Diversity Oriented, Computer-Guided Catalyst Design: Application of Chemoinformatics to Catalysis

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 workflow that combines 3D chemoinformatics with diversity oriented synthesis concepts to guide the optimization of catalytic, enantioselective transformations. Expansive in silico libraries for different ligand and catalyst scaffolds (bisoxazolines, chiral phosphoric acids, and TADDOL-phosphoramidites) have been constructed and used to design and select universal test sets for each scaffold type. These test sets are then synthesized and used to screen catalytic, enantioselective reactions. The data from these screens is then used to develop 3D-QSAR models for further catalyst optimization. The development of universal test sets comprised of diverse catalyst structures 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 process is currently being used to optimize several reactions utilizing chiral, non-racemic bisoxazoline ligands, including the Cu-catalyzed aziridination of styrenes.