Directed Coevolution of Chemicals

Antonio J. LaPorte and Martin D. Burke

Cold start problems, such as chemical reactions with 0% yield even after extensive screening, cannot be solved using traditional or AI-guided optimization because the corresponding data sets lack dynamic ranges needed for learning. Here we show that directed coevolution of chemicals, inspired by nature and bioengineering, can solve such problems in a systematic manner. This strategy was paired with automated modular synthesis and real time HPLC kinetic analysis to discover a previously inaccessible stereospecific Csp^3 cross-coupling enabled by a novel phosphaadamantane-based ligand. Repeating this coevolution campaign with selective pressure for generality yielded second generation conditions that are applicable across most polyketide natural product chemical space. This strategy provides a roadmap for systematically pursuing novel chemical reactivity and potentially many other types of cold start problems.