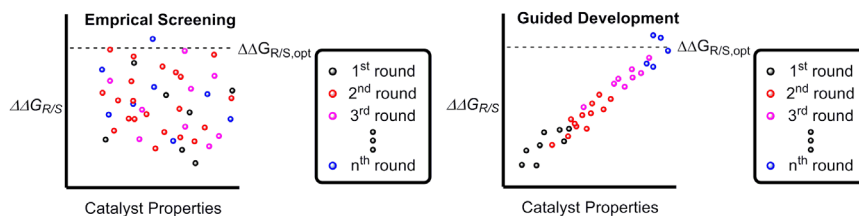


Diversity Oriented, Computer-Guided Catalyst Design: A New Paradigm in Catalyst Design and Evaluation in Organic Synthesis

Jeremy Henle and Scott E. Denmark

The use of computational methods to probe and investigate the origins of catalytic activity and selectivity is well known in organic synthesis. These methods generally require transition-state calculations that are not amenable to predictive modeling. In these laboratories, we have developed a method using statistical 3D chemoinformatic methods to guide the development of catalysts. By combining combinatorial synthesis to obtain diverse libraries of catalysts with 3D-QSAR modeling methods, meaningfully diverse initial screening sets can be systematically generated. This strategy maximizes the chance that a selective catalyst will be found in initial screening studies. Further model development can lead to efficient and focused progress toward selective catalyst structures. This method is currently being used to develop novel APTC methods.



General Allylic C–H Alkylation with Tertiary Nucleophiles

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A general method for intermolecular allylic C–H alkylation of terminal olefins with tertiary nucleophiles is presented. Palladium(II)/bis-sulfoxide catalysis affords alkylation products in good yield (avg. 64%) with excellent chemo-, region- and stereoselectivity (>20:1 linear:branched, >20:1 E:Z). Notably, both activated (aromatic, heteroaromatic, 1,4-dienes) and unactivated aliphatic olefins are successfully alkylated for the first time under the same general and mild reaction conditions. Facile diversification of phenolic natural products is demonstrated by combining known allylation reactions with allylic C–H alkylation. The tertiary nucleophile scope is broad and tolerant of latent functionality that may be further elaborated. The generality of this method in both reaction partners enables its use to streamline synthesis via expedient generation of molecular complexity. Underscoring this concept is a tandem allylic C–H alkylation/Diels-Alder reaction cascade used to rapidly furnish the common tricyclic core found in the class I Galbulimima alkaloids: a reactive diene is generated via intermolecular allylic C–H alkylation and subsequently engages in cycloaddition with a dienophile in the tertiary nucleophile.

