

MECHANISTIC INSIGHT INTO LIGAND FREE COPPER CATALYZED SUZUKI CROSS-COUPLING REACTION USING DENSITY FUNCTIONAL THEORY

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ABSTRACT

Suzuki coupling reaction is a powerful tool that enable the construction of new C-C bonds efficiently. Owing to the toxic nature of traditional palladium catalysts, copper based catalysts are identified as greener and cheaper alternatives in Suzuki reactions. Unlike palladium catalysts, deeper insights into copper catalyzed Suzuki coupling reactions are still in dearth. A Computational study using Density Functional Theory (DFT) by employing Becke3LYP (B3LYP) functional is carried out for exploring the mechanism of ligand free copper catalyzed Suzuki coupling of aryl boronic acids with alkynyl bromides. Our calculations indicate that the reaction proceeds via an initial transmetalation step followed by a concerted oxidative addition-reductive elimination. Instability of Cu(III) species reduces activation barrier for the coupling. Cu(I) species is identified as the active catalyst and the overall reaction is exergonic in nature.

INTRODUCTION

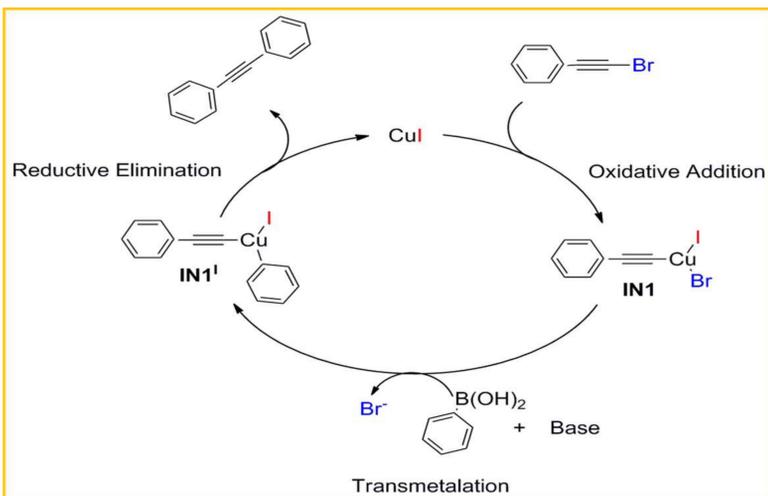
Transition metal catalyzed cross coupling reactions have proved to be versatile and convenient method in the establishment of C-C bond formation. However, requisite for cheap and safe metal catalysts are necessary owing to the high cost, toxicity, high catalyst loadings and excess ligand requirements of the traditional palladium and nickel catalysts. In this regard, copper is proving to be a cost effective and non toxic metal source for cross-coupling reactions. Our study provides the first theoretical data into the novel mechanism of ligand free copper catalyzed C(sp²)-C(sp) Suzuki cross coupling. Copper iodide is employed as the catalyst with K₃PO₄ as base and ethanol as solvent. This study could aid in understanding and overcoming the deficiencies of conventional copper assisted coupling reactions. The mechanism involves a transmetalation followed by a concerted oxidative addition reductive elimination. The role of ancillary ligands and solvent in the mechanism is also studied.

COMPUTATIONAL METHODOLOGY

All the geometries involved in the model system are optimized using Density Functional Theory (DFT), by using Becke3LYP (B3LYP) functional. 6-31+G(d) basis set was used for C, H, B, O, P atoms, while LANL2DZ with an effective core potential was used for I, Br and K atoms. Solvent effects were incorporated using the Conductor-like Polarizable Continuum Model (CPCM) by employing ethanol as solvent.

FOCUS OF THE WORK

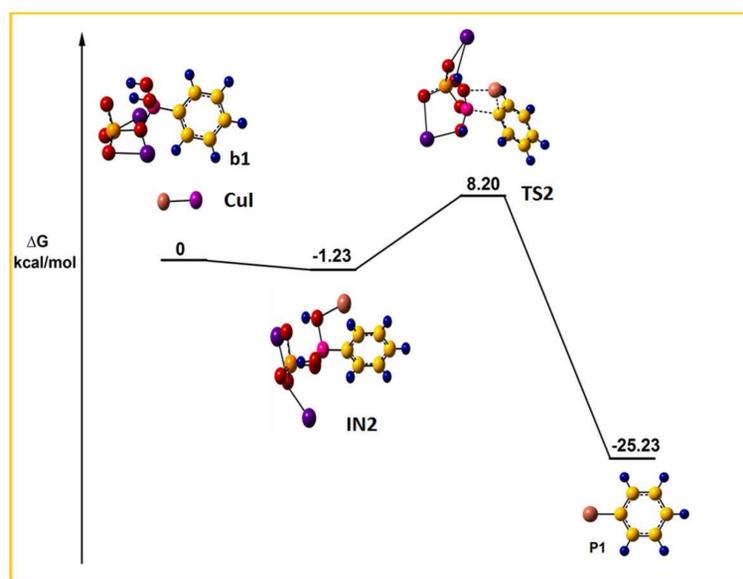
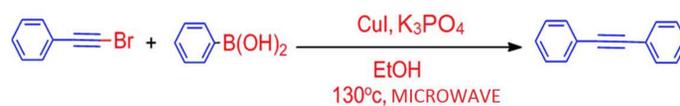
- ❖ In this poster, we explored the plausible mechanism involved in ligand free copper catalyzed Suzuki coupling of aryl boronic acids with alkynyl bromides, using Density Functional Theory.
- ❖ We have investigated the feasibility of the mechanism (Scheme 1) based on the traditional palladium catalyzed Suzuki reaction for our model system.



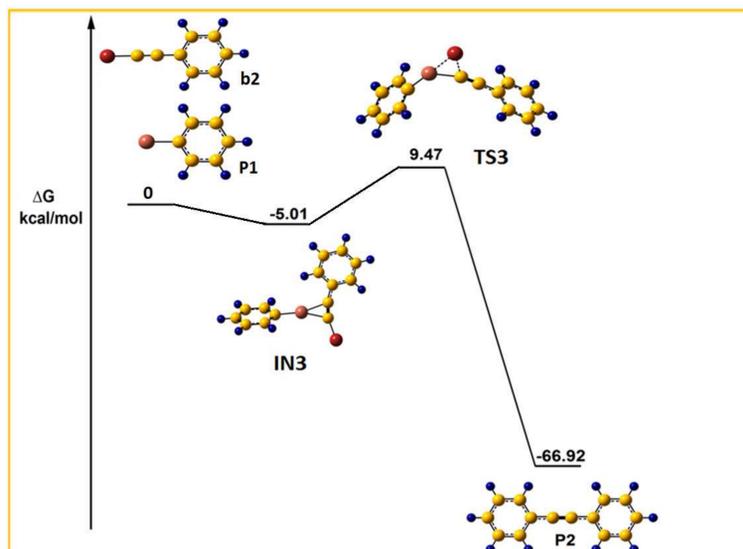
Scheme 1: Proposed catalytic cycle based on established palladium catalyzed Suzuki reaction mechanism.

RESULTS AND DISCUSSIONS

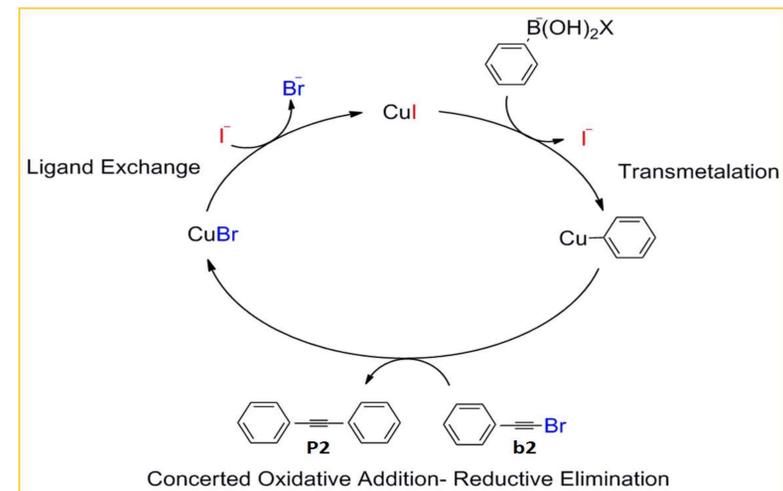
The plausibility of oxidative addition-transmetalation-reductive elimination sequence in the mechanism is unlikely to occur. None of the intermediates or transition state in Scheme 1 were traceable. Hence an alternate pathway have been proposed (Scheme 4). Here, iodine is replaced from copper by base activated boronic acid (b1). Subsequent transmetalation yields a stable Cu-Ar intermediate (P1). Attack of phenyl bromoacetylene (b2) on P1 results in an η² intermediate (IN3), which then leads to a concerted oxidative addition-reductive elimination process yielding the coupled product (P2). Instability of Cu(III) species and the ease of C(sp²)-C(sp) bond formation corroborates the lower energy barrier in the concerted process. The ESP mapped surface as given by Figure 1 shows the poor pi donation and synergic effect between Cu and I that destabilizes the Cu(III) system and obstructs an initial oxidative addition. Every attempt to optimize the intermediates and transition state involved in reductive elimination directly yielded the coupled product. Cu(I) is found to be the catalytically active state. The presence of ethanol as the solvent reduces the activation barrier for various steps involved in the reaction. The overall reaction is found to be exergonic.



Scheme 2: Energy profile for the transmetalation step in ligand free Cu catalyzed Suzuki Coupling. The base activated aryl boronic acid forms the intermediate IN2 with copper(I). A four membered transition state (TS2) leads to the formation of Cu-Ar species (P1).



Scheme 3: Energy profile for the concerted oxidative addition-reductive elimination in ligand free Cu catalyzed Suzuki Coupling. Phenyl bromoacetylene (b2) forms an η² intermediate (IN3) with P1. A three membered transition state leads to the coupled product diarylacetylene (P2).



Scheme 4: Proposed mechanism for ligand free Cu catalyzed Suzuki Coupling between aryl boronic acid and phenyl bromoacetylene. An initial transmetalation followed by concerted oxidative addition- reductive elimination. Finally, regeneration of the catalyst CuI via ligand exchange reaction.

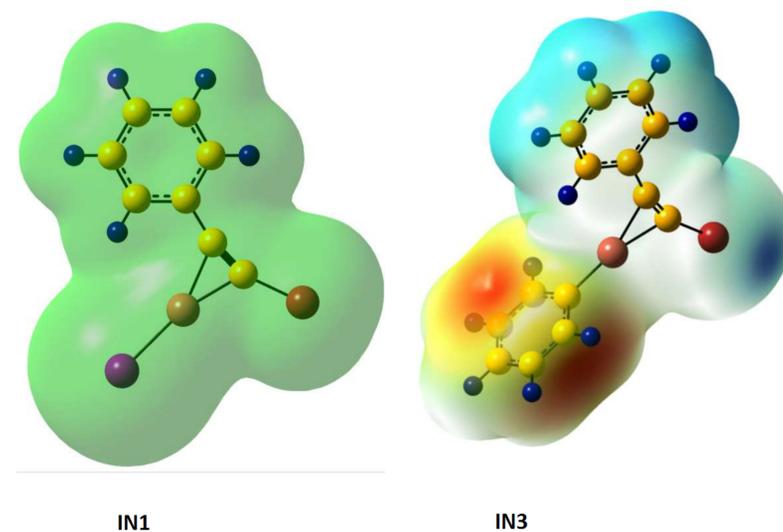


Figure 1: Electrostatic potential (ESP) mapped electron density surface revealing the electron density in the presence of I and phenyl ligands.

CONCLUSIONS

- The mechanism of ligand free copper catalyzed Suzuki coupling reaction have been investigated by means of DFT calculations.
- Catalytic pathway involving transmetalation and concerted oxidative addition-reductive elimination have been proposed.
- Distinct intermediates and transition states for reductive elimination step were untraceable.
- Weak synergic effect and poor pi donation by I hinders the oxidative addition on CuI.
- The stability of Cu(I)/Cu(III) system plays significant role in the mechanism.
- Overall the reaction is exergonic.
- The solvent ethanol reduces the activation barrier for the process.

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