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Editorial

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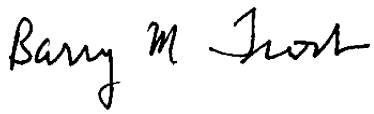
The Toolbox of Synthetic Reactions: A Key to Unlock the Design of Structure for Function

One of the most important consequences of World War II has been the creation of a phenomenon, the scientific enterprise, which has played a major role in improving the general well-being of society. Government stimulated scientific exploration by enhancing its funding through many organizations including the National Institutes of Health and various defense agencies as well as the creation of the National Science Foundation. Investment in basic science was rewarded with many innovations in many areas ranging from material science to medicine. The successes derive from understanding of how structure begets function. Scientists in many disciplines operating at the interface are the bridge in going from structural design to function. In such tasks, many scientists are limited to structures that already exist. Chemists operating at the interface are freed from such limitations since, if the structure they design is not currently available, they can go into the laboratory and synthesize it regardless of its structural complexity. Time efficiency becomes the limitation.

The creation of time-efficient synthetic strategy to complex targets depends upon the toolbox of synthetic reactions. Reactions must be selective—chemo-, regio-, diastereo-, and enantioselective. Such reactions will reduce detours such as use of protecting groups and create molecular complexity more directly. While some sentiments suggest that we have all the synthetic reactions we need, such conclusions ignore a basic principle simply stated that "we don't know what we don't know!" The prospects for new reactions to be discovered are potentially limitless. Catalysis is transforming the very basic science. We need to look no further than two recent Nobel prizes in chemistry for olefin metathesis and cross-coupling reactions to see how large an impact new synthetic reactions can have at the interface. Progress at the interface depends critically on progress at the core. This interdependence tends to be ignored in times of limited resources. Investing in the core of synthetic chemistry is critical in allowing us to optimize our design of complex structures for function both for the problems of today as well as tomorrow. By making complex molecule synthesis a more time-efficient operation, we increase our prospects of more optimized structure for function.

Drug discovery illustrates the challenge. How do we design new and novel structures that can be truly differential without resorting to natural products? If the structure of penicillin had not been discovered through the study of the constituents of bioactive organisms, would we have invented the field of β-lactam antibiotics? At the time that the structure of penicillin was being examined, β-lactams were thought not to be able to even exist. Obviously, efforts to make such structures would not be given any serious thought unless basic studies in pushing the limits of strained molecules would have occurred. Morphine represents another natural product that was a game changer. Would we have even been able to design morphinoids de novo? Could the understanding of the structure of the enkephalin receptor lead to the "rational" design of morphine? In today's world, I would guess not. To the extent that we improve our synthetic prowess so that molecules of such complexity can be available in a time efficient manner, we will at least improve the prospect. At a minimum, it would allow us to more properly probe the function of structure by using total synthesis as a strategy for establishing structure–activity relationships. Truly optimizing structure for function at the interface does require the evolution of the core, the toolbox. Maintaining funding of the basic chemistry that creates new tools which, in turn, allows new strategies for simplification of complex molecule synthesis is critical for the well-being of the integrated scientific activity necessary for solving the problems of society today and tomorrow.



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