A NEW LIGAND FOR BUCHWALD-HARTWIG AMINATION

Jonas Paukstys[1,2], Tomas Paskevicius[1], Linas Labanauskas[1]

[1]Center for Physical Sciences and Technology (FTMC)
[2]Vilnius University
jonas.paukstys@ftmc.lt

Heteroaromatic components are widely encountered in small-molecule drugs [1]. Efficient functionalisation of these compounds is key for the discovery and testing of new therapeutics. Palladium catalysis is widely applied for this purpose, particularly in amination reactions. Despite extensive research, ligands currently used for amination of heteroaromatic compounds are prone to deactivation, necessitating high catalyst loadings and extended reaction times. In 2024 novel O-bound electron deficient phosphine ligand (Figure 1A) was shown to be resistant to the deactivation processes [2]. However, the reported system relied on an air- and temperature-sensitive palladium precatalyst, making the reactions difficult to reproduce.

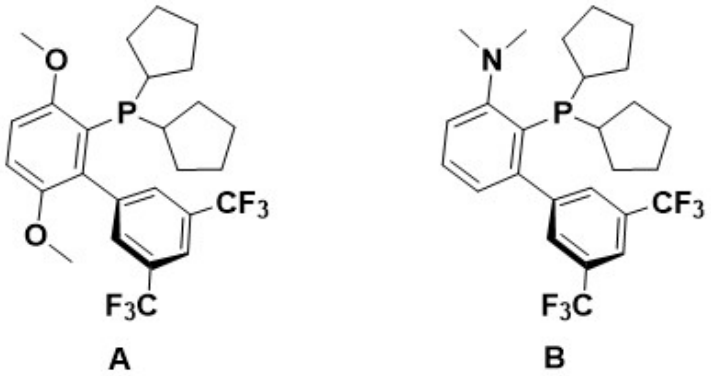

Fig. 1. Deactivation resistant ligand (A), new ligand synthesised in our work (B)

In this work, a series of ligands were synthesised and evaluated for their ability to support Buchwald–Hartwig amination of diverse heteroaromatic substrates. A catalytic system utilising a stable palladium source and a new ligand (Figure 1B) was developed. This system was shown to be compatible with a broad range of heteroaromatic compounds while requiring low catalyst loadings.

[1] E. Vitaku, D. T. Smith, and J. T. Njardarson, “Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals,” Journal of Medicinal Chemistry, vol. 57, no. 24, pp. 10257–10274, Sep. 2014, doi: 10.1021/jm501100b.

[2] K. Feng et al., “Development of a Deactivation-Resistant dialkylbiarylphosphine ligand for PD-Catalyzed arylation of secondary amines,” Journal of the American Chemical Society, vol. 146, no. 39, pp. 26609–26615, Sep. 2024, doi: 10.1021/jacs.4c09667.