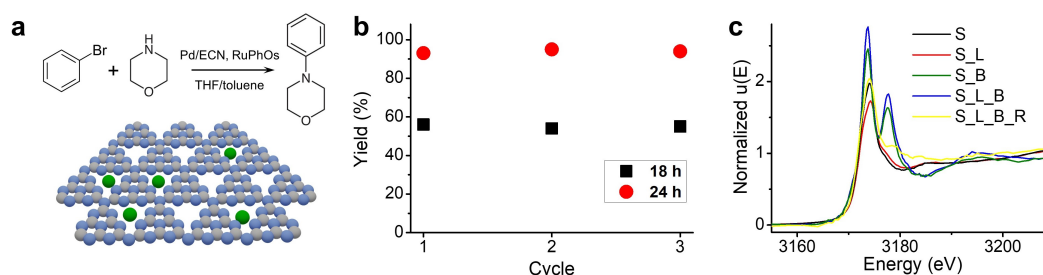


**Efficient C-N cross couplings via heterogeneous single-atom catalysis**G. Giannakakis<sup>1</sup>, S. Fantasia<sup>2</sup>, S. Mitchell<sup>1</sup>, K. Puentener<sup>2</sup>, J. Pérez-Ramírez<sup>1\*</sup><sup>1</sup>ETH Zurich, <sup>2</sup>F. Hoffmann-La Roche Ltd.

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.<sup>[1]</sup> The use of heterogeneous catalysts would enable process intensification, simplify downstream processing, and reduce waste.<sup>[2]</sup> 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.<sup>[3]</sup>

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).

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[3] Z. Chen *et al.* *Nat. Nanotechnol.* **2018**, 13, 702-707.