Developing a molecular explanation for solvation effects in the Suzuki-Miyaura reaction

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The Suzuki-Miyaura reaction is widely used for carbon-carbon couplings in organic and pharmaceutical synthesis. Its ability to function in a broad range of solvents naturally leads to the question how solvation impacts the reaction and what makes a solvent a strong choice for the reaction. *This work analyzes correlations between physicochemical properties of the solvent and the reaction mechanism and aims to unravel molecular explanations for the observed trends.*

To study solvent effects on the reaction, the free energy of activation for the rate-determining step was predicted using density functional theory in combination with geometry optimization respectively transition state searches. For a representative test reaction, the aryl-aryl coupling reaction between p-chlorotoluene and phenylboronic acid catalyzed by the N-heterocyclic carbene/palladium catalyst $[\mathrm{Pd(IPr)(allyl)Cl}]$, where $\mathrm{IPr} = \mathrm{N,N'-bis[2,6-(diisopropyl)phenyl]imidazol-2-ylidene}$ was studied. Geometries and free energy corrections were predicted at the PBE-D3(BJ)/def2-SVP level of theory. Single point energies were calculated at the ωB97X-D3/def2-TZVPP level of theory. Solvation effects were investigated using different solvation models, including C-PCM and SMD.

It was found that the solvent choice has substantial impact on the activation barrier of the reaction. Correlations with physicochemical properties of the solvents were studied and the strongest correlation was found with solvent polarity, as described by the solvent dielectric constant. Correlations with other physicochemical properties such as the refractivity are also present, but were found to be less important. Interestingly, some contributions to the free energy of activation exhibit different trends. For example, electronic energy contributions behaved strictly monotonically, whereas the free energy corrections exhibited a more complex behavior. *These contributions to the free energy were analyzed in-depth and, when possible, molecular explanations for the observed trends were formulated.*

In summary, trends in solvent impacts on the activation barrier of the Suzuki-Miyaura coupling were studied and molecular origins analyzed. This study leads to better molecular understanding of solvent impacts and aids in the formulation of simple criteria for the selection of solvents for this important reaction.