Reaction conditions for cross-coupling reaction of aryl chlorides with amines [24].

transition states, intrinsic reaction coordinate (IRC) calculations were performed on the transition state geometries. Single-point energy calculations in DMSO were performed on the stationary points with the CPCM solvation model [30–32] to take account of the solvent effects. The single point energy calculations were carried out with 6-311 + G(d, p) basis sets for H, C, N, O and Cl atoms, while for Cu atom, cc-PVTZ basis set was used.

3. Results and discussion

Zhou et al. have carried out cross-coupling reaction of aryl chlorides with amines in the presence of CuI, potassium phosphate and thirty different oxalic amide and oxalic diamide ligands [24]. Among them, N,N′-bis(2,4,6-trimethoxyphenyl)-oxalamide (BTMPO) ligand provided the best yield and was selected for mechanistic studies (see Scheme 1).

3.1. Equilibrium between different intermediates in the reaction solution

According to the experimental and the theoretical studies [33–43], the first step in the Cu^1 catalyzed reactions is the formation of ligated Cu^1 complex (LCu^1) by the coordination of chelating ligands with Cu^1. Relative free energies of different possible copper complexes formed by the reaction of CuI and BTMPO were compared to locate the reactive intermediate in the reaction solution. Similar approach has been adopted for copper catalyzed C—N and C—O coupling reactions [41–43]. Different possible Cu^1 intermediates present in the reaction solution are given in Scheme 2. In intermediate **Int1**, oxalic diamide compound BTMPO, deprotonated at one of the NH groups and a benzylamine ligand is coordinated with Cu^1. The second NH group of BTMPO in **Int1** could also be deprotonated to give **Int2** which is 5.9 kcal/mol more stable than **Int1**. Intermediate **Int2** can isomerize to **Int3** in which one NH group of BTMPO and NH_2 group of benzylamine are deprotonated. **Int3** is 4.4 kcal/mol higher in energy than **Int2**. Chlorobenzene in the reaction solution can coordinate with Cu^1 through η^2-linkage replacing benzylamine ligand from **Int1** and **Int2** to yield **Int4** and **Int5** respectively. **Int4** and **Int5** are 17.0 and 13.4 kcal/mol higher in energy than **Int1** and **Int2** respectively.

The optimized geometries of **Int1**–**Int5** are shown in Fig. 1. In **Int1**, Cu—N1 and Cu—N3 bond lengths are 1.89 and 1.95 Å respectively. Cu and O2 atoms are at a distance of 2.35 Å. Cu—N bond lengths of Cu—N1, Cu—N2 and Cu—N3 bonds in **Int2** are in the range of 1.90–2.15 Å. The Cu—N bond lengths of Cu—N1 and Cu—N3 bonds of **Int3** are 1.93 and 1.86 Å, respectively, while Cu and O2 atoms are at a distance of 2.67 Å. In **Int4** Cu—N1 and Cu—O2 bonds are 1.95 and 2.08 Å, respectively, while the bond lengths of Cu—C1 and Cu—C2 bonds are in the range of 2.08–2.09 Å. The Cu—N1 and Cu—N2 bonds in **Int5** are 1.97 and 1.96 Å, respectively. The bond lengths of Cu—C1 and Cu—C2 bonds are in the range of 2.06–2.09 Å.

3.2. Activation of C—Cl bond of chlorobenzene

Copper catalyzed activation of carbon-halogen bond of aryl iodides and aryl bromides has been investigated experimentally [33–35] and also theoretically [36–43] by many research groups. Oxidative addition/reductive elimination mechanism and single electron transfer mechanism have been the focus of the most of the theoretical studies. All [37–43] except one [36] theoretical studies favor oxidative addition/reductive elimination mechanism for the activation of carbon-halogen bond in aryl iodides and bromides. We have investigated the oxidative addition/reductive elimination and single electron transfer mechanisms for the activation of C—Cl bond of chlorobenzene catalyzed by CuI/BTMPO catalytic system.

3.2.1. Oxidative addition/reductive elimination mechanism

Copper complexes **Int1**–**Int5** could undergo oxidative addition reaction with chlorobenzene. The calculated activation energies for oxidative addition step are given in Table 1. The benzylamine coordinated complex **Int2** is energetically the most favorable intermediate (Scheme 2), it shows 23.5 kcal/mol activation energy for the oxidative addition reaction. **Int3** is energetically the next favorable intermediate with + 4.4 kcal/mol energy relative to **Int2**. Activation energy for the oxidative addition reaction of **Int3** is 32.9 kcal/mol and the overall barrier relative to **Int2** is 37.3 kcal/mol. Overall activation energy barrier for oxidative addition reaction of **Int1**, **Int4** and **Int5** is 35.1, 35.8 and 25.4 kcal/mol respectively. Benzylamine coordinated intermediate **Int2** shows the lowest activation energy for the oxidative addition reaction and was selected for further calculations.

The energy level diagram for oxidative addition/reductive elimination mechanism of **Int2** is given in Fig. 2. Oxidative addition of chlorobenzene with **Int2** produces intermediate **Int2-M1.** Activation energy for the oxidative addition reaction is 23.5 kcal/mol. In **Int2-M1**, there is coordinate covalent bond between NH_2 group of benzylamine and Cu^1. One proton of NH_2 group must eliminate as HCl to produce **Int2-M2** which has suitable linkage for reductive elimination reaction. The base present in the solution facilitates the extraction of proton. Formation of **Int2-M2** is exothermic by 24.5 kcal/mol. **Int2-M2** could undergo reductive elimination reaction to yield C—N coupling product; the activation energy for the reductive elimination reaction is only 6.3 kcal/mol. Therefore the oxidative addition of chlorobenzene is the rate determining step. The overall reaction is exothermic by 61.4 kcal/mol.

Optimized geometries of **Int2-TS$_{OA}$**, **Int2-M1**, **Int2-M2** and **Int2-TS$_{RE}$** are given in Fig. 3.

3.2.2. Single electron transfer mechanism

Intermediates **Int1**–**Int5** can transfer single electron to chlorobenzene. Transfer of electron can take place either in a stepwise manner or in a concerted manner [36]. For stepwise electron transfer, the activation energy is estimated by outer sphere Marcus-Hush model