Mechanochemically Accelerated N-Arylation: A Scalable and Solvent-Minimized Approach Bypassing Friction Sensitive Reagents

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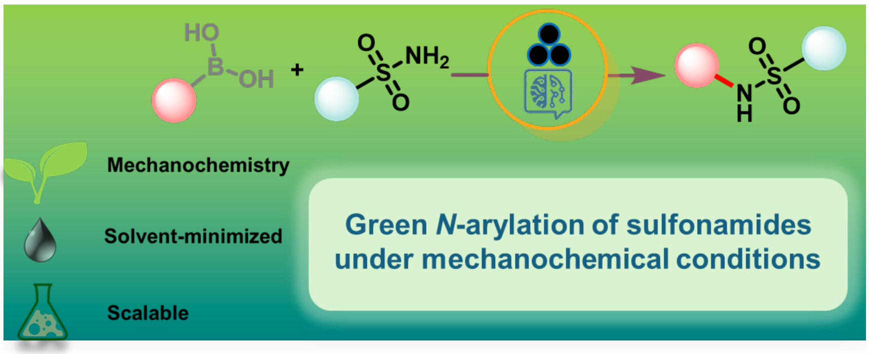
We report a comprehensive mechanochemical strategy for the solvent-minimized *N*-arylation of sulfonamides via C-N coupling, using commercially available copper powder as the catalyst and water as a green LAG additive. Inspired by the limitations of traditional solution-phase protocols-such as substrate dependency, over arylation, and poor sustainability, we developed a scalable, efficient and eco-compatible protocol under ball-milling conditions.[1]



Initial screening revealed the high thermal reactivity of *masked amine* reagent, prompting a shift toward primary sulfonamides as safer and more robust nitrogen nucleophiles.[2] The protocol tolerated a wide range of aryl, heteroaryl and halogenated boronic acids, affording moderate to high yields, although alkyl and chelating 8-quinolinyl substrates remain challenging.[3] Furthermore, data-driven modeling based on molecular descriptors enabled as an exploratory QSAR tool, which guided successful extension to new substrates. The process was readily scaled to gram quantities and applied to late-stage functionalization of sulfonamide-containing bioactive scaffolds,[4] underscoring its potential as a practical and green synthetic strategy for medicinal and process chemistry applications.[5]

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