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COMPUTATIONAL STUDY OF THE COPPER-FREE SONOGASHIRA CROSS-COUPLING REACTION

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Since the discovery of cross-coupling reactions in the first half of the 1970s, the application of transition metals, especially metals in the subgroup of palladium, as catalysts in organic synthesis has become an accepted and valued tool [1]. Cross-coupling reactions include numerous carbon-carbon bond forming reactions and are distinguished on the basis of the used co-catalyst or transmetalating agent. In case of Sonogashira coupling, copper co-catalyst is used and conjugated acetylenes are produced from arylhalide and terminal acetylene[2]. Copper can also induce Glaser-type oxidative homocoupling of the terminal acetylene to yield a diyne. To suppress the formation of this undesired side product, several copper-free versions of the Sonogashira coupling have been developed [3].

A computational study of the copper-free Sonogashira reaction between phenylacetylene and phenylbromide, catalyzed by Pd(PPh₃)₂, is reported here. The cross-coupling reaction begins with the oxidative addition of bromobenzene onto the palladium catalyst Pd(PPh₃)₂, which is followed by the formation of *cis*-Pd(PPh₃)₂BrPh complex. The subsequent step is isomerisation leading to *trans*-Pd(PPh₃)₂BrPh complex. Phenylacetylene reacts with *trans*-Pd(PPh₃)₂BrPh complex by substituting one of the ligands. The presence of amine (sec-butylamine) is required to deprotonate phenylacetylene and produce complex *cis*-Pd(PPh₃)₂(Ph)C≡CPh, which decomposes into palladium di(triphenyl)phosphine, Pd(PPh₃)₂, and diphenylacetylene, Ph-C≡C-Ph, during reductive elimination. The complete catalytic cycle is exothermic and has a negative Gibbs' free energy change in gas phase ($\Delta H = -27.5$ kcal/mol, $\Delta G = -16.9$ kcal/mol).

References

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3. Komaromi, A; Gergely, L; Novak, Z. *Tetrahedron Lett.* **2008**, 49, 7294.