NANOMOLE SCALE HIGH THROUGHPUT CHEMISTRY: PLATFORM DEVELOPMENT AND APPLICATIONS TO LIBRARY SYNTHESIS

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At the forefront of new synthetic endeavors, such as drug discovery or natural product synthesis, large quantities of material are rarely available and timelines are tight. A miniaturized automation platform enabling high-throughput experimentation for synthetic route scouting to identify conditions for preparative reaction scale-up would be a transformative advance. Because automated, miniaturized chemistry is difficult to carry out in the presence of solids or volatile organic solvents, most of the synthetic “toolkit” cannot be readily miniaturized. Using palladium-catalyzed cross-coupling reactions as a test case, we developed automation-friendly reactions to run in dimethyl sulfoxide at room temperature. This advance enabled us to couple the robotics used in biotechnology with emerging mass spectrometry–based high-throughput analysis techniques. More than 1500 chemistry experiments were carried out in less than a day, using as little as 0.02 milligrams of material per reaction.