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Novel Transformation Development of Acid–Amine Coupling Facilitated by Ultra-high Throughput Experimentation

Amide coupling accounts for one-fourth of the reactions that medicinal chemists most frequently use in the pursuit of drug candidates. We have developed an algorithm to enumerate the transformations of unorthodox acid–amine coupling reactions that complement the amide formation. We propose to discover reactions that we have enumerated that are theoretically feasible but, as of yet, experimentally unknown. To this end we have already discovered a novel esterification methodology, a deaminative C–O bond formation from aryl amines and carboxylic acids catalyzed by a copper(I) salt. The reaction conditions were optimized with the assistance of high throughput experimentation (HTE), and an ultra-HTE screen in 1,536 wellplates was executed to investigate the general substrate scope. Using TTP mosquito® robotics, we investigated the coupling of 96 carboxylic acids with 4 activated aryl amines. My presentation will detail our development of a robust HTE workflow, and address some of the challenges we have solved in traditional HTE and ultra-HTE screening campaigns. We will also disclose the application of reactions discovered in HTE studies in the late-stage diversification of drugs.