Discovery, Evaluation, and Target Identification of a Potent Anticancer Compound

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High throughput screening is the dominant method for discovering new drug leads. However, most screening collections consist of planar molecules that lack the structural complexity necessary for the modulation of novel drug targets. To rapidly enhance the complexity of the screening libraries, we have developed the Complexity to Diversity (CtD) method. This method utilizes the molecular complexity of natural products to synthesize structurally diverse scaffolds. Herein we report the phenotypic screening of the CtD library of >300 compounds synthesized from 10 natural products in multiple cancer cell lines. A class of compounds derived from the natural product pleuromutilin were discovered as active anticancer compounds. Current efforts are focused towards understanding the mode of action and target identification of these scaffolds.

An Efficient Aerobic Linear Allylic C-H Amination: Overcoming Benzoquinone Inhibition

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Recent advances in aerobic Pd(II)-oxidation catalysis have sparked interest in developing new reactions which replace stoichiometric organic oxidants (such as benzoquinone) with O2 in these processes. While these reactions have demonstrated the feasibility of using molecular oxygen as a stoichiometric oxidant for a variety of Pd(II)-oxidations, many suffer from limited efficiency and/or harsh, forcing conditions. We have developed a mild, aerobic, intermolecular allylic C—H amination reaction that harnesses molecular oxygen (1 atm.) as the stoichiometric oxidant. Through the intermediacy of a dioxygen coupled *triple catalysis* platform, catalytic quantities of Pd(0)-selective benzoquinone oxidant are utilized to effect Pd(0)/Pd(II) turnover. The reduced hydroquinone byproduct is continuously reoxidized to active BQ *via* a cobalt co-catalyst that selectively reacts with molecular oxygen. By utilizing catalytic quantities of quinone, we have observed a significant increase in reaction efficiency, generally obtaining *higher* yields of aminated products with lower Pd(II) catalyst loadings than we have previously reported. We attribute this effect to a reduction in BQ oxidant present in the reaction mixture, which likely inhibits catalysis at elevated concentrations. In support of this hypothesis, initial rate measurements have revealed a progressive decrease in reaction rate as the concentration of BQ is increased from catalytic to stoichiometric levels.