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Hartwig, John F

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## Catalyst-Controlled Site-Selective Bond Activation

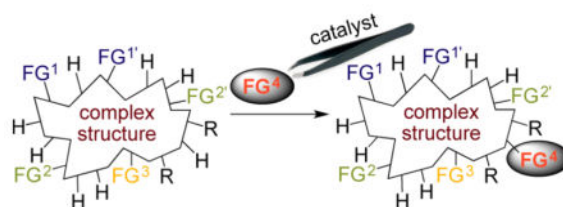
John F. Hartwig\*

Division of Chemical Sciences, Lawrence Berkeley National Laboratory, and Department of Chemistry, University of California, Berkeley, California 94720, United States

### Abstract

One ultimate goal of synthetic chemistry is to install or manipulate any functional group at any position of a molecule. This Account discusses the potential and possible approaches to use catalysis to enable a reaction to occur at one of many C–H bonds or at one of several nearly identical functional groups.

### Graphical Abstract



Twenty years ago, one-third of the articles in the “Holy Grail” issue of *Accounts of Chemical Research* focused on catalysis,<sup>13</sup> and spectacular advances have been made in catalysis since that time. Homogeneous catalysis has changed from a collection of reactions for special purposes (albeit some producing billions of pounds of product per year) to mainstream chemistry that has revolutionized all types of organic synthesis. The number and scope of new catalytic processes that have been discovered during these two decades is staggering, ranging from reactions with general utility to reactions that seem merely curious and hard to envision using, but triggering new ideas.

These catalytic reactions occur in many cases with remarkable selectivity for one functional group over another, including selective reactions at a functional group that is typically less reactive toward most reagents in the absence of a catalyst. Perhaps best known is the selectivity of ruthenium complexes for reaction at an alkene to cleave the C–C bond during catalytic olefin metathesis in the presence of ketones, esters, amides, and alcohols.<sup>4</sup> Although catalysts have changed the order of reactivity of functional groups toward many reagents, even the most spectacular reactions occur, in many cases, where the molecules

\*Corresponding Author: jhartwig@berkeley.edu.

#### ORCID

John F. Hartwig: 0000-0002-4157-468X

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dictate, not where chemists and their catalysts dictate. Reactions occur at the less hindered alkene, ketone, or alcohol over the more hindered ones, at a ketone over an ester, or at an ester over an amide. They occur at the more acidic C–H bonds over the less acidic C–H bond, at the weaker C–H bond over the stronger C–H bond, or at the more electron-rich C–H bond over the more electron-poor C–H bond.

No doubt, some catalysts violate these trends in site selectivity. For example, many catalysts react at stronger aryl C–H bonds over weaker alkyl C–H bonds.<sup>5</sup> But what catalyst reacts at the more electron-rich, more hindered aryl C–H bond or the stronger and more electron-rich of the alkyl C–H bonds? Or what catalyst reacts selectively at one of two ketones or one of two alcohols or one of two C–H bonds that have equivalent steric and electronic properties but are chemically nonequivalent due to the remaining structure of the molecule. And what catalyst reacts at the C–C bonds in the framework of a molecule, rather than the periphery? No catalyst reacts with unstrained versions of such C–C bonds to restructure it from within.

Thus, we are far from achieving the most general goal of synthetic chemistry that could be achieved with catalysts—conducting a reaction at any bond of a molecule to install any atom or group of atoms by selection of the proper catalyst and reagent (Figure 1). Obviously no single catalyst could achieve this general task. However, one can imagine creating a suite of catalysts that a well-versed synthetic chemist can use to induce reactions at positions dictated by the catalyst, rather than positions dictated by the local environment of a C–H bond, C–C bond, or functional group. Progress has been made toward this goal, as described in the next few sections. Yet, we remain far from achieving it; therefore, this Account also describes potential new paths to achieve this general goal of synthetic chemistry.

## SELECTIVITY FOR ONE FUNCTIONAL GROUP OVER ANOTHER

Discoveries of catalysts over the past 20 years have given chemists in the field of homogeneous catalysis confidence that one can conduct reactions at a functional group that is typically less reactive toward classical reagents in the presence of a functional group that is typically more reactive toward such reagents and even at a single C–H bond over common functional groups in the molecule (Figure 2). As just noted, olefin metathesis occurs at a nonpolar C = C bond in preference to alternative processes at more polar and, therefore, typically more reactive C=O or O–H bonds. Palladium-catalyzed cross-coupling reactions are exquisitely selective for an aryl halide over many other functional groups, as exemplified by Suzuki couplings used in the synthesis of vancomycin (Figure 2A),<sup>6</sup> whereas iridium catalysts (at least for the borylation and silylation of C–H bonds) are exquisitely selective for aryl C–H bonds over aryl C–X bonds in which X is any of the halogens.<sup>7,8</sup> This selectivity was recently exploited in the 100 kg preparation of doravirine for phase III clinical trials (Figure 2B).<sup>9</sup> Likewise, many palladium-catalyzed reactions occurring through oxidation states of palladium higher than Pd(0) occur at aryl C–H bonds over aryl carbon–halogen bonds.<sup>10</sup>

However, many molecules contain multiple functional groups of the same class. They often contain multiple alkenes or carbonyl groups or alcohols or amines. The selective reaction at one of these functional groups over the other with one catalyst but selective reaction at

another of these functional groups with a different catalyst remains a challenge. For example, the catalytic hydrogenation of an ester or amide over a ketone is rare if not unknown.

Although this challenge of conducting a reaction at one type of functional group over another or at one of multiple functional groups of the same type constantly arises during multistep syntheses, the selectivity for reaction at one C–H bond over another is the most striking challenge of site selectivity. This challenge arises because many molecules have many C–H bonds that are similar to each other. The need to achieve selective reactions at one C–H bond over another highlights the limitations of our capabilities to achieve site-selective reactions, but this need has led to progress suggesting that the general goal of catalyst controlled site selectivity can be achieved.

Twenty years ago, Bergman wrote that selectively activating a C–H bond in the presence of functional groups was one holy grail of chemistry.<sup>3</sup> Now, perhaps due to articulating this challenge, chemists have discovered many catalysts that achieve this task. In our own work, the borylation of aryl C–H bonds occurs in the presence of ketones, esters, amides, nitriles, amines, all four halides bound to an arene, basic and protic nitrogens of heterocycles, and even phenols (Figure 3A).<sup>8,11</sup> The reactions occur with unusually reliable site selectivity in arenes controlled by steric effects and directing effects. Metal-catalyzed functionalizations of aryl C–H bonds occur ortho to a wide range of substituents, first ortho to a ketone<sup>12</sup> and now ortho to many groups including carboxylic acid units located varied distances from the arene (Figure 3B).<sup>13</sup> Thus, a suite of catalysts provides remarkable, although far from absolute, control of the position at which a reaction occurs on aromatic C–H bonds.

We are much further from creating a suite of catalysts that control the site of reaction at aliphatic C–H bonds. Many functionalizations of alkyl C–H bonds are oxidative processes, and the cleavage of the C–H bond occurs with an electron-poor site on a metal complex or reagent. As a result, these reactions occur at the most electron-rich, typically weak C–H bond.<sup>14</sup> In other words, these types of functionalizations occur at tertiary C–H bonds and electron-rich secondary C–H bonds. Although chemical catalysts for the functionalization of primary C–H bonds are now known,<sup>15</sup> such catalysts that functionalize primary C–H bonds in a practical way without a functional group to direct the catalyst to the primary C–H bond are not known. Likewise, catalysts that functionalize the more electron-poor C–H bond of a set of nonacidic methylene C–H bonds are not known, and catalysts that react at the more hindered C–H bond among a set of electronically similar C–H bonds are not known. How one would create a small-molecule catalyst that reacts at the more hindered C–H bond of a set of C–H bonds having similar bond strengths and electronic properties is hard to imagine.

Even if a catalyst exists that functionalizes a C–H bond selectively at a specific position, the range of functional groups or substituents that chemists would like to install at such a position is large. Thus, it might seem that dozens of catalysts must be discovered to install dozens of functional groups at each C–H bond. However, one strategy followed by our group and others to avoid this requirement is to discover reactions that create versatile synthetic intermediates. By doing so, one can diversify the intermediate to create a series of products with various functional groups or substituents at a specific position or use one system for C–

H bond functionalization to address a wide range of synthetic needs. We did so by discovering complexes that catalyze the borylation and silylation of aromatic and heteroaromatic C–H bonds. The products of these reactions can be converted to those containing a new C–C, C–N, C–O, or C–halogen bond in biaryls, alkylarenes, aminoarenes, arylamine derivatives, aryl ethers, phenols, or aryl halides, as shown in Figure 3A.<sup>16–18</sup>

Others<sup>19–22</sup> have outlined a similar strategy using enzymatic oxidation of C–H bonds. By this strategy, the combination of P450-catalyzed hydroxylation of an alkyl C–H bond, followed by deoxyfluorination (Figure 3C) or by acylation or alkylation of the alcohol is used to create a set of molecules with functional groups introduced at a specific aliphatic C–H bond.<sup>22</sup> Thus, a programmed method to install groups that can be readily derivatized at one position over others would be a significant step toward enabling the installation any functional group at any C–H bond in a molecule.

## INSPIRATIONS FOR FUTURE DIRECTIONS

Given these current limitations, but recent progress, how can we create additional catalysts that ultimately lead to complete control over site selectivity? Classically, control over site selectivity has been achieved with protective groups. Protection of the more reactive alcohol or ketone as an ether or acetal renders it less reactive, and this protection allows a reaction to occur at the less reactive alcohol, ketone, or carbonyl group. Although successful in many cases, an important goal of selective catalysis is to eliminate our reliance on protective groups that add steps to the sequence used to prepare complex molecules and that is impractical for the synthesis of bulk chemicals. The potential use of biomass feedstocks, which possess multiple functional groups, illustrates the challenge of conducting a reaction at one functional group among many as part of potential production of bulk chemicals.

The functionalization of aromatic C–H bonds suggests that site-selective reactions can be achieved more generally. Recently, researchers at Merck<sup>23</sup> used a few examples of medicinally active molecules to illustrate how one can functionalize a C–H bond in many positions selectively with current methods by choosing the proper reagent and catalyst. Of course, one cannot place any group at any position, but many positions of the molecule are accessible. An adaption of their analysis of the ability to functionalize C–H bonds in clopidogrel is provided in Figure 4 and shows that one type of C–H bond functionalization or another allows a reaction to occur selectively at almost any of the C–H bonds in this molecule. However, a similar depiction of their analysis of the potential to functionalize quinine shows that some positions can be functionalized by current methods, but a similar number of positions of the quinine scaffold cannot be functionalized site-selectively.

How can one develop catalytic reactions at positions that are inaccessible by current methods? Certainly the discovery of new modes of reactivity that lead to reactions at typically unreactive positions can address this issue. However, approaches to use existing reactivity but to change the site at which these reactions occur can provide an additional approach to this synthetic problem.

Studies using the combination of supramolecular chemistry and catalysis to redirect a catalyst to one functional group or one C–H bond over another is being pursued in several ways. As noted in the introduction, the selective reaction at one hydroxyl group over another, particularly in a carbohydrate or polyol natural product, is a synthetic challenge that lies at the heart of biosynthetic pathways to important carbohydrate biopolymers, peptide natural products, or macrolide natural products. Although we do not have enzymes that catalyze a reaction at every individual hydroxyl group selectively in any carbohydrate, work with peptide catalysts points toward a path to create such catalysts. Libraries of peptides with varying structures have been created that recognize portions of organic substrates and catalyze the selective acetoxylation, sulfonation, or phosphorylation of one hydroxyl group over others.<sup>24</sup> With access to a library of peptides, a catalyst of this type can be chosen that reacts at a specific hydroxyl group that is not the inherently most reactive hydroxyl group in complex molecules, such as erythromycin A, teicoplanin (Figure 5), or D-myoinositol.<sup>24–26</sup> Likewise, libraries of peptide catalysts have been created for the halogenation of arenes, and members of this peptide library catalyze the halogenation of one arene over other arenes in complex structures, like vancomycin, due to their ability to recognize the overall structure of the molecule.<sup>27</sup>

Nature attacks the problem of site selectivity by evolution (and accompanying lengthy time scales). Perhaps the most striking examples are the selective hydroxylations of C–H bonds in largely hydrocarbyl reactants, including steroids, fatty acids, and alkanes. However, additional classes of enzymes react at aryl C–H bonds with high selectivity. For example, a series of halogenases react at the 5, 6, or 7 position of the indole in tryptophan exclusively, and studies are being conducted to improve activity and broaden the scope of substrates that react with these enzymes.<sup>28</sup> Of course, glycosyltransferases also catalyze reactions at one hydroxyl group over the many other hydroxyl groups in carbohydrates as part of the synthesis of complex carbohydrates and glycoproteins.<sup>29</sup>

Although many enzymes catalyze many reactions selectively, there are positions of molecules at which no known enzyme causes a reaction to occur. Thus, chemists, biochemists, and engineers have developed approaches to access these positions of a molecule by evolving the catalyst in the laboratory. Again, research on this topic has been conducted intensively with enzymes that catalyze hydroxylations of C–H bonds. The methods of directed evolution have been used to create artificial P450s that catalyze the hydroxylation of steroids at positions where natural enzymes do not react (Figure 6A) and with light hydrocarbons that hardly react at all with natural P450s.<sup>30–32</sup>

Although these methods for evolution of enzymes in the laboratory are powerful, these enzymes undergo a limited range of reactions. The promiscuous reactivity of a heme active site has been shown to encompass the additions of carbenes<sup>33,34</sup> and nitrenes<sup>35</sup> to alkenes, as well as insertions of carbenes into Si–H bonds<sup>36</sup> and nitrenes into C–H bonds.<sup>37,38</sup> However, the scope of these reactions is severely limited and chemical synthesis requires the installation of a wide range of functional groups, such as amino groups, cyano groups, fluorine atoms, trifluoromethyl groups, substituted carbonyl groups, or entire substituted aryl or heteroaryl groups. Enzymes are not known that catalyze the installation of these structural units onto an organic scaffold. Thus, several groups, including ours, are seeking methods to

combine protein architectures with computational design and directed evolution to create artificial enzymes,<sup>39</sup> including artificial metalloenzymes,<sup>40</sup> that catalyze the reactions of chemists, instead of the reactions of Nature. To do so, active sites are needed that catalyze the installation or interconversion of functional groups at or near room temperature with a tolerance for water and with ligands that comprise the side chains of natural amino acids or that can be installed as unnatural amino acids or as cofactors bound to the protein by noncovalent interactions. Clearly, the community is far from achieving this goal in a general way, but some progress has been made in this direction.

In our own group, we have developed approaches to replace, in a formal sense, the iron in heme proteins with metals that catalyze reactions that are different from those catalyzed by iron–porphyrin complexes (Figure 6B).<sup>41,42</sup> Although such systems are far from catalyzing multiple reactions at programmed sites, they do catalyze reactions that are not induced by natural enzymes and that can be evolved to react with high selectivity. To do so, we expressed native and mutant myoglobins and cytochromes P450 that lack the heme unit and then loaded these apo proteins with native porphyrins containing non-native metals, such as rhodium, ruthenium, iridium, silver, cobalt, etc. We found that the metalloprotein containing a methyliridium unit in place of the iron catalyzes a wide range of atom-transfer processes that are not catalyzed by iron. For example, these systems catalyze the stereoselective insertion of a carbene into a C–H bond and the stereoselective cyclopropanation of unactivated alkenes,<sup>42,43</sup> in some cases with kinetics that rival those of natural enzymes in biosynthetic pathways.<sup>42</sup>

Over the past decade, others have pioneered the development of systems that combine streptavidin and organometallic compounds containing a tether to biotin to create artificial metalloenzymes that catalyze stereoselective reactions characteristic of organometallic systems, such as hydrogenation, allylic substitution, annulation by C–H bond activation, and olefin metathesis.<sup>40</sup> These studies collectively show that the ability to use mutagenesis to change the environment around such catalysts complements typical variations of ligands in transition metal chemistry. This approach to the generation of artificial metalloenzymes enables the generation of libraries of catalysts that can be stereoselective and, perhaps, ultimately site selective for reaction at one C–H bond or one functional group of a molecule over another to install the functional groups of chemists and not just those of Nature.

Most of the discussion in this Account has focused on conducting reactions at bonds or groups of atoms at the periphery of molecules, such as C–H bonds, O–H bonds, and C=O bonds of carbonyl groups. As noted in the introduction, perhaps the most challenging transformations are those at carbon–carbon bonds in the cyclic framework of organic molecules, as well as specific carbon–carbon bonds in a chain. Catalysts are being developed that cleave C–C bonds in strained rings, such as cyclopropanes and cyclobutanes.<sup>44,45</sup> However, little progress has been made on methods to restructure complex molecules by cleaving C–C bonds in the unstrained rings of the core. Of course the driving force for such a process must stem from the reagent or from forming another strong bond in an accompanying step if C–C bonds in stable structures are to be cleaved.



Synthetic chemistry is a complex web of chemical reactions that is rapidly increasing in size and number of connections between the radii of this web. Thus, there will be no single development that will allow chemists to catalyze a reaction at any position they desire. However, novel reactivity, in conjunction with novel approaches to control regioselectivity discussed in this Account, should make it possible to conduct reactions at positions of molecules previously inaccessible, whether inaccessible due to the lack of reactivity of these positions or due to the presence of positions in the same molecule that are inherently more reactive toward most reagents in the absence of a catalyst.

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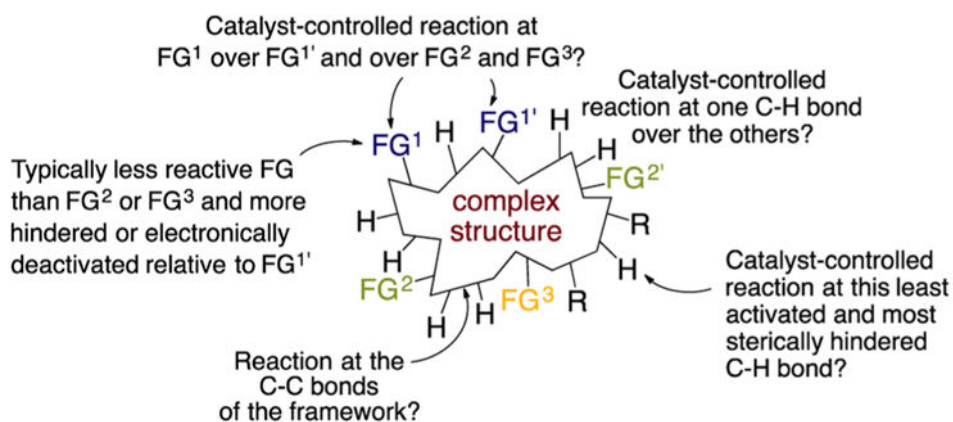
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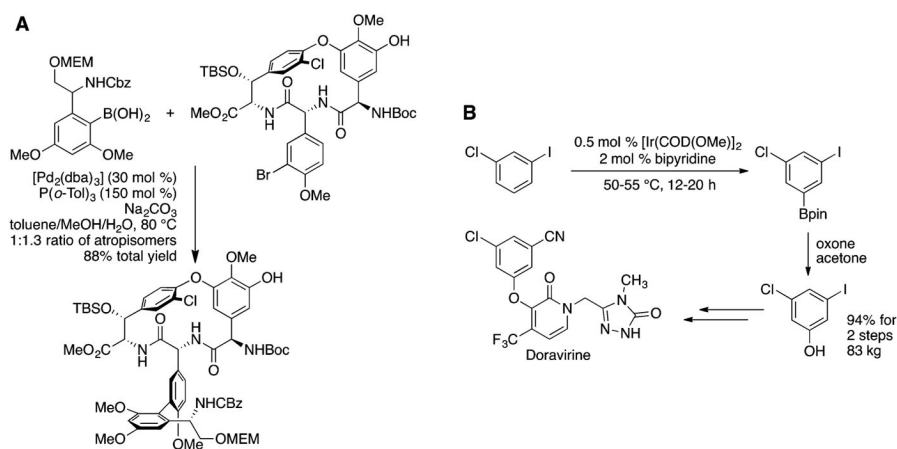


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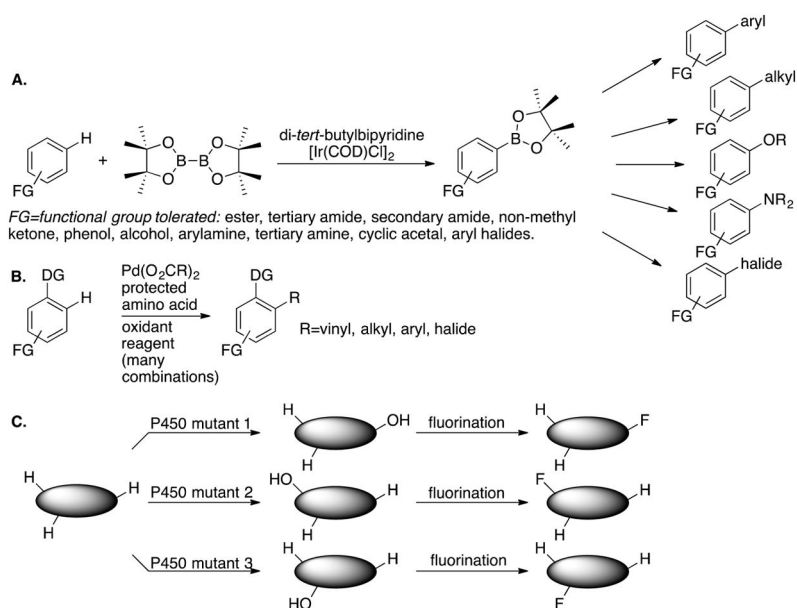
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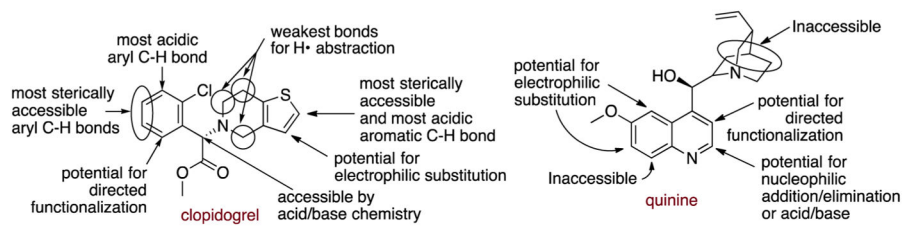
**Figure 1.** Challenge of controlling site-selectivity for one functional group over other similar or more reactive functional groups, for one C–H bond over another, and for C–C bonds.

**Figure 2.**

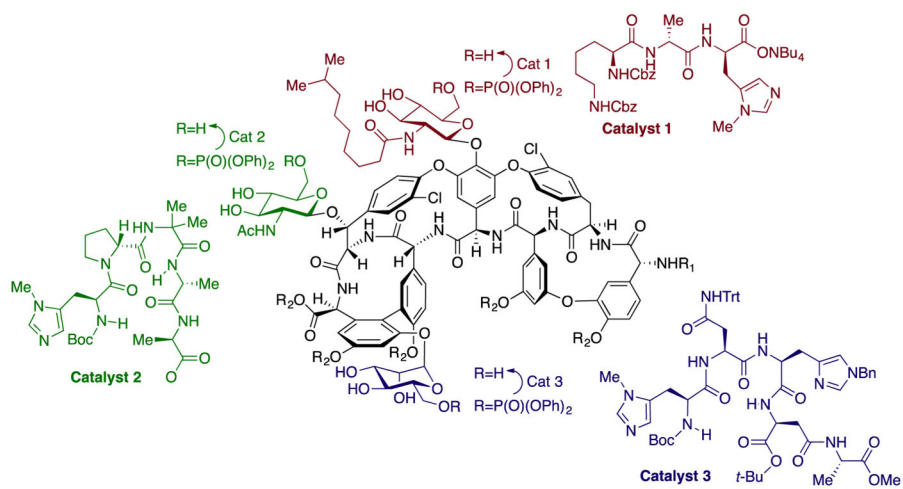
(A) Suzuki coupling in the synthesis of vancomycin showing the remarkable selectivity of the palladium catalyst for aryl bromide bonds over other potentially reactive bonds. (B) C–H borylation in the synthesis of doravirine showing the remarkable selectivity of the iridium catalyst for an aryl C–H bond over aryl halide bonds.

**Figure 3.**

Several approaches to install functionality at specific C–H bonds. (A) General scheme for the combination of borylation of an aryl C–H bond and functionalization of the intermediate arylboronate. (B) Generic scheme for palladium-catalyzed directed functionalization of aryl C–H bonds under oxidative conditions. (C) Chemoenzymatic methods for fluorination of specific C–H bonds and different positions controlled by the site-selectivity of mutant P450 enzymes.

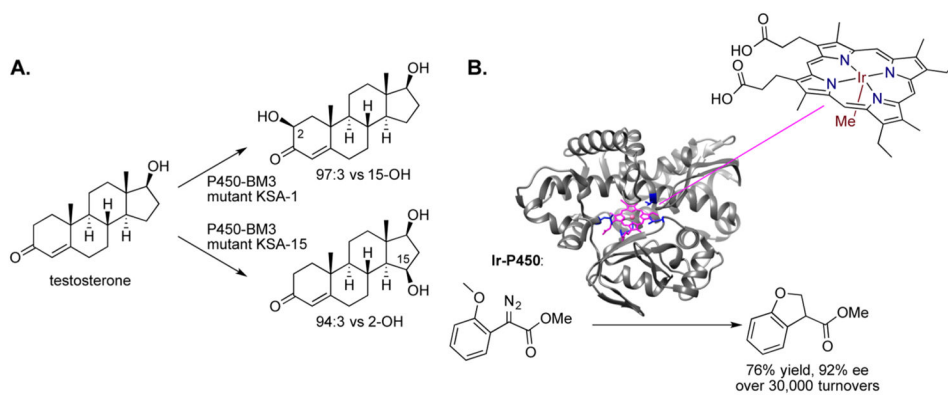


**Figure 4.** Depiction of an analysis by researchers at Merck<sup>23</sup> of the potential to functionalize specific C–H bonds in two medicinally active compounds.



**Figure 5.**  
Use of a peptide catalyst to functionalize one of many alcohols of teicoplanin.





**Figure 6.** (A) Directed evolution of P450 enzymes leading to non-native site selectivity for hydroxylation of steroids. (B) Directed evolution of P450 analogs containing iridium in the porphyrin of the active site catalyze enantioselectively.