

Simple and Selective Negishi Cross-Coupling in Deep Eutectic Solvents

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Negishi coupling is a valuable synthetic protocol for the formation of C-C bonds. However, the use of highly reactive alkyl- or arylzinc reagents in these reactions usually requires them to be performed under strictly anhydrous conditions using Schlenk techniques. This limits their use to laboratories and other settings with access to facilities for highly sensitive chemistry.

Deep eutectic solvents (DES) can allow some reactions that would traditionally require air sensitive conditions to be carried out in air with no protection from water, first observed by Hevia and colleagues, where it was possible to use Grignard reagents in the presence of water^[1]. Capriati and colleagues reported Negishi coupling in DES, without protection from water, using Pd(^tBu₃)₂ as the catalyst for cross-coupling.^[2]

It has been possible to adapt this work to develop simple, selective protocols for Pd-catalysed Negishi cross-coupling reactions under mild conditions, without the need for protection from water in the solvent or the atmosphere. These reactions proceed using a cheap and readily available Pd pre-catalyst, Pd₃(OAc)₆, and allow coupling of some *ortho*-functionalised aryl iodides without the need for a supporting phosphine ligand. An unusual solvent-induced regioselectivity is demonstrated, which allows highly regioselective C-C bond formation to take place. This is shown even when multiple halogen atoms are present on the aryl iodide precursor, without the need for any protecting groups and the waste associated with protection/deprotection.

This work is part of a larger project that aims to understand the speciation of catalysts in DES, including work on iridium catalysts using NMR spectroscopy. In turn, this may allow us to better understand the role of DES in catalytic reactions, where it is often non-innocent.

References

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2. G. Dilauro, C.S. Azzollini, P. Vitale, A. Salomone, F.M. Perna, V. Capriati; Scalable Negishi Coupling between Organozinc Compounds and (Hetero)Aryl Bromides under Aerobic Conditions when using Bulk Water or Deep Eutectic Solvents with no Additional Ligands, *Angewandte Chemie*, **2021**, *60* (19), 10632-10636. DOI: 10.1002/anie.202101571.



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