Efficient C-N cross couplings via heterogeneous single-atom catalysis

G. Giannakakis[1], S. Fantasia[2], S. Mitchell[1], K. Puentener[2], J. Pérez-Ramírez[1]*

[1]ETH Zurich, [2]F. Hoffmann-La Roche Ltd.

Palladium-catalyzed Buchwald-Hartwig aminations provide a crucial methodology for accessing arylamines in pharmaceuticals manufacture. These reactions currently rely on expensive and unrecoverable soluble metal complexes, which pose challenges for sustainability and product purification.[1] The use of heterogeneous catalysts would enable process intensification, simplify downstream processing, and reduce waste.[2] However, traditional catalytic materials have struggled to match the activity and selectivity of homogeneous systems due to the lack of uniformity and specific properties of active sites. Single-atom heterogeneous catalysts (SACs) present promising new opportunities, where metal atoms anchored on carefully selected host materials, resemble the structural characteristics of metal complexes.[3]

This study explores the reactivity of isolated palladium atoms anchored on a graphitic carbon nitride host (Pd/ECN) in Buchwald-Hartwig amination reactions (**Fig. 1a**) with diverse coupling partners and conditions. Remarkably, the catalyst exhibits high yields for a wide range of aryl halides and amines, highlighting its versatility. Notably, the catalyst can be recycled several times without significant loss of reactivity (**Fig. 1b**). Analysis of the interaction between the individual reaction components (solvent, ligand, base, reactants) and the metal sites by *in situ* X-ray absorption spectroscopy (XAS) studies sheds light on the C-N coupling mechanism over SACs revealing differences from the anticipated mechanisms over organometallic catalysts (**Fig. 1c**). The results highlight the potential of SACs as a complementary tool for exploring a broader chemical space within C-N coupling reactions.

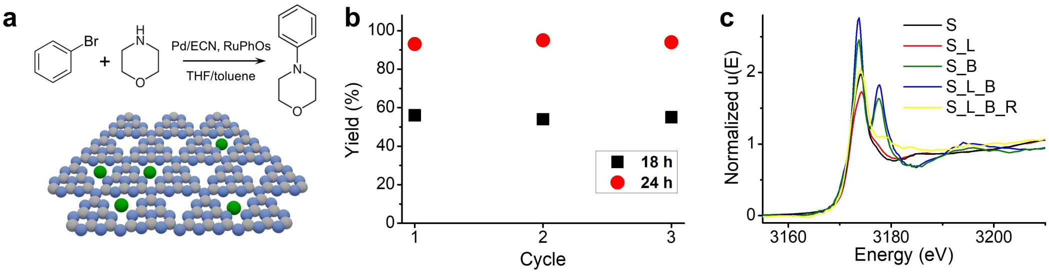

Fig. 1a Schematic of the Buchwald-Hartwig coupling catalyzed by Pd/ECN SAC. **b** Measured yield over 3 reaction cycles after 18 h and 24 h. **c** Pd L_3-edge X-ray absorption near-edge structure analysis under varying environments comprising solvent (S), base (B), ligand (L), and reactants (R).

[1] D. Faust Akl *et al. Green Chem.* **2022**, 24, 6879-6888.
[2] G. Giannakakis, S. Mitchell, J. Pérez-Ramírez, *Trends Chem.* **2022**, 4, 264-276.
[3] Z. Chen *et al. Nat. Nanotechnol.* **2018**, 13, 702-707.