

# Mechanistic Views on First-row Earth-Abundant Transition Metal Catalyzed Ullmann-type O-Arylation Reactions

Parvathi Santhoshkumar<sup>§</sup>, C. Rajalakshmi, Lydia Elizabeth Mathews, Rehin Sulay, and Vibin Ipe Thomas\*

<sup>§</sup>SCS-DSM award for best poster in Computational Chemistry

**Abstract:** Transition metal-catalyzed reactions have attracted much attention in synthetic organic chemistry due to their important role in the formation of C-heteroatom bonds. Ullmann coupling has risen in prominence in recent decades owing to its utilization in the synthesis of biaryl ethers found in a wide range of natural products together with biologically essential molecules, including antibiotics and major industrial polymers. In this article we provide the current understanding of the theoretical aspects of the underlying mechanism of the Ullmann-type O-arylation reaction.

**Keywords:** Density Functional Theory · Mechanistic studies · O-arylation · Transition-metal catalysis



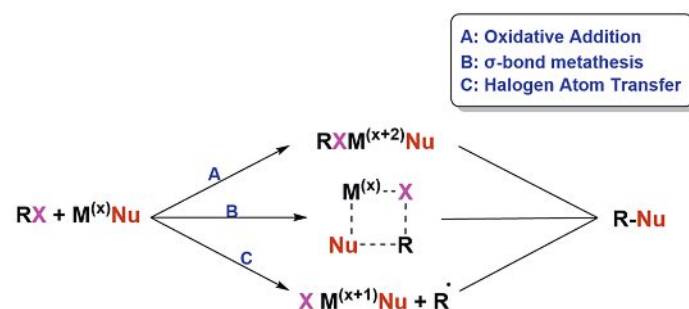
**Parvathi Santhoshkumar** obtained her Bachelor's and Master's degrees in Chemistry from CMS College Kottayam, (Mahatma Gandhi University) Kerala, India in 2020 and 2022 respectively. She received the prestigious Dr. Thomas award for the best outgoing postgraduate student from CMS college Kottayam in 2022. Currently she is working as a project assistant in the research group of Dr. Vibin Ipe Thomas at

CMS College Kottayam, Kerala, India.

## 1. Introduction

Transition-metal catalyzed O-arylation reactions have made a pivotal momentum in synthetic organic chemistry. This is attributed to the construction of carbon–oxygen bonds which are paramount structural building blocks in a diverse range of compounds from agrochemicals to pharmaceuticals.<sup>[1]</sup> During the early 20<sup>th</sup> century, the seminal work of Ullmann on carbon–carbon cross-coupling reactions induced an upsurge in transition-metal-catalyzed cross-coupling reactions by making use of copper as the catalyst. However, these reactions remain confined to research labs apart from the large-scale synthesis of vital organic scaffolds. This sub-optimal potential of cross-coupling reactions is attributed to the harsh reaction conditions necessitated by the copper catalyst including high temperature, a stoichiometric amount of copper, long reaction times, *etc.* Nonetheless, after the discovery of the classical Ullmann coupling reaction, several endeavors have been devoted to cross-coupling reactions, such as the introduction of ancillary bidentate ligands to overcome the barriers of copper catalysis. The constant efforts for more adequate strategies have also paved the way to palladium-catalyzed C-heteroatom cross-coupling reactions like Buchwald-Hartwig amination reactions. Though palladium-based catalysis was advantageous, these

methods suffer from toxicity and high cost. The search for more efficient Ullmann-type cross-coupling reactions gave rise to several ground-breaking eco-friendly, earth-abundant, economical strategies through the exploitation of first-row transition metals such as iron, manganese, cobalt, zinc, *etc.*<sup>[2]</sup> A thorough understanding of the underlying mechanism of these chemical transformations is imperative in obtaining a clear insight regarding the nature of the reaction, thereby aiding in the design of better reaction protocols. Generally, there are three mechanisms that have been proposed for the Ullmann-type O-arylation reactions which include the non-radical pathways such as oxidative addition–reductive elimination (OA-RE),  $\sigma$ -bond metathesis, and the radical pathways incorporating the halogen atom transfer (HAT) mechanisms (Scheme 1). Recently, quantum chemical methods employing density functional theory (DFT) have emerged as an efficient tool for predicting the delineated mechanism of chemical reactions, thus generating a spur in computational transition-metal catalysis. Thus, in this article, we intend to provide detailed mechanistic aspects of the Ullmann-Type O-arylation reactions catalyzed by earth-abundant first-row transition metals.



Scheme 1. The plausible mechanistic pathways for O-arylation reactions.

\*Correspondence: Dr. V. I. Thomas, E-mail: vibin@cmscollege.ac.in  
Department of Chemistry, CMS College Kottayam (Mahatma Gandhi University) Kerala, India

## 2. Oxidative Addition-Reductive Elimination Mechanism

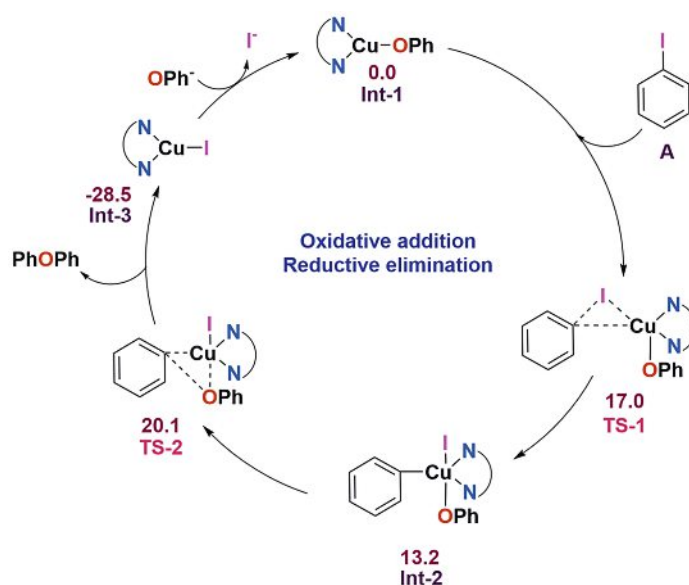
The oxidative addition-reductive elimination pathway, a two-electron process, was reported to be the underlying mechanism for several cross-coupling reactions. In this well-known mechanism, the oxidation state of the metal changes by two during the oxidative addition step. The metal regains the low valent state by releasing the cross-coupled product in a reductive elimination step.

In 2002, Buchwald pioneered a momentous strategy in the establishment of C–X (X = O and N) coupled products by exploiting copper as a catalyst using  $\beta$ -amino alcohols.<sup>[3]</sup> Furthermore, ligand selectivity was also demonstrated through the utilization of 1,10-phenanthroline and  $\beta$ -diketone as the ligands. The formation of the C–O coupled moiety was accompanied by the inclusion of 1,10-phenanthroline while contrasting results were obtained when  $\beta$ -diketone was incorporated which prompted the formation of a C–N coupled product. To shed further light on the observed selectivity of the Ullmann-type coupling reaction, several groups thoroughly investigated the underlying mechanism for the C–O coupling process.

After the discovery of the HAT mechanism for the copper-catalyzed O-arylation of methanol, Liu and coworkers revisited the reaction and proposed an alternative oxidative addition-reductive elimination (OA-RE) pathway using  $\text{NH}_2(\text{CH}_2)_3\text{OH}$ , a  $\beta$ -amino alcohol as the substrate.<sup>[4]</sup> The theoretical discussion of Liu described the oxidative addition of aryl halide to the Cu center as the rate-limiting step for O-arylation instead of the aryl activation step as proposed by the previous group. In this coupling process, a three-coordinated deprotonated alcohol-coordinated Cu(I) complex was found to be the active catalyst owing to its higher stability due to the presence of the strongly acidic alcohol moiety for the C–O coupling process. The coordination of an aryl halide to the copper center further forms an  $\eta$ -2 coordinated copper complex which then undergoes oxidative addition via a three-centered transition state to form a five-coordinated Cu(III) intermediate with the 1,10-phenanthroline ligand. The O-coordinated complex undergoes reductive elimination seamlessly with a relatively low barrier via a three-centered transition state to form a final C–O coupled product with the 1,10-phenanthroline ligand. Further, the computed activation barrier for the radical pathway, HAT was found to be exceedingly high, contradictory to previous studies. Similarly, a high activation barrier was obtained for the  $\sigma$ -bond metathesis mechanism.

Later on, in 2017 Andrada *et al.* demonstrated the favorability of the oxidative addition-reductive elimination mechanism for the copper-catalyzed C–O cross-coupling reaction with the aid of the DFT technique.<sup>[5]</sup> As shown in Scheme 2, a three-coordinated T-shaped Cu(I) complex served as the active catalyst for the reaction. This complex endures oxidative addition on the introduction of iodobenzene via a three-centered transition state (TS-1) with a barrier of 17.0 kcal/mol generating a five-coordinated Cu(III) complex. Further, the Cu(III) complex undergoes a facile reductive elimination by surmounting a relatively low barrier of 7.5 kcal/mol with the release of a C–O coupled product. On the inclusion of a dispersion correction, the barrier height for the OA-RE was enormously reduced, although in its absence, both HAT and OA-RE showed comparable energies. Besides, the authors recomputed the O-arylation using methanol as the substrate. However, the activation barrier was lowered to 25 kcal/mol with the inclusion of dispersion correction for the oxidative addition-reductive elimination pathway.

Recently, Chen *et al.* grabbed the attention of the scientific community by bringing about an efficient breakthrough in organic synthesis through the development of a photoinduced radical-involved catalytic asymmetric intermolecular copper-catalyzed C–O cross-coupling protocol.<sup>[6]</sup> In this work, oxime esters and 1,3-dienes were employed as the substrates. To understand the

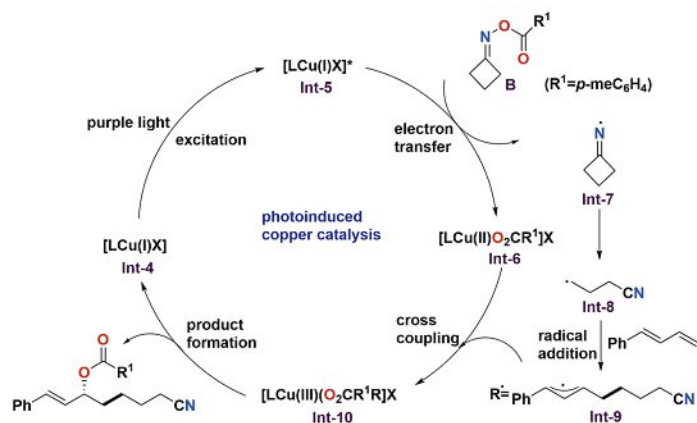


Scheme 2. The plausible oxidative addition-reductive elimination pathway for the copper catalyzed C–O cross-coupling reaction by Andrada *et al.*<sup>[5]</sup>

underlying mechanism of the C–O cross-coupling reaction they carried out a theoretical investigation with the aid of DFT methods. Scheme 3 describes the mechanism suggested by the authors. As shown in Scheme 3, the reaction is initiated by the photoexcitation of the copper complexes upon irradiation by a purple LED. Further, the photoexcited triplet copper species undergoes an oxidative quenching with a redox-active radical precursor, oxime ester (**B**) via a single electron transfer, forming a radical (**Int 7**) along with a Cu(II) species in the ground state (**Int 6**). Moreover, the generation of the allyl radical from **B** was accompanied by three crucial elementary steps; N–O bond cleavage,  $\beta$ -C–C bond cleavage, and finally the radical attack. In the first step, the N–O bond cleavage takes place by overcoming an activation barrier, 7.1 kcal/mol, generating a radical. Moreover, the spin density analysis showed the localization of spin density on the nitrogen of the N–O bond cleaved intermediate. Thus, **B** generates an iminyl radical along with the release of carboxylate anion ( $\text{R}^1\text{CO}_2^-$ ). The iminyl radical further undergoes a  $\beta$ -C–C bond cleavage, thereby giving rise to a cyanoalkyl radical (**Int 8**) by surmounting an activation barrier of 8.5 kcal/mol. This radical undergoes an easy attack of the 1-phenylbutadiene via a transition state with a relatively low energy barrier (5.1 kcal/mol) to generate the desired allyl radical (**Int 9**). Subsequently, the allyl radical gets coordinated to the copper(II) complex in two ways, either via the coordination of the C2 or C4 carbon of the radical intermediate to furnish the  $\pi$ -allyl/benzyl Cu(III) complex. Then, both the Cu(III) complexes undergo reductive elimination and afford the C–O coupled product along with the regeneration of the ground state Cu(I) complex. However, the reductive elimination of the  $\pi$ -allyl copper(III) complex is favored owing to the stable  $\pi$ -allyl copper interaction.

## 3. $\sigma$ -Bond Metathesis Mechanism

In this mechanism, the oxidation state of the metal remains intact during the reaction. Here, cleavage of the C–I bond of the aryl halide takes place with simultaneous C–O bond formation. However, this concerted pathway was reported as the most unfavorable mechanism for the Cu-catalyzed C–O cross-coupling reactions in literature. Recently, our group has revealed a  $\sigma$ -bond metathesis mechanism as a favorable pathway for the cobalt-catalyzed C–O cross-coupling reaction employing L-valine as the ligand.<sup>[7]</sup> Together with the identification of a four-coordinated high spin active catalyst, (**Int 11**) based on DFT studies, the mech-



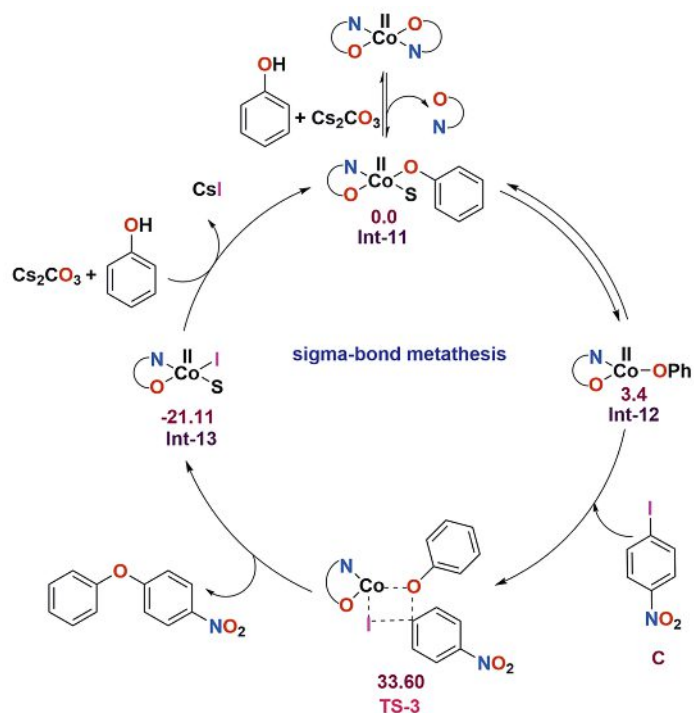
Scheme 3: The plausible catalytic cycle for the copper-catalyzed photo-induced radical involved C–O cross-coupling reaction by Chen *et al.*<sup>[6]</sup>

anistic pathway for the aforementioned cross-coupling reaction reported by our group is shown in Scheme 4. In this proposed mechanism, the active catalyst (**Int 11**) is formed *via* the exchange of one of the valine ligands in the pre-catalyst with phenoxide and through the explicit coordination of the solvent molecule acetonitrile. The active catalyst (**Int 11**) then expels the coordinated solvent molecule and prompts the formation of a three-coordinated cobalt (II) complex (**Int 12**). The **Int 12** reacts with the aryl halide *via* a four-centered transition state followed by the release of the C–O coupled product with an activation barrier of 33.60 kcal/mol which matches well with the experimental conditions. Thus,  $\sigma$ -bond metathesis becomes the most promising mechanism for the cobalt-catalyzed O-arylation reaction. We have also computed the activation barrier for other commonly proposed radical mechanisms. However, these pathways were kinetically prohibited owing to the high barrier. Moreover, manganese also demonstrated its exceptional ability in the O-arylation reaction under ligand-free conditions.<sup>[8]</sup> Similar to the cobalt-catalyzed arylation reaction, the underlying mechanism for the ligand-free Mn(II) catalyzed C–O coupling reaction was also expected to proceed *via* a four-membered transition state owing to the higher oxidation state of the metal center and the stable d5 electronic configuration. Extensive theoretical studies on the aforementioned reaction are progressing in our research lab.

#### 4. Halogen Atom Transfer Mechanism

Among the radical pathways, the halogen atom transfer pathway entails the transfer of a halogen atom from the electrophilic coupling partner aryl halide to the metal center and leads to the formation of a radical intermediate. Subsequently, the phenyl radical generated attacks the oxygen of the phenoxy group in the metal complex to furnish the cross-coupled product *via* a reductive elimination step.

A mechanistic investigation of the copper-catalyzed C–O coupling reaction using iodobenzene and alkyl alcohol was performed by Houk and coworkers with the aid of DFT methods.<sup>[9]</sup> This was considered to be the earliest computational investigation of the Ullmann-type O-arylation reaction. The theoretical studies seemed to confirm that the O-arylation reaction proceeds *via* a halogen atom transfer radical pathway with the assistance of an electron-poor 1,10-phenanthroline ligand. In this proposed mechanism, the transfer of a halogen atom from the aryl halide to the copper (I) center of the active catalyst initiates the reaction and leads to the formation of a Cu(II) intermediate and a phenyl radical. The resulting phenyl radical further attacks the phenoxy oxygen atom of the Cu(II) intermediate. The activation barrier for the aforementioned mechanism was estimated with the help of Saveants model. The low electrophilicity of 1,10-phenanthroline



Scheme 4. The plausible  $\sigma$ -bond metathesis pathway for the cobalt (II) catalyzed C–O coupling reaction by Kundu *et al.*<sup>[7]</sup>

promoted the C–O coupling between the reactants. The authors ruled out other possible reaction pathways for Ullmann-type Coupling reactions owing to the calculated higher activation barriers. However, recent studies have revealed oxidative addition-reductive elimination as the favorable mechanistic pathway for the aforementioned reaction which has been already discussed in section 2.

Further, Zhang *et al.* in 2012 performed a systematic study on the O-arylation reaction employing bromobenzene and phenol as the model substrates.<sup>[10]</sup> This study revealed the HAT mechanism to be the most favorable plausible mechanism for the O-arylation reaction in both polar and non-polar solvents. Fig. 1 illustrates the proposed HAT mechanism for the C–O coupling reaction in which a concerted breaking of the strong Ph–Br bond and formation of the Cu–Br bond and a phenyl radical takes place. The phenyl radical further attacks the oxygen of the phenoxy to afford the final C–O coupled product along with the regeneration of the active catalyst.

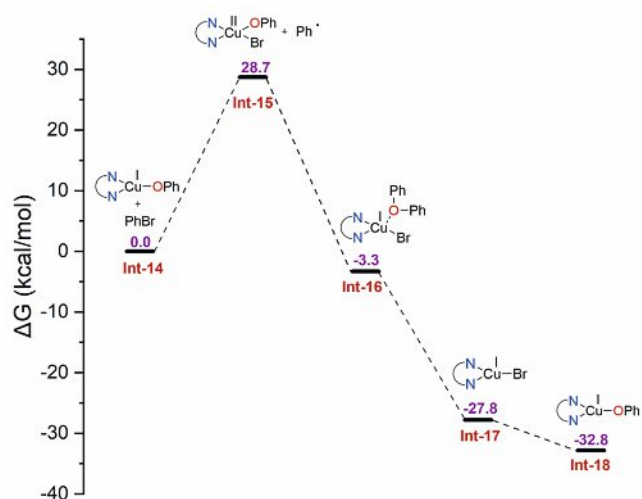


Fig. 1. The free energy profile for the copper-catalyzed C–O coupling reaction *via* the halogen atom transfer pathway by Zhang *et al.*<sup>[10]</sup>

## 5. Conclusions

This article describes the mechanistic details governing the transition-metal catalyzed Ullmann-type O-arylation reactions from a theoretical perspective. The puzzling mechanisms of the Ullmann-type O-arylation reactions are concerned with the nature of the substrates, ligands, base *etc.* Moreover, the computational methodology should be benchmarked while investigating mechanistic studies in organic transformation. Among the commonly proposed mechanisms, the non-radical oxidative addition-reductive elimination and the radical halogen atom transfer mechanisms are found to be the most favorable mechanism for the O-arylation reactions. Recently,  $\sigma$ -bond metathesis was also reported as a favorable mechanism for Ullmann-type O-arylation reactions employing eco-friendly transition metal catalysts. We hope that this review will provide a clear insight into the developments made so far, thereby aiding in exploring its untapped potential.

## Acknowledgements

The authors thank the Swiss Chemical Society and DSM for the best poster award. C.R and R.S thank university grants commission for a senior research fellowship.

Received: February 5, 2023; revised: February 28, 2023

- [1] H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K. Itoh, *Organometallics* **1989**, *8*, 846, <https://doi.org/10.1021/om00105a047>.
- [2] K. R. Rohit, S. Radhika, S. Saranya, G. Anilkumar, *Adv. Syn. Catal.* **2020**, *362*, 1602, <https://doi.org/10.1002/adsc.201901389>.
- [3] G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3703, <https://doi.org/10.1021/ol026655h>.
- [4] H.-Z. Yu, Y.-Y. Jiang, Y. Fu, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 18078, <https://doi.org/10.1021/ja104264v>.
- [5] D. M. Andrada, S. M. Soria-Castro, D. A. Caminos, J. E. Argüello, A. B. Peñéñory, *Catalysis* **2017**, *7*, 338, <https://doi.org/10.3390/catal7120388>.
- [6] J. Chen, Y.-J. Liang, P.-Z. Wang, G.-Q. Li, B. Zhang, H. Qian, X.-D. Huan, W. Guan, W.-J. Xiao, J.-R. Chen, *J. Am. Chem. Soc.* **2021**, *143*, 13382, <https://doi.org/10.1021/jacs.1c06535>.
- [7] D. Kundu, M. Tripathy, P. Maity, B. C. Ranu, *Chem. Eur. J.* **2015**, *21*, 8727, <https://doi.org/10.1002/chem.201500058>.
- [8] K. R. Rohit, S. Saranya, N. A. Harry, G. Anilkumar, *ChemistrySelect* **2019**, *4*, 5150, <https://doi.org/10.1002/slct.201901031>.
- [9] G. O. Jones, P. Liu, K. N. Houk, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 6205, <https://doi.org/10.1021/ja100739h>.
- [10] S. Zhang, Z. Zhu, Y. Ding, *Dalton Trans.* **2012**, *41*, 13832, <https://doi.org/10.1039/c2dt31500a>.

## License and Terms



This is an Open Access article under the terms of the Creative Commons Attribution License CC BY 4.0. The material may not be used for commercial purposes.

The license is subject to the CHIMIA terms and conditions: (<https://chimia.ch/chimia/about>).

The definitive version of this article is the electronic one that can be found at <https://doi.org/10.2533/chimia.2023.246>