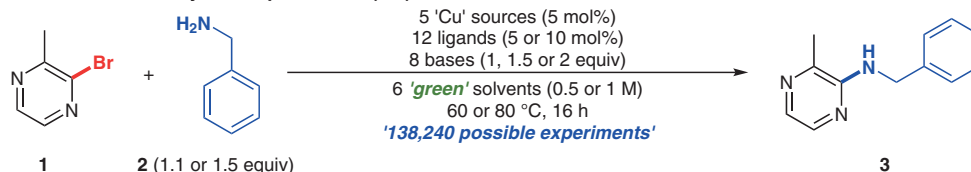


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Bayesian Optimization as a Sustainable Strategy for Early-Stage Process Development? A Case Study of Cu-Catalyzed C–N Coupling of Sterically Hindered Pyrazines
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Efficient Exploration of Reaction Space to Optimize Sustainable Cu-Mediated Ullmann Couplings

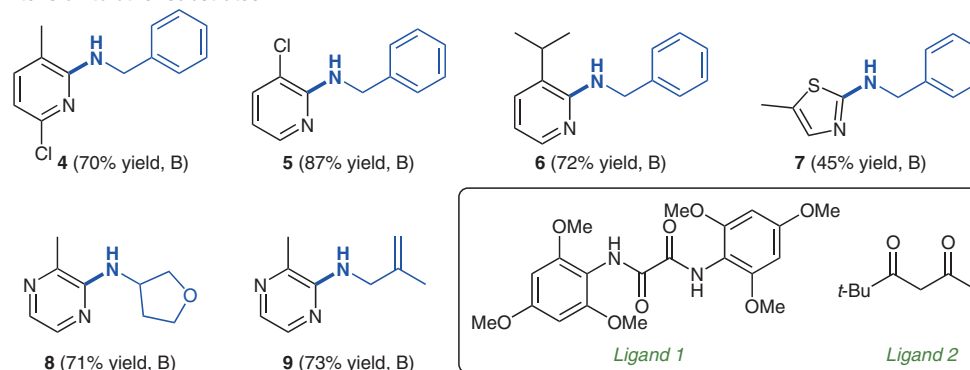
Model reaction for Bayesian Optimization (BO) studies:



Optimized conditions from BO platforms evaluated (80 experiments: 10 cycles):

Conditions A (EDBO-TS)	Conditions B (EDBO-EI)	Conditions C (AUTOMUS-UCB)
Cu(OAc) ₂ (5 mol%), <i>Ligand 1</i> (5 mol%) 2 (1.1 equiv), K ₃ PO ₄ (2 equiv) <i>t</i> -BuOH (1 M), 80 °C, 65% yield	CuBr (5 mol%), <i>Ligand 2</i> (5 mol%) 2 (1.5 equiv), K ₃ PO ₄ (2 equiv) EtOH (1 M), 80 °C, 86% yield	Cu ₂ O (5 mol%), <i>Ligand 1</i> (10 mol%) 2 (1.5 equiv), K ₂ CO ₃ (2 equiv) DMSO (1 M), 80 °C, 78% yield

Extension to other substrates:



Significance: The formation of C–N bonds on heteroaromatic systems is an important transformation in both agrochemical and pharmaceutical research that is typically achieved through either a nucleophilic aromatic substitution or through Pd-(Buchwald–Hartwig) or Cu-mediated (Ullmann) catalysis. While Pd-catalyzed reactions are more robust and general, from sustainability and economic perspectives, there are significant benefits to shifting to Cu-based systems. One of the main challenges in developing these catalytic transformations is the number of discrete and continuous variables that must be optimized in tandem for each reaction, and the ability to achieve this in an expeditious manner. The current report describes the use of Bayesian Optimization (BO) algorithms to derive conditions for the Cu-mediated functionalization of 2-bromopyrazine through performing 80 reactions (10 cycles of 8 experiments) from a possible total experimental space of 138,240 reactions.

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Comment: While there are several approaches for the optimization of a chemical transformation, BO presents an advantage in being able to explore a large reaction space in fewer experiments through iterative cycles switching between 'exploration' and 'exploitation' modes. Three BO algorithms were investigated for the reaction between 1 and 2 under Cu-catalyzed conditions leading to optimum yields between 65–87% from each across the ten rounds of experimentation. Gratifyingly, though employing different BO algorithms, common themes emerged in the best conditions from each campaign around temperature, base, and stoichiometry. The value of the approach within research is further demonstrated with the application of the optimal protocols to the C–N couplings of other amines with other heterocyclic bromides.