

## Introduction to Selective Functionalization of C–H Bonds

C–H activation has long been considered a problem of major interest, but progress, while steady, long remained concentrated on certain limited classes of transformations. For example, heterogeneous catalytic processes as well as superacid catalysis were both well-established from an early date and used widely in industry, but extension of C–H activation to the selective conversion of complex organic molecules proved to be much harder than initially expected. Likewise, biological C–H activation is widespread in nature and was established at an early date, but practical applications remained limited.

One brake on development has been that catalytic reduction, a better-behaved class of reaction in terms of selectivity, developed earlier historically than catalytic oxidation. Yet many C–H activation and functionalization reactions necessarily involve the oxidation of C–H to C–X units. One general difficulty in such cases is preventing overoxidation because the product H–CX bond is generally more reactive than the reactant C–H bond. Classical organic pathways often fail to overcome this problem, but some of the more recently developed catalytic procedures get around this difficulty in a variety of ways.

It now seems that we have at last reached a “tipping point” that implies an accelerating rate of advance into the future, probably resulting from the advent of a number of favorable new factors. The rise of Green Chemistry has increased the emphasis on low-waste transformations. By redirecting the site at which a chemical transformation typically occurs from a traditionally reactive H–CX bond to a typically less reactive C–H bond, and by developing methods to functionalize the C–H bond after it is cleaved, we can more easily achieve this goal. The same strategy generally also reduces reagent toxicity and cost.

The problem of developing energy resources with low environmental impact—perhaps the most important scientific and technological problem of the century—is also a new factor. Of the three major resources, coal, oil, and gas, the latter is the fuel with the lowest CO<sub>2</sub> output per unit of energy extracted. Abundant but remote gas is hard to transport and distribute because its main constituent is methane, a non-condensable gas at economically accessible temperatures and pressures. A major research goal has thus been finding routes to a transportable fuel such as MeOH or Me<sub>2</sub>O by selective partial oxidation.

Recent successes in the application of CH activation to selective functionalization of complex organic molecules are certain to attract increasing interest from the organic community. One example covered here is the asymmetric metal-catalyzed insertion of carbenes into CH bonds.

Likewise, cyclometalation has been known for decades, but only recently have procedures been developed to harness this C–H activation step for practical functionalization reactions. For maximal utility, an activation step must be followed by a functionalization step, a problem that proved unexpectedly difficult in earlier work.

Historically, C–H activation was often considered only in relation to reactions of hydrocarbons, but C–H activation steps can also occur when functionalized compounds react with transition metal catalysts. Such is the case for  $\beta$ -elimination reactions of alcohols, for example, a process with growing impact in bond-construction strategies based on hydrogen transfer.

Biological aspects of the topic have always been of interest, but commercial applications of biotransformations are now becoming practical, with C–H activation a significant target for development. Intellectual puzzles associated with the presence of multiple spin states in enzyme metal centers have only been tackled in recent years, leading to a much-improved understanding of the mechanisms involved. C–H activation of nucleic acids has proved important in a number of different contexts and is now much better understood than it was just a few years ago.

The biological work has also led to the development of synthetic catalysts based on the same metal oxo centers that typically occur in the enzyme active species. Mechanistic work has also proved somewhat easier in these simpler systems than in the full enzymes.

Of all the fields that contribute to the C–H activation problem, computational chemistry has perhaps made the greatest strides in power and breadth of applicability. In early work, computation was rare and its compass and impact was limited. Now, many experimental reports are accompanied by a computational analysis of the problem. Often computation can even clarify points that are not accessible to experimental investigation, while maintaining contact with experimentally accessible properties of the system to assess the adequacy of the model.

This special issue brings together some of the areas that are currently contributing to expanding the bounds of the field. I hope it will prove stimulating to readers, and I thank the contributors for their incisive analyses of current issues.

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