Synthesis of Gigantic Nanocarbon Molecules via Optimization of Macrocyclization by Design-of-Experiments and Machine Learning

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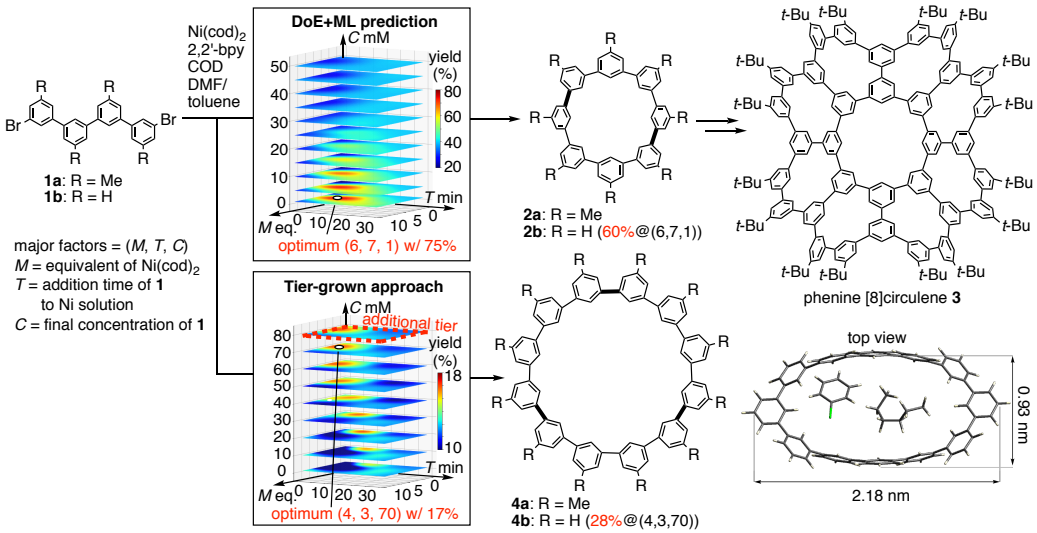
Establishing models of scientific phenomena is an important part of science, and rational mechanistic models of reactions have been traditionally elucidated via one-factor-at-a-time optimizations in synthetic experiments. In this study, we developed a method to elucidate empirical models of reactions via Design-of-Experiments (DoE) optimization with machine learning (ML) supplements.[1,2] The empirical model was first established for a 3D parameter space of oligomeric macrocyclization of **1**. Three factors, *M* = equivalent of $Ni(cod)_2$, *T* = addition time of **1** and *C* = final concentration of **1**, were adopted for optimization, runs were specified by DoE, and the model was generated as heatmaps of yields with ML supplements through examinations of four ML methods. The yield of dimer (**2b**) was consequently improved to 60%, which allowed for synthesis of phenine [8]circulene (**3**) with a molecular formula of $C_{256}H_{240}$. This "DoE+ML" approach of model constructions was further developed, and the heatmap empirical model was rationally expanded for trimerization to **4** by integrating an additional tier without ruining efficient space coverage of DoE. This tier-grown approach led to synthesis of the largest congener of [*n*]cyclo-*meta*-phenylene with *n* = 12.



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