SOLVENT-FREE BUCHWALD-HARTWIG AMINATION: TOWARDS SUSTAINABLE CATALYSIS FOR SYNTHESIS

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Résumé

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Amines are an integral part of biologically active molecules. The pharmaceutical industry heavily relies on robust and reproducible reactions for the formation of aryl amine moieties, with the Buchwald-Hartwig (BH) amination playing a central role. Its widespread use is spans various stages of drug discovery and process development.1 Traditionally, BH amination is performed in organic solvents such as THF and toluene. Unfortunately, at multi-kg scale pharmaceutical manufacturing, these conditions become extremely costly for the environment, with the solvents accounting for up to 80% of mass use.2 To address this environmental concern and to provide efficient and safe methodology, our aim was to develop eco-compatible conditions for this crucial chemical transformation. We tackled this issue using mechanochemical ball milling.3 By eliminating the need for bulk solvent use, this strategy provides cleaner and ecological synthesis alternatives. While many cross-coupling reactions have been explored under mechanochemical conditions, research on solvent-free BH amination conditions in the literature remains limited.4–7 Building on our previous work developing a novel precatalytic system featuring (Pd(π-allyl)tBuXPhos)Cl in green alcoholic solvents,8 in this study, we demonstrate the application of the same precatalyst in mechanochemical solvent-free reaction conditions.9 We have demonstrated the coupling of aryl halides with various nitrogen-containing substrates including amines, amides, carbamates, ureas, among others. This expansion of reaction scope underscores the potential of our approach in facilitating sustainable and atom-efficient synthesis for synthesis of biologically active molecules.

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