Undirected, Homogeneous C−H Bond Functionalization: Challenges and Opportunities

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ABSTRACT: The functionalization of C−H bonds has created new approaches to preparing organic molecules by enabling new strategic "disconnections" during the planning of a synthetic route. Such functionalizations also have created the ability to derivatize complex molecules by modifying one or more of the many C−H bonds. For these reasons, researchers are developing new types of functionalization reactions of C−H bonds and new applications of these processes. These C−H bond functionalization reactions can be divided into two general classes: those directed by coordination to an existing functional group prior to the cleavage of the C−H bond (directed) and those occurring without coordination prior to cleavage of the C−H bond (undirected). The undirected functionalizations of C−H bonds are much less common and more challenging to develop than the directed reactions. This outlook will focus on undirected C−H bond functionalization, as well as related reactions that occur by a noncovalent association of the catalyst prior to C−H bond cleavage. The inherent challenges of conducting undirected functionalizations of C−H bonds and the methods for undirected functionalization that are being developed will be presented, along with the factors that govern selectivity in these reactions. Finally, this outlook discusses future directions for research on undirected C−H functionalization, with an emphasis on the limitations that must be overcome if this type of methodology is to become widely used in academia and in industry.
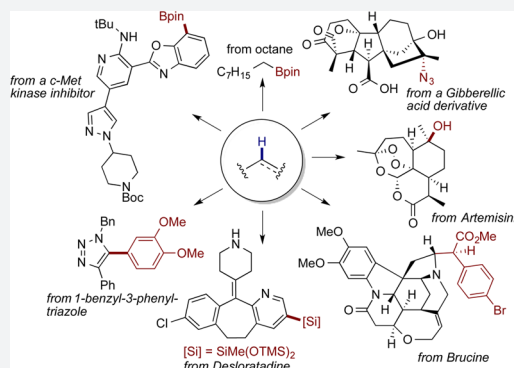
INTRODUCTION

The replacement of an unactivated C−H bond with a functional group, termed C−H bond functionalization, has the potential to change the strategies used to prepare organic molecules.[1,2] Such reactions could convert light alkanes to higher-value, functionalized chemical feedstocks,[3] or they could introduce functionality at specific positions of molecules already possessing one or many other functional groups.[2,4] In classical organic chemistry some functional groups will make nearby C−H bonds acidic and sites for the classical sequence of deprotonation and quenching of the resulting nucleophiles with electrophilic reagents (Scheme 1A). In contrast, "C−H bond functionalization" refers to catalytic reactions that introduce functional groups at C−H bonds that lack the activating influence of existing functional groups (Scheme 1B). So far, most practical

functionalizations of C−H bonds have occurred to add new groups at typically unreactive C−H bonds in molecules containing existing functionality.

BACKGROUND ON DIRECTED FUNCTIONALIZATIONS

In many cases, such functionalizations occur near existing functional groups, often after modification of this existing functionality.[5] Such modifications often convert a common functional group to one that can serve as a ligand for a transition-metal complex (eq 1). For example, a ketone has
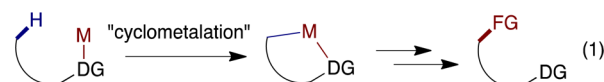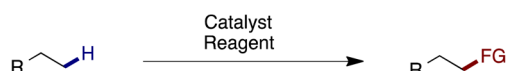
been converted to an imine, which binds the catalyst as a Lewis base.[6] Alternatively, a carboxylic acid has been converted to a picolinamide that chelates a transition metal center and binds as a formally anionic ligand.[7] A carboxylic acid has even been converted to an amide that possesses a "U-shape" and will cause the catalyst to react at a C−H bond distal to the position of the existing functionality.[8−10] After the C−H bond functionalization occurs, the directing group is removed and the original

Scheme 1. Functionalization of C−H Bonds: Classical vs Catalytic

A. Classical Functionalization of Acidic C-H Bonds

EWG−H →(Base)→ EWG−⊖ →(E+)→ EWG−E

B. Catalytic Functionalization of Unactivated C-H Bonds

R−H →(Catalyst Reagent)→ R−FG

$$\text{H} \xrightarrow[\text{DG}]{\text{M "cyclometalation"}} \xrightarrow[\text{DG}]{\text{M}} \xrightarrow[\text{DG}]{\text{FG}} \quad (1)$$

functional group is restored to its original form. Such reactions are often termed "directed" C−H bond functionalization.[11]

This effect of a nearby functional group on the reactivity of a metal complex toward cleavage of a C−H bond has been known for more than 50 years.[12−14] The stoichiometric step involving the cleavage of a C−H bond within a ligand to form a cyclic product containing a metal−carbon bond is termed "cyclometalation" (eq 1). Such cyclometalation was shown to control site selectivity many years ago, but it was much more recently that practical systems for directed functionalization involving a cyclometalation process were developed.

"Directed" functionalizations often require the installation and subsequent removal of a substituent that renders a functional group more capable of binding the catalyst. However, many molecules with activity in medicinal or agrochemistry are heterocycles or otherwise functionalized molecules that possess an inherent ability to bind a catalyst and direct a C−H bond functionalization process. For example, the halogenation of an agrochemical intermediate occurs at the position ortho to a carboxylic acid,[15] and halogenation at this site was desired for the synthetic sequence. This palladium-catalyzed directed halogenation is conducted on large scale. Moreover, catalysts are being developed that undergo reactions at C−H bonds directed by functional groups that bond more weakly than a pyridine, imine, or picolinamide.[16]

Given the diversity of structures containing Lewis basic functional groups, the opportunities for development of directed reactions are diverse, and the applications of such reactions to the synthesis of molecules with important functions will surely be widespread. In many cases, the activity of a molecule containing a small halogen or a methyl group near an existing functionality is not known and can be superior to that of the parent structure lacking this small addition to the structure.[17] Directed C−H bond functionalization can introduce new functional groups at these positions without the need to repeat a full synthetic sequence to form the molecule with the new substituent. This "late stage" functionalization allows the modified molecules to be prepared rapidly and their properties tested.[2] For these reasons, the directed functionalization of C−H bonds has been investigated extensively.

BACKGROUND ON UNDIRECTED FUNCTIONALIZATIONS

A greater challenge of C−H bond functionalization is to install a functional group at a position that cannot be reached by chelation to a transition metal, or to install a functional group selectively in a section of a molecule that lacks functional groups altogether. Such reactions of C−H bonds would create synthetic capabilities that could impact many areas of organic chemistry. For example, such reactions could create alpha−omega functionalized alkyl chains to be used as monomers for commodity polymers;[18,19] or they could convert hydrocarbons directly to detergent alcohols or carboxylic acids; or they could introduce functional groups at positions remote from the many functional groups in complex natural products or medicinally active compounds to complement the regioselectivity achieved by directed functionalizations. Such reactions are typically called "undirected" functionalizations of C−H bonds.

Undirected C−H bond functionalization reactions are much less developed than directed C−H bond functionalizations, but not for lack of effort. The functionalization of a C−H bond without the assistance of chelation is more difficult to achieve, and selective functionalization without an existing group

controlling regioselectivity is a challenge, even when undirected functionalization is observed. Yet, systems have been discovered that catalyze undirected functionalizations of C−H bonds, and several strategies that bridge the gap between directed and completely undirected functionalization have been followed. Such strategies include the exploitation of noncovalent interactions in both small molecules and enzymes. The remainder of this Outlook will describe the opportunities that undirected C−H bond functionalization presents, the challenges that confront the development of such reactions, and the approaches that have been taken to point the way toward practical, undirected functionalizations of C−H bonds.

CHALLENGES CONFRONTING UNDIRECTED FUNCTIONALIZATION OF C−H BONDS

Undirected functionalization of C−H bonds is more challenging to develop than directed functionalization because the interaction of a directing group with the catalyst increases the reaction rate of the substrate with the catalyst, increases the thermodynamics for adding the substrate to the catalyst, and controls regioselectivity. The absence of such a directing group makes it necessary that the catalyst cleave and functionalize the C−H bond without any assistance from the binding energy of the substrate to the catalyst and chelation within the initial product of C−H bond addition. During a directed functionalization of a C−H bond, coordination of the substrate to the metal center should enhance the rate of C−H bond cleavage, due to the intramolecularity of this reaction step, and cause the product of addition to be more stable than it would be in the absence of a link between the C−H bond and a coordinating group, due to the chelate effect. Without this chelation, the C−H bond cleavage step is intermolecular and often slower than it is in the absence of chelation.

In the absence of a directing group, one might expect selectivity to be an equal challenge, and many functionalizations of C−H bonds generate a mixture of products. One might expect the reactivity of one C−H bond to be similar to the reactivity of others, and most secondary C−H bonds in linear alkanes react at equal rates (Figure 1).[20] However, different
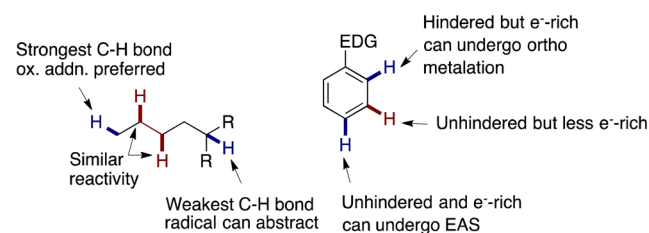

Figure 1. Attributes of C−H bonds contained in alkanes and arenes that are relevant to C−H functionalization.

types of C−H bonds in alkanes are well-known to react with different rates.[21] For example, tertiary C−H bonds are weaker than secondary C−H bonds and are known to be more reactive toward many radicals. Primary C−H bonds are stronger than secondary C−H bonds and are less reactive toward radicals. Unfortunately, the terminal positions of an alkane are often the sites at which the functional groups are most desired for commodity chemicals. For example, plasticizer and detergent alcohols contain a hydroxyl group at the end of an alkyl chain;[22] diols or diamines for polymerization contain two hydroxyl or amino groups at either end of the alkyl chain.[23,24] Fortunately, alkyl C−H bonds in more functionalized molecules are not

equally reactive, and useful properties of these molecules do not require the functionalization of a primary C–H bond. Indeed, many reagents and catalysts are known that react with potentially useful selectivities for one C–H bond over another.

Likewise, the C–H bonds at different positions of an aryl ring could be assumed to be equally reactive. However, classical electrophilic aromatic substitution[25] and deprotonation of aryl or heteroaryl rings[26,27] already hints that functionalization of C–H bonds of aromatic systems can be regioselective. Moreover, the difference in strength of aryl vs alkyl C–H bonds can lead to selective reactions at alkyl over aryl C–H bonds with one type of catalyst or reagent, while the presence of a π-system and the greater acidity of an aryl C–H bond[28] can cause the aryl or heteroaryl C–H bond to be the most reactive with another.

It is important to note that careful studies have documented that the "reactivity–selectivity principle" has little basis in fact or theory for reactions that occur at rates below those controlled by diffusion.[29] Reagents, such as a hydroxyl radical, that react with rates approaching diffusion control are unselective, but reagents or catalytic intermediates that react at rates that are controlled by free energies of activation can be selective. Thus, one can achieve selective, undirected C–H bond cleavage, even if the system is sufficiently reactive to cleave a strong C–H bond.

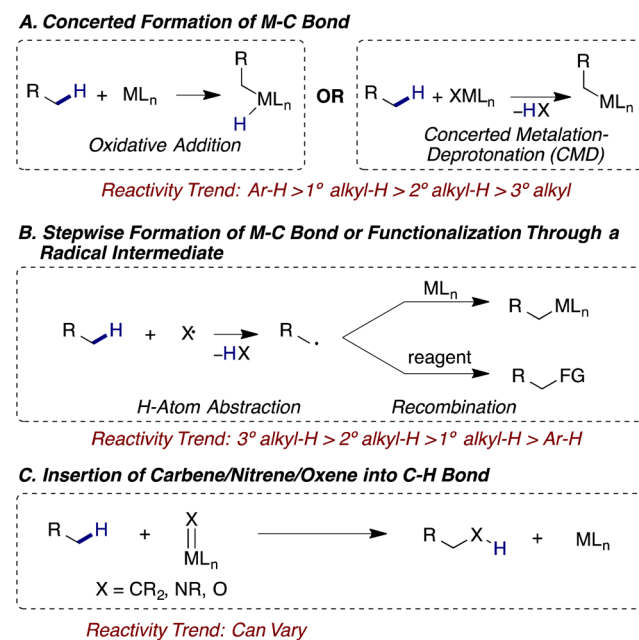## ■ EXAMPLES OF CATALYTIC, UNDIRECTED C–H BOND FUNCTIONALIZATION

Multiple methods are being developed that lead to the selective functionalization of the strongest C–H bonds in alkyl chains: the primary C–H bonds. In parallel, reactions are being developed that occur at unactivated secondary and tertiary C–H bonds in more densely functionalized systems. In some of these cases, selective reactions occur at specific secondary C–H bonds, due to steric or electronic effects (or both), and in other cases, reactions occur selectively at tertiary C–H bonds.

Before describing the specific examples of undirected C–H bond functionalization, it is valuable to review the relative reactivity of different classes of C–H bonds toward the various mechanisms by which C–H bonds are cleaved by transition-metal complexes or organic reagents to form intermediates that react with transition-metal complexes. Reactions that form a metal–carbon bond by C–H bond cleavage tend to occur by concerted pathways, rather than stepwise radical pathways (Scheme 2). Reactions occurring without formation of a metal-carbon bond can occur by either concerted or stepwise pathways. For example, many oxidation reactions occur by the formation of alkyl radicals and recombination of the radical with a metal complex or reagent that delivers the functional group to the alkyl radical. In contrast, some catalytic reactions of nitrene and carbene precursors with alkyl C–H bonds occur by direct insertion of a nitrene or carbene unit into the C–H bond without forming a metal–alkyl intermediate.

The selectivity of reactions that form metal–carbon bonds is often dictated by the strength of the metal–carbon bond in the potential organometallic intermediates, relative to the strength of the C–H bonds.[30–33] For this reason, C–H bond functionalization reactions that occur by formation of a metal–carbon bond occur at aryl over alkyl C–H bonds; it is also the reason that reactions forming metal–carbon bonds tend to occur at primary over secondary C–H bonds, and at secondary over tertiary C–H bonds.

In contrast, reactions that occur by abstraction of a hydrogen atom to form an alkyl radical tend to occur at the position of

Scheme 2. Types of C–H Bond Cleavage

A. Concerted Formation of M-C Bond

Oxidative Addition **OR** Concerted Metalation-Deprotonation (CMD)

Reactivity Trend: Ar-H > 1° alkyl-H > 2° alkyl-H > 3° alkyl

B. Stepwise Formation of M-C Bond or Functionalization Through a Radical Intermediate

H-Atom Abstraction   Recombination

Reactivity Trend: 3° alkyl-H > 2° alkyl-H > 1° alkyl-H > Ar-H

C. Insertion of Carbene/Nitrene/Oxene into C-H Bond

X = CR₂, NR, O

Reactivity Trend: Can Vary

the weaker C–H bond and often the most electron rich of the weaker C–H bonds because the species abstracting the C–H bond is electron poor.[21] However, steric factors also influence the position of hydrogen atom abstraction, and hindered reagents have been developed that favor abstraction of a secondary C–H bond over a tertiary C–H bond.[34] The presence of a heteroatom also can influence the site of reaction. With a few exceptions,[35] both C–H bond activation to form organometallic intermediates and hydrogen atom abstraction are favored at the position alpha to oxygen and nitrogen.[36–38]

■ UNDIRECTED FUNCTIONALIZATION OF ALKYL C–H BONDS

Examples of undirected functionalizations of C–H bonds of saturated hydrocarbons include the oxidation of alkanes,[39] the dehydrogenation of alkanes to alkenes,[40–42] the insertion of carbenes containing one donor and one acceptor group,[43] and the borylation of C–H bonds.[44–46] These reactions are shown in Scheme 3. Among these reactions, the borylation is the unique example that leads to catalytic functionalization of primary C–H bonds with high selectivity in the absence of a directing group.[47–50] The thermal dehydrogenation of alkyl C–H bonds occurs by cleavage of the primary C–H bond and subsequent β-hydrogen elimination to form the terminal alkene,[51] but the same species that catalyzes dehydrogenation also catalyzes isomerization.[52] Physical separation of the alkene from the catalyst or photochemical conditions have been reported recently to improve the selectivity of the dehydrogenation of alkanes.[53]

Alternatively, the terminal alkene can be intercepted by a second reaction. For example, the alkene has been intercepted by catalysts for olefin metathesis as part of a tandem reaction that does not "functionalize" alkanes but creates higher alkanes from lighter alkanes. This process, known as alkane metathesis, occurs by the combination of dehydrogenation, alkene metathesis, and hydrogenation of the resulting alkene with the hydrogen created by dehydrogenation.[54] The stepwise combination of alkane dehydrogenation, followed by hydrosilylation of internal alkenes to linear alkylsilanes, also has been reported recently.[55]

Scheme 3. Examples of Undirected Functionalization of Alkyl C−H Bonds
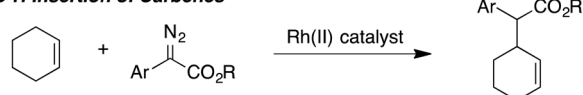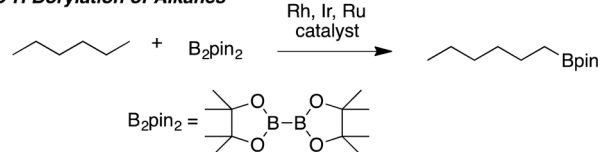
A. Oxidation of Alkanes


B. Dehydrogenation of Alkanes

i.

Ir catalyst

tBu

ii. Alkane metathesis

2 x

Ir catalyst
Schrock-Type
Metathesis Catalyst
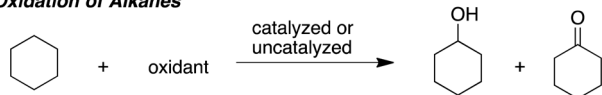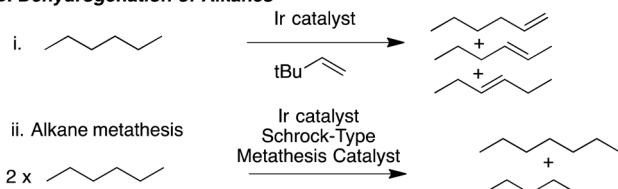
C. C-H Insertion of Carbenes

Rh(II) catalyst

D. C-H Borylation of Alkanes

Rh, Ir, Ru
catalyst

+ B_2pin_2

B_2pin_2 =

The direct oxidation of C−H bonds has been studied most extensively, both to understand the mechanism of enzymatic oxidation by cyctochromes P450 and to develop catalysts for synthetic applications. Shilov reported some of the earliest evidence that transition metals could catalyze the oxidation of alkyl C−H bonds. For example, Shilov demonstrated that alkanes undergo halogenation in the presence of a Pt(II) catalyst and a stoichiometric Pt(IV) oxidant.[56] Although these were seminal reports on C−H bond functionalization, the low regioselectivity and use of stoichiometric Pt make this method impractical.

However, methods have been developed more recently that obviate the need for stoichiometric Pt. For example Sen showed that $CuCl_2$ as a cocatalyst and oxygen as the oxidant leads to the catalytic oxidation of alkyl sulfonates with moderate selectivity for primary C−H bonds, due to the deactivation of the secondary C−H bonds proximal to the electron-withdrawing functionality (eq 2).[57] Sanford recently reported
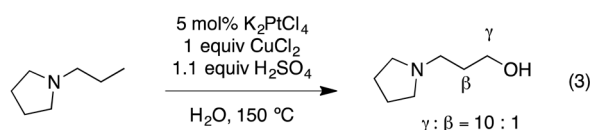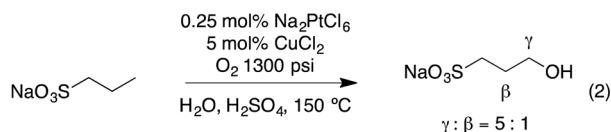

similar selectivity for the oxidation of primary C−H bonds in ammonium salts due to the electronic deactivation of C−H bonds proximal to the protonated nitrogen (eq 3). Periana reported the oxidation of methane to methyl bisulfate with SO_2 as the oxidant, but these reactions do not lead to clean oxidation of higher alkanes, in part, due to the instability of the product to acidic conditions.[58]

As noted earlier in this Outlook, the oxidation of cyclohexane is conducted on commodity chemical scale (eq 4); this process

is possible because the issue of regioselectivity does not arise with a cyclic substrate and oxidation deactivates the C−H bonds of the product toward further oxidation. However, no catalyst is known that will oxidize alkyl C−H bonds in more complex structures with high regioselectivity and high turnover numbers. Current catalysts can generate products from oxidation of complex molecules with significant selectivities and can generate sufficient material for discovery-based applications, but the catalysts give products with moderate turnover numbers (example in eq 5).[59] Reactions at benzylic or
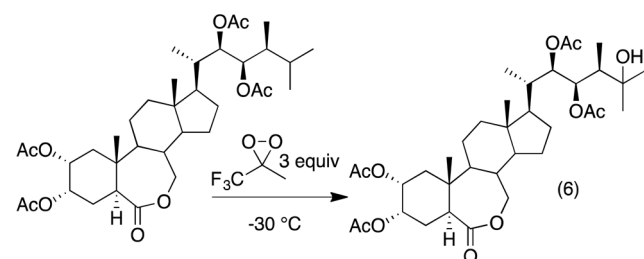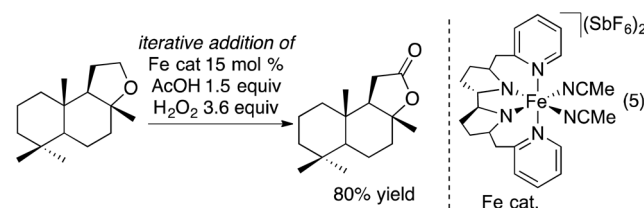

allylic positions can occur in a fashion suitable for technical applications; of course acrylic acid is produced by oxidation of the allylic C−H bonds in propene.[60]

Uncatalyzed oxidation of alkyl C−H bonds is well-known and can occur with selectivity for one C−H bond over another due to the electronic differences in these bonds.[61−63] These selectivities and their origins have been reviewed.[21] Briefly, sources of oxene units insert into tertiary C−H bonds in preference to secondary C−H bonds,[64] and they insert into secondary C−H bonds in preference to primary C−H bonds. Among similar classes of C−H bonds, they insert into the more electron rich C−H bond. An example of the selective oxidations by trifluoromethyl dioxirane is shown in eq 6.[65,66]

Metal-catalyzed insertions of nitrenes into C−H bonds are also being developed. A majority of the insertions of nitrenes into C−H bonds have been intramolecular reactions. Although applications of these reactions have included landmark examples of the applications of C−H bond functionalization to the syntheses of complex natural products,[67] the development of a system for general, undirected intermolecular insertion of nitrenes into C−H bonds has been more challenging. Recently, the combination of a dirhodium catalyst, oxidant, carboxylic acid additive, and an aryloxysulfonamide as the nitrene source has been reported to effect the intermolecular C−H amination of tertiary C−H bonds (eq 7).[68] This system suggests that intermolecular insertion of nitrenes into C−H bonds could become a valuable synthetic method.

Reactions of radicals with C−H bonds typically occur with related selectivities for tertiary, secondary, and primary C−H bonds. Most of the radicals that abstract hydrogen atoms from alkyl positions are electrophilic and, therefore, abstract the

$$(7)$$
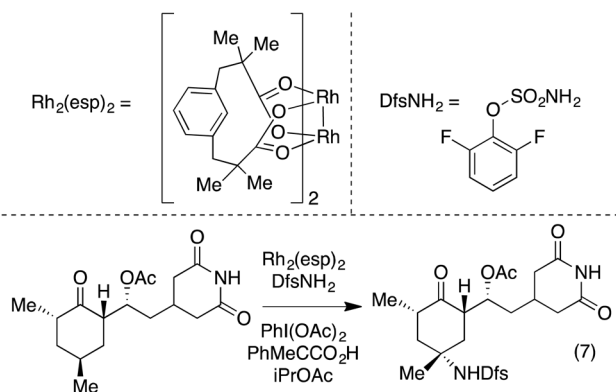
hydrogen atom from the most electron rich tertiary or secondary C−H bond. A recent example of a catalytic amination process that appears to occur by abstraction of a C−H bond with a reagent that is selective and tolerant of an array of functional groups and recombination of the radical with a metal complex has been reported. This process installs azido groups at tertiary C−H bonds, benzylic C−H bonds, and allylic C−H bonds in good preparative yields and high selectivities with complex molecules (eq 8).[69]

$$(8)$$

$$X = Br, Cl, F \quad (9)$$
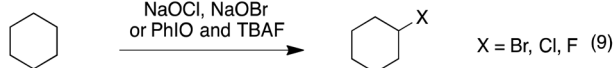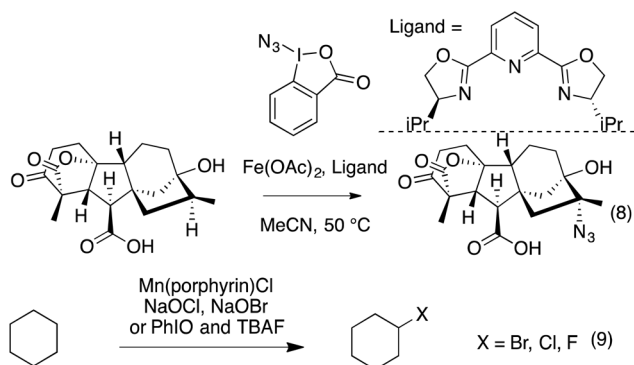
The halogenation of alkyl C−H bonds occurs in some cases with systems related to those that oxidize C−H bonds with selectivities resulting, in part, from steric effects.[70] The chlorination[71] and fluorination of alkyl and benzyl C−H bonds occurs with manganese porphyrin complexes as catalyst (eq 9).[72−74] These reactions occur without directing groups with selectivities closely related to those for the oxidation of C−H bonds with iron–porphyrin catalysts.

The bromination of C−H bonds is a well-established classical reaction, although conditions for the bromination of alkyl C−H bonds are often incompatible with other functional groups.[75] Recently, a reagent that is based on an *N*-bromo amide for the bromination of alkyl C−H bonds was reported (eq 10).[34] The


$$66 : 1 \ (2° : 3°) \quad (10)$$
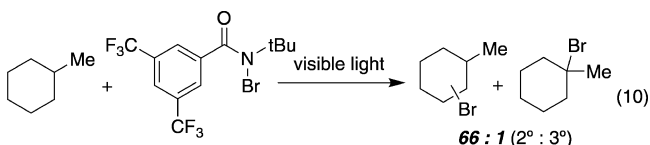
amidyl radical formed photochemically abstracts an alkyl C−H bond. In this case, a large *tert*-butyl group on the amide nitrogen leads to selectivity for secondary over tertiary C−H bonds.

The undirected functionalization of alkyl C−H bonds that occurs with the broadest scope and pertains to the synthesis of of compounds relevant to medicinal chemistry is the insertion of carbenes into secondary and tertiary C−H bonds.[43,76]

The reactions occur with site selectivities that result from a combination of steric effects, electronic effects, and bond strengths.[77] The reactions occur preferentially at secondary C−H bonds because they are more electron rich and weaker than primary C−H bonds, but less hindered than tertiary C−H bonds. The reactions also occur preferentially at the C−H bonds located alpha to alkoxy, siloxy, and amino groups.[78]

Thus, the reactions occur with high regioselectivity at the C−H bonds of cycloalkanes,[78] cyclic ethers,[78] and cyclic amine derivatives,[79] and these reactions occur with high enantioselectivity (eq 11). The reactions also occur alpha to oxygen in

$$(11)$$
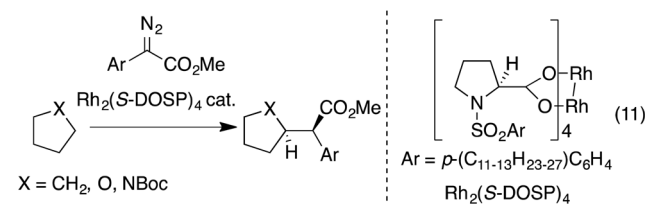
linear, allylic silyl ethers[80] to form products that are equivalent to those from aldol reactions. They also occur at methyl C−H bonds that are benzylic[81] or alpha to nitrogen,[82] and they occur site selectively at weak benzylic[81] and allylic[83] C−H bonds. With these site selectivities, the reactions have been used to prepare a series of medicinally active compounds.[84] A wide range of applications of the insertions of carbenes into C−H bonds involve substrates that undergo intramolecular reactions, and such reactions are some of the earliest examples of the application of C−H bond functionalization to synthesis.[85,86]

Yet, several syntheses have been completed by the application of undirected, intermolecular insertions of carbenes into alkyl C−H bonds. A synthesis of (−)-α-conidendrin was completed using Rh-catalyzed carbene insertion into a benzylic C−H bond, as shown in Scheme 4.[87]

Scheme 4. Synthesis of (−)-α-Conidendrin
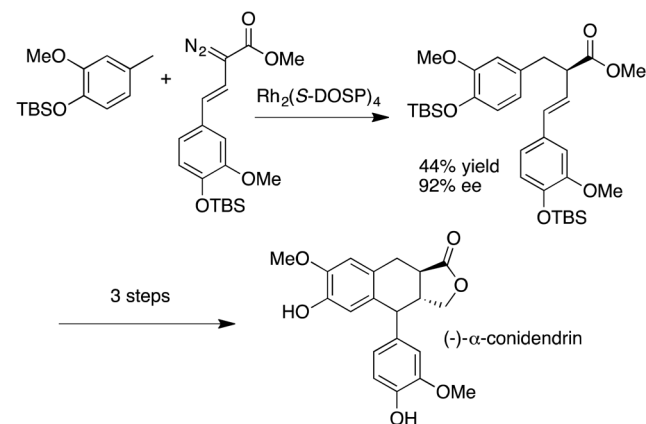
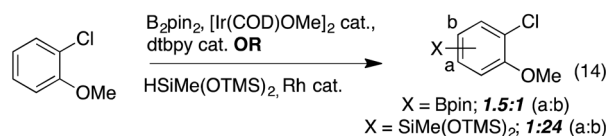## UNDIRECTED FUNCTIONALIZATION OF ARYL C−H BONDS

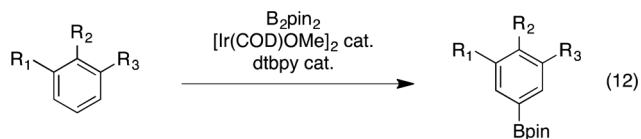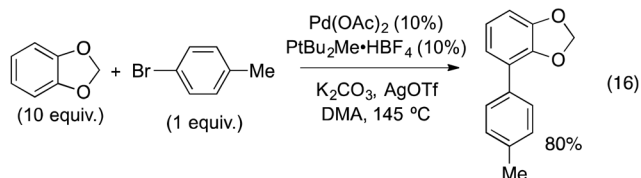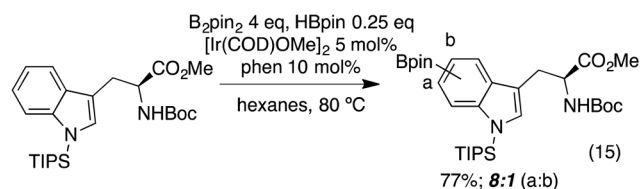The undirected functionalization of aryl C−H bonds is likely to be used more often than the undirected functionalization of alkyl C−H bonds with current catalysts or with catalysts that are derivatives of current catalysts because of the challenges that remain in developing practical undirected functionalizations of alkyl C−H bonds. Catalytic borylation of arenes and

heteroarenes and the reactions of heteroarenes with aryl and heteroaryl halides are currently the most widely used undirected functionalization of aromatic C−H bonds. These two reactions occur with related regioselectivity, reflecting the selectivities observed for reactions that form organometallic intermediates. Recently published silylations of arenes[88] address some of the limitations on the regioselectivity of the borylation of 1,2-substituted arenes and the moderate stability of the products from the borylation of heteroarenes.[89]

The hallmark of the undirected borylation and silylation of aryl C−H bonds is the selectivity controlled by the steric properties of arenes (eqs 12 and 13).[90] Thus, 1,3- or 1,2,3-sub-

$$ \text{(12)} $$

Rh cat. = [Rh(COE)$_2$OH]$_2$, MeO-BIPHEP
Ir cat. = [Ir(COD)OMe]$_2$, 2,4,7-Me$_3$phen

$$ \text{(13)} $$

X = Bpin; **1.5:1** (a:b)
X = SiMe(OTMS)$_2$; **1:24** (a:b)

$$ \text{(14)} $$
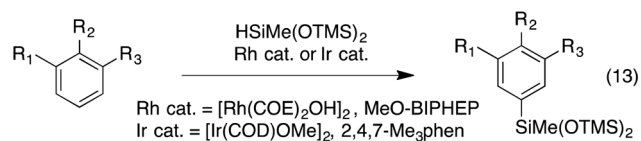
stituted arenes form products containing 1,3,5- or 1,2,3,5-substitution patterns. Recently reported rhodium-catalyzed silylations of arenes form products regioselectively from reactions of unsymmetrically 1,2-substituted arenes containing substituents with distinct steric or electronic properties (eq 14),[91] and a recent study suggests that certain unsymmetrically substituted arenes fused to heteroarenes can react regioselectively (eq 15).[92]

$$ \text{(15)} $$

77%; **8:1** (a:b)

$$ \text{(16)} $$

80%

The silylation and borylation of arenes occur with arene as the limiting reagent, making these processes some of the few practical, undirected functionalizations of arenes.

The reactions of arenes with aryl halides is becoming a useful method to prepare biaryl compounds, particularly from arenes containing directing groups. In principle this reaction could be used to prepare biaryl compounds in the absence of such a group. However, current reactions of arenes lacking functional groups to direct the C−H bond cleavage require an excess of arene (eq 16).[93]

Both the borylation and direct arylation of C−H bonds occur in a practical fashion with heteroarenes (eqs 17 and 18). The

$$ \text{(17)} $$

58-91%

$$ \text{(18)} $$
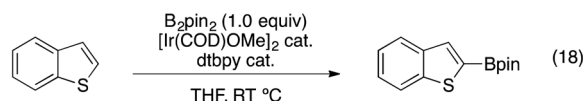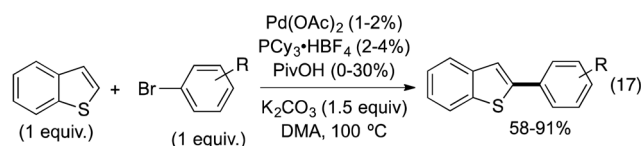
regioselectivity of these reactions results from a combination of the steric and electronic properties of the C−H bonds. In general, the reaction occurs at the most acidic, sterically accessible C−H bond.[89,94,95] For example, both reactions occur at the C−H bond alpha to the heteroatom in furans and pyrroles and occur at the five-membered ring of benzofurans and indoles. However, substituents at nitrogen can modify this selectivity; a large substituent at the pyrrole or indole nitrogen blocks reaction alpha to this atom in the ring and leads to reactions beta to nitrogen.[96−99]

The scopes of the two classes of reactions of six-membered ring heteroarenes are distinct from each other. Direct arylation of a pyridyl ring requires that the ring be activated, for example by generating the pyridine oxide.[100] The reactions of pyridine oxides occur alpha to nitrogen. In contrast, the borylation of pyridines occurs without activation and occurs at the positions beta and gamma to nitrogen with the specific site depending on the steric properties of substituents.[89,96,101] Although some six-membered ring heteroarenes containing two nitrogens do not undergo borylation, they do undergo silylation in good yield with recently developed catalysts, in part because the hetero-arylsilane product is more stable than the heteroarylboronate.[88] These results illustrate that undirected functionalization of heteroarenes can occur in a selective fashion and that the proper reaction must be selected for specific applications.

Heteroarenes containing multiple heteroatoms in a five-membered ring are among the most reactive toward direct arylation, due to the acidity of the C−H bonds at certain sites. Many examples of such reactions have been reported,[102] and the site for these reactions tends to be the C−H bond that is most acidic (eq 19).[103] In contrast, the borylation of C−H

$$ \text{(19)} $$

46-86%

$$ \text{(20)} $$

91%
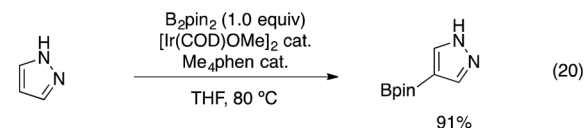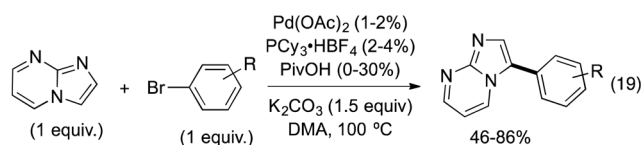
bonds in such rings tends to occur at the position beta to nitrogen (eq 20). During the borylation process, the N−H bond reacts with the boron reagent to place a large boryl substituent on the N−H nitrogen, thereby blocking reaction at the position alpha to this group;[99,104] in addition, the borylation at positions alpha to basic nitrogen atoms tends to be disfavored, relative to borylation at the C−H bond beta or gamma to a basic nitrogen.[89] These data illustrate that the selectivities for reactions of boranes and silanes at five-membered ring heteroarenes are distinct from those of direct

arylation. They also show that C−H bond functionalizations of heteroarenes are among the most practical undirected C−H bond functionalization reactions. The increased reactivity and the site selectivity do not result from directing effects of a coordinating functional group; rather, they result from the effect of the heteroatoms in the ring on the properties of the C−H bonds attached to the ring.

■ UNDIRECTED, ENZYMATIC FUNCTIONALIZATION OF C−H BONDS

The functionalization of alkyl C−H bonds catalyzed by heme and non-heme enzymes has been studied for decades.[105] These studies show how site selectivity can be controlled by the orientation of a substrate controlled by the matrix surrounding the catalytically active metal center. Non-heme iron enzymes catalyze the selective conversion of methane to methanol (eq 21),[106−108] as well as the conversion of alkylarenes, such as

$$CH_4 + O_2 + NADH \xrightarrow{\text{methane monooxygenase}} CH_3OH + NAD^+ + H_2O \quad (21)$$
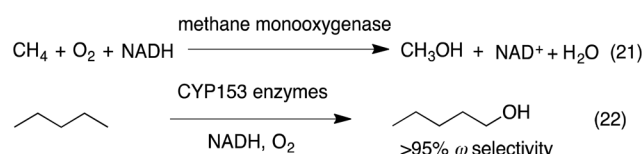
$$\text{>95\%}\ \omega\ \text{selectivity} \quad (22)$$

toluene, to phenols with high regioselectivity.[109] Heme iron enzymes are most active for the hydroxylation of secondary and tertiary C−H bonds. Because the reductase domain and the hydroxylase domain of the heme protein (BM3) of the soil bacterium *Bacillus megaterium* are contained in one fusion protein, this protein is the simplest P450 to use for synthetic purposes and for identifying mutants with increased reactivity or modified site selectivity.[110]

Such heme proteins are part of the metabolism of fatty acids[111,112] and the biosynthesis of many secondary metabolites.[113,114] Most of these proteins that catalyze the reactions of fatty acids react to form mixtures of the products of hydroxylation at the omega-1 and omega positions,[111,115] but isoforms that react with high selectivity for the terminal position have been identified and applied to the hydroxylation of simple alkanes (eq 22)[116] These studies show that a catalyst reacting by pathways that inherently favor functionalization of a secondary C−H bond can react at the primary C−H bond if the substrate is oriented properly. The control of the site selectivity for functionalization by the binding site has led several groups to conduct the directed evolution of BM3 to oxidize distinct positions of substrates that are not functionalized by the wild-type enzyme.[117,118] For example, phenylacetic acid propyl ester undergoes oxidation at the α position with 99% selectivity over oxidation of the alkyl chain (eq 23).[117] Also, testosterone undergoes oxidation at C15 with mutant forms of BM3, as shown in eq 24.[119]

$$\text{99\% selectivity} \quad (23)$$
$$\text{85\% ee}$$

96% selectivity
mutations = R47Y/T49F/V78L/A82M/F87A (24)
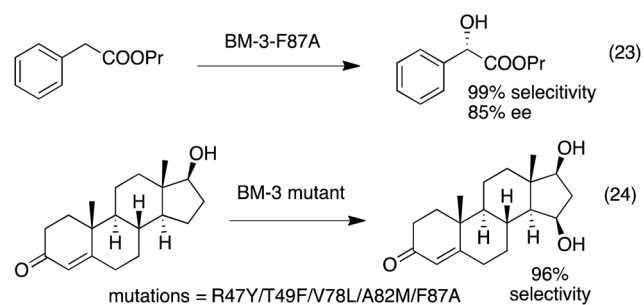
■ APPROACHES TO IMPROVE UNDIRECTED FUNCTIONALIZATIONS OF C−H BONDS

The selectivity of enzymes for functionalization of C−H bonds at specific positions, resulting from the docking of a substrate in a specific orientation, has inspired the synthesis of catalysts that possess a reactive site and a site or structural element that orients substrates in specific positions by noncovalent interactions. In some cases these systems bind substrates predominantly through hydrophobic interactions; more recent systems bind substrates through hydrogen bonds. Reactions catalyzed by systems that bind substrates through noncovalent interactions bear some of the qualities of undirected functionalizations occurring at one site over another due to the steric and electronic properties of a C−H bond and some of those occurring at specific positions due to the direct covalent binding of the substrate to the catalyst prior to cleavage of a C−H bond.

Many years ago, manganese porphyrin catalysts were synthesized containing cyclodextrin units for binding of steroids.[120] These catalysts oxidized androstane-3,17-diol at the 6α position with high turnovers after several improvements to the catalyst (eq 25).[121] In a similar vein, a manganese−porphyrin catalyst

$$(25)$$
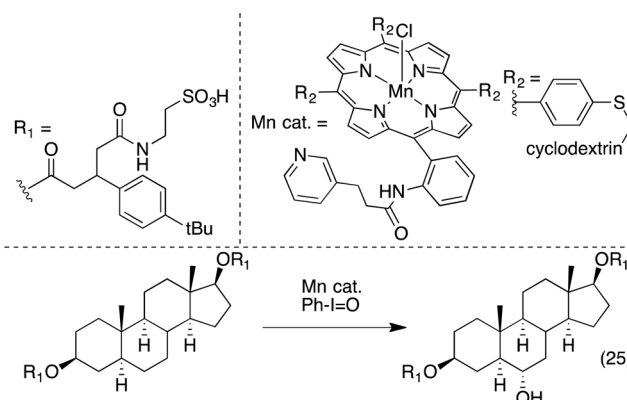
containing 2′,4′,6′-triphenylphenyl groups on the porphyrin catalyzed the oxidation of alkanes with enhanced reactivity at primary over secondary positions and at the omega−1 over omega−2 positions (eq 26).[122]

$$(26)$$

26% : 52% : 17% : 4%
(α : β : γ : δ)
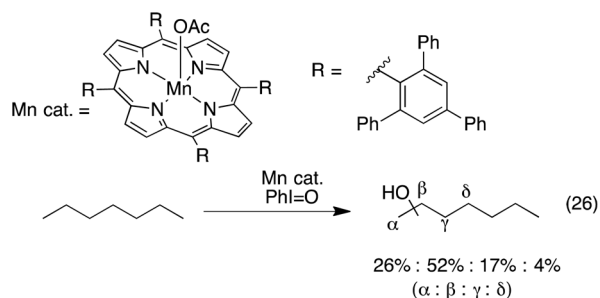
More recently, systems have been reported that catalyze site-specific functionalization of alkyl or aryl C−H bonds due to hydrogen bonding interactions. A manganese catalyst for the oxidation of unactivated C−H bonds in several carboxylic acids was generated by the combination of a terpyridine binding group and a carboxylic acid recognition element (eq 27).[123] With this catalyst, oxidation occurred site selectively at the less acidic benzylic C−H bond of ibuprofen and the trans C−H bond of cyclohexylacetic acid. A strategy involving hydrogen

catalyst = [H$_2$O(L)Mn(μ-O)$_2$Mn(L)(OH)$_2$](NO$_3$)$_4$

L1; R = H

L2; R = (structure)

L = **L1**; 3 : 1 (**A** : **B**)
L = **L2**; 39 : 1 (**A** : **B**)

(27)
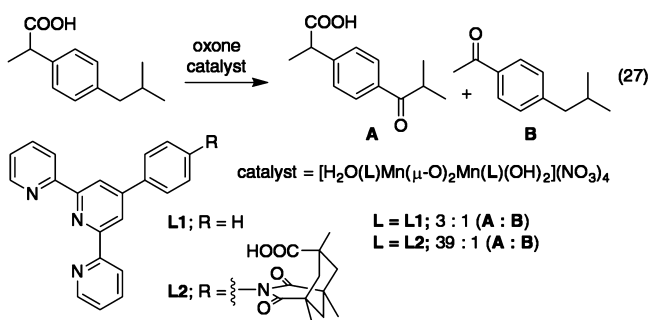
bonding of aromatic esters and phosphate esters to a thiourea unit of a bipyridine ligand has led to selective borylation of the arenes at the meta position (eq 28).[124] This result shows that

(28)

17 : 1 (meta : para)
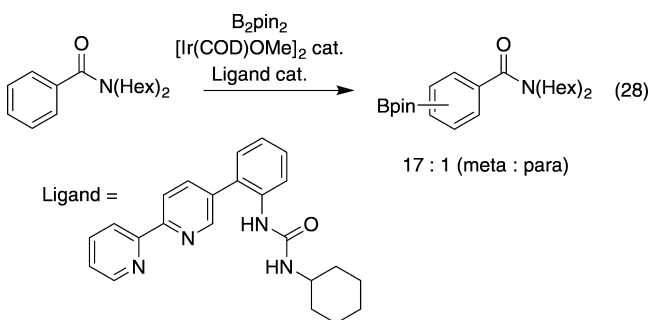
Ligand = (structure)

regioselective reactions can be achieved at positions distal to the functional group by exploiting noncovalent, rather than direct covalent, interactions of the ligand with the catalyst structure.

■ FUTURE OF UNDIRECTED FUNCTIONALIZATION

As noted in the Introduction to this Outlook, undirected functionalization of C−H bonds could enhance the efficiency of synthesis and modify complex structures with selectivities that complement those of directed functionalizations. However, undirected functionalization of C−H bonds is more challenging to achieve than directed functionalization because of the lack of rate enhancement due to coordination of the substrate to the catalyst prior to cleavage of the C−H bond. Of course, undirected functionalization of C−H bonds is also more challenging than undirected reactions at existing functionality, due to the lower reactivity of these C−H bonds. Thus, several limitations must be lifted before undirected functionalizations become synthetic methods that are used widely.

First, reagents for the functionalization of C−H bonds must be available at an appropriate cost and with appropriate stability. The boron reagents used for the functionalization of alkyl and aryl C−H bonds are appropriate for the synthesis of molecules for discovery and for products with high value, but these reagents are too costly for the synthesis of commodity chemicals. For this reason, among others, the author's group has been developing related reactions with commodity silanes. Likewise, since the diazoesters used for cyclopropanations can be suitable for the synthesis of products on a 100 kg scale,[125−128] the use of diazoesters for C−H insertion reactions on a similar scale may be a reality in the near future. Direct arylation reactions are currently cost-efficient C−H bond functionalizations for the synthesis of structures with an aryl or heteroaryl ring linked to a heteroarene. However, undirected reactions that occur with close to 1:1 stoichiometry of the reaction partners are limited to reactions of relatively acidic heteroarenes.

Oxidation reactions with hydrogen peroxide or oxygen could be suitable for large-scale applications, but the catalysts for C−H bond functionalization with such reagents do not generate technically useful amounts of materials. The enzymatic, terminal functionalization of alkanes or fatty acids currently occurs to form milligrams of product, at best.[116,129] Enzymes for oxidation of propane to i-propanol with high activity have been created by directed evolution,[130] but this alcohol and ketone already are produced on multiton scales as a coproduct of the synthesis of phenol. As noted in the body of this Outlook, the activity of catalysts for undirected oxidations of unactivated, alkyl C−H bonds occurs with low turnover numbers. Thus, reactions with reagents that are practical for technical applications are one large gap in the current scope of undirected functionalization.

Yet, one must not overlook the power of C−H bond functionalization to the discovery chemist. The value of synthetic efficiency during the discovery of an active pharmaceutical ingredient, agrochemical, or new material is high, and catalysts that react with new selectivities and activities will create capabilities to access new molecules directly with new functions. In fact, powerful separations technology has made it possible to utilize undirected functionalization reactions that form mixtures of products to generate libraries of molecules for medicinal chemistry or generate sufficient quantities of a desired product to be isolated in pure form from a mixture.[131]

Although it is difficult to predict the route to systems that catalyze selective functionalization of C−H bonds with high activity and selectivity without direct coordination to the catalyst through a covalent dative bond, current research points in several potential directions. First, as noted in the final section of this Outlook, several groups have reported catalysts in which supramolecular interactions between the ligand and the substrate orient one C−H bond closer to the catalyst than other C−H bonds. The origin of this approach can be traced back 40 years,[132,133] but predictable control over site selectivity has only recently begun to be realized.

Second, catalysts that are hybrids of enzymes and organometallic systems or mutants of existing enzymes have the potential to control site selectivity of the reactions of abiological catalysts.[134,135] Recently, such catalysts for the annulation of amides[136] and for the intramolecular amination[137−141] of C−H bonds have been reported. However, small-molecule complexes still catalyze all of these reactions with superior activity and selectivity to the artificial metalloenzymes.[142−144] Thus, much research is required before such artificial metalloenzymes catalyze abiological reactions in a practical fashion.

It is now clear that one or more of these classes of small-molecule and macromolecular catalysts are likely to give rise to practical, undirected functionalizations of C−H bonds. Catalysts for silylation, borylation, and direct arylation with increased reactivity, particularly for alkyl C−H bonds, are likely to be reported, catalysts for oxidation reactions, including oxidative amination and halogenation, that react with higher activity and longevity are likely to be discovered, and catalysts that have sites for noncovalent binding of the substrate to increase reactivity and to control the site at which functionalization occurs are likely to be devised. With such systems, the functionalization of C−H bonds is likely to continue to change the way synthetic chemists, including those preparing commodity chemicals, specialty chemicals, and fine chemicals, envision the way to design the synthesis of molecules.

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Notes

The authors declare no competing financial interest.

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