Location matters…no compound operates in isolation without interacting with its local environment. Metalloproteins are example systems whose active sites contain intricate structures that aid the performance of specific functions with high selectivities and efficiencies. The complexity of these systems complicates the study of their function and the understanding of the properties that give rise to their reactivity. One approach that has contributed to the current level of knowledge is the study of synthetic constructs that mimic one or more aspects of the native metalloproteins. These systems allow for analysis of individual components of structure and how they affect function. We are thus able to establish structure-function correlations that are necessary for evaluating mechanisms. Using key architectural features from active sites of metalloproteins as inspiration, my group has developed design approaches to prepare systems that regulate local environments around a metal center. These systems are used to study the activation of small molecules (e.g., O₂ and H₂O) that are essential in maintenance of human health. This presentation will highlight our molecular designs from small synthetic complexes to the use of larger, more diverse protein hosts.