

## James & Esther King Biomedical Research Program

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2007 Program  
New Investigator (3-year project)

**Project Title:** Chiral Organic Cations as Catalysts for Enantioselective Synthesis

**Project Summary:** Medicinal chemistry (biomedical research aimed at drug discovery and development) is one of the most successful and reliable paradigms to provide new treatments for cancer and other tobacco-related diseases. Its strength derives from the systematic refinement of a lead compound into a true drug via multiple steps of testing and synthesizing analogs. The advent of efficient organic synthetic methods has shortened the timelines for this drug discovery process. However, in order to cope with the continual needs for efficacious new drugs, it invariably comes down to the ability to make the absolutely "correct" molecule in a timely and cost-effective manner. Hence, medicinal chemistry research is restricted by limitations in organic synthesis. Asymmetric organic synthesis is dedicated to the preparation of handed (chiral) compounds with defined three-dimensional molecular structure (stereochemistry). The importance of stereochemistry in chemical interaction is probably best appreciated in the context of drug-receptor interactions because most biological targets are chiral entities. Hence, there is enormous pressure to devise viable and practical methods for preparing chiral compounds in pure form. Indeed, 9 of the top 10 pharmaceutical drugs have chiral active ingredients, 7 of which are in a single-hand form. Of course, methods based on chiral catalysts rather than on stoichiometric chiral reagents can be advantageous from the standpoints of efficiency and economy. This grant focuses on discovery and development of efficient catalytic synthetic methods for the preparation of organic molecules in a single-hand form, which is critical to successful development of efficacious new therapeutics. Such methods allow therapeutics to become accessible in a highly pure form, at a low cost, and without toxic byproducts, and thus can significantly reduce the amount of time between the initial discovery and availability to patients from all economic segments of society. Among such methods, those that promote carbon-carbon bond formation (one of the most common bonds in drug molecules) are particularly significant. It is thus our interest to design and develop several new efficient catalysts for the preparation of carbon-carbon bonds that will prove critical to the synthesis of a wide range of medically important and biologically active molecules. Our project has several important features: (1) New catalysts that can be used on other important reactions and not just those that will be studied by us; that is, our new catalysts are expected to have a broad impact on other scientists interested in accomplishing the above goals. (2) Development of methods that deliver medically important molecules, which are either inaccessible or very difficult to prepare by any other protocol. Successful realization of ideas in this grant will allow chemists to take readily available and relatively inexpensive materials and convert them to highly valuable compounds that can be used to access precious medically active agents. Such research endeavors will not only accelerate the drug discovery process of medicinal chemistry but also lower costs of prescription drugs, and thus promote prevention (e.g., anti-depressant drugs to alleviate nicotine withdrawal symptoms), treatment, and cure of tobacco-related diseases.