A Simple, Multi-Dimensional Approach to High-Throughput Discovery of Catalytic Reactions

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Transition metal complexes catalyze many important reactions used in medicine, materials science and energy production. Mechanistic data often provide the foundation for catalyst development and optimization. However, many reactions were discovered serendipitously while seeking a different synthetic transformation. The advent of combinatorial methods for the discovery of new drug candidates and new enzymes for organic synthesis has raised the prospect of applying analogous high-throughput experimental methods to the discovery of catalytic transformations. Although high-throughput methods for catalyst discovery that would mirror related approaches for the discovery of medicinally active compounds have been the focus of much attention, these methods have not been sufficiently general or accessible to typical synthetic laboratories to be adopted widely.

Most published methods for the high-throughput discovery of catalysts evaluate one of the two catalyst-reactant dimensions. In other words, these methods have examined either many catalysts for a single class of reaction or a single catalyst for many reactions. A two-dimensional approach in which many catalysts for many catalytic reactions are tested simultaneously would create a more efficient discovery platform, if the reactants and products from such a system could be identified. Here, we disclose a method to discover catalytic reactions by conducting experiments in an x-y array on pools of substrates having similar masses, and analyzing combinations of these pools by mass spectrometry. This format evaluates thousands of reactions at one time and pinpoints with just a few mass spectral measurements the coordinates of the metal and ligand that effect a reaction between two or more substrates. We report a method to evaluate a broad range of catalysts for potential coupling reactions using simple laboratory equipment. Specifically, we screen an array of catalysts and ligands with a diverse mixture of substrates, and then utilize mass spectrometry to identify reaction products that, by design, exceed the mass of any single substrate. Using this method, we discovered a copper-catalyzed alkyne hydroamination and two nickel-catalyzed hydroarylation reactions, each of which displays excellent functional group tolerance.