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C–H Bond Functionalization in Complex Organic Synthesis

Kamil Godula and Dalibor Sames*

Direct and selective replacement of carbon-hydrogen bonds with new bonds (such as C–C, C–O, and C–N) represents an important and long-standing goal in chemistry. These transformations have broad potential in synthesis because C–H bonds are ubiquitous in organic substances. At the same time, achieving selectivity among many different C–H bonds remains a challenge. Here, we focus on the functionalization of C–H bonds in complex organic substrates catalyzed by transition metal catalysts. We outline the key concepts and approaches aimed at achieving selectivity in complex settings and discuss the impact these reactions have on synthetic planning and strategy in organic synthesis.

Organic compounds consist of chains or rings of consecutive carbon atoms, each capped with one or more hydrogen atoms. This scaffolding, interrupted and adorned with occasional "heteroatoms" (mainly oxygen, nitrogen, phosphorus, sulfur, and the halogens), underlies the extraordinary array of small molecules and biopolymers that comprise living organisms as well as such diverse materials as crude petroleum, pharmaceuticals, molecular switches, and plastics (Fig. 1).

Organic synthesis relies on the transformation of functional groups, or structural features exhibiting relatively high chemical reactivity. C–H bonds are not generally viewed as functional groups in this context. Thus, installment of a new bond requires the presence of either a heteroatom, such as oxygen or a halogen, or unsaturation (i.e., absence of hydrogens) in the carbon backbone (Fig. 2). This logic underpins the process of synthetic planning or synthetic strategy (*1*). The reactive sites or functional groups are typically incorporated by means of multiple transformations; consequently, the starting materials are often rather dissimilar from the final products. This is illustrated by the sequence of several steps that converts compound **1** to product **2** (Fig. 3).

In this light, it becomes clear that the introduction of new functionality directly through transformation of C–H bonds unlocks opportunities for markedly different synthetic strategies. For example, the same target molecule (**2** in Fig. 3) may be accessed in a single step by displacement of a hydrogen atom. Considering the high abundance of C–H bonds, precise one-step substitution of carbon-hydrogen bonds with C–C or C–X bonds (where X is O or N), without disruption of the surrounding molecular structure, carries considerable appeal for synthesis. Thus, selective C–H bond functionalization, as exemplified by the direct conversion of compound **3** to product **2** (Fig. 3), provides straightforward and concise approaches where the topology, or the overall skeletal structure, of the starting material resembles that of the product ("topologically obvious assembly").

In addition to the assembly of specific target molecules, C–H bond functionalization also reshapes synthetic strategies for preparation of series of compounds ["structural core diversification" (Fig. 4)]. The ability to selectively target a number of different C–H bonds in a complex substrate permits direct access to multiple analogs from a common structural predecessor. This sharply contrasts with traditional approaches, wherein multistep, and often distinct, de novo sequences are required for each derivative.

Thus, by viewing C–H bonds as "ubiquitous functionality," we are opening a new chapter in organic synthesis with many exciting opportunities. Advances in homogeneous transition metal catalysis have identified a number of new transformations of C–H bonds, and the strides made in elaborating simple hydrocarbons have been amply reviewed elsewhere (*2*, *3*). Here, we highlight C–H bond functionalization in the context of complex organic molecules—which contain many different kinds of C–H bonds, as well as reactive functionalities—and outline the key approaches leading to selective functionalization. We also discuss the impact of these reactions on synthetic planning and strategy in organic synthesis.

Radical Beginnings: Intramolecular Radical Reactions

Early approaches to functionalization of isolated alkyl C–H bonds (unactivated sp^3 bonds) relied on highly reactive intermediates, including free oxygen and nitrogen radicals. In complex substrates, regioselectivity was achieved by exploiting structural proximity between the high-energy radical, generated transiently in the reaction mixture, and the alkyl group resulting in the intramolecular hydrogen atom abstraction (Fig. 5). The long history of these reactions dates back to the studies carried out by Hoffmann in the late 1800s (*4*), showing that homolysis of bromamines and chloramines led to functionalization of δ-methylene or methyl groups. The synthetic possibilities presented by this process, known today as the Hoffmann-Löffler-Freytag reaction, were realized in the synthesis of nicotine (*5*) and, much later, in the synthesis of conanine steroidal alkaloids (Fig. 5) (*6*, *7*). Analogous pro-

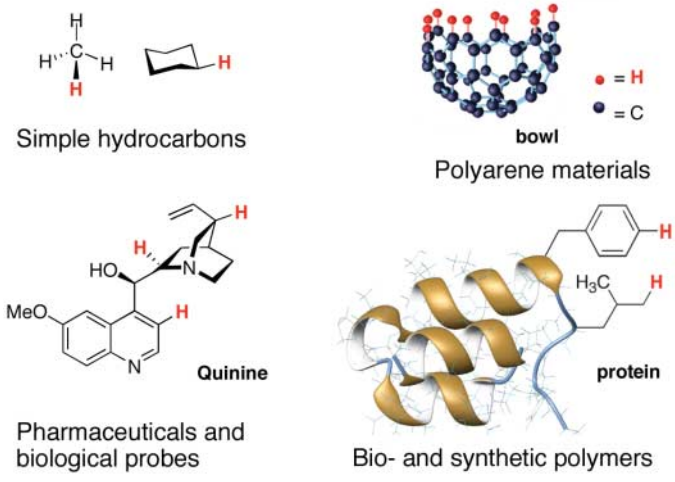

Fig. 1. C–H bonds are found in nearly all organic compounds. C–H bond functionalization will influence the broad field of chemical synthesis. Hydrogen atoms in red designate examples of different C–H bonds in diverse organic compounds.

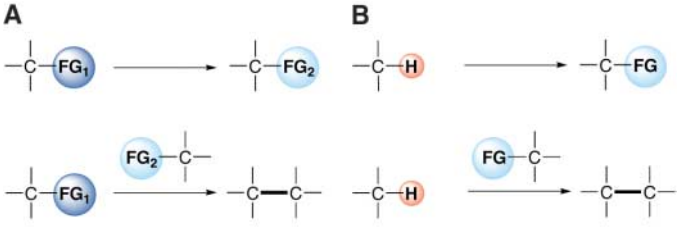

Fig. 2. (**A**) Traditional approach to organic synthesis by means of functional group (FG) transformation. (**B**) Synthesis by means of C–H bond functionalization.

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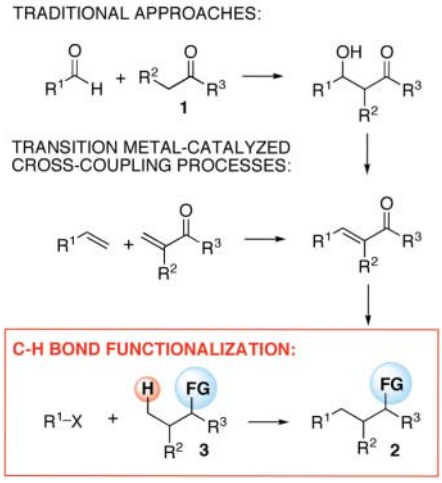

Fig. 3. Evolving algorithms in organic synthesis. R, alkyl or aryl group.

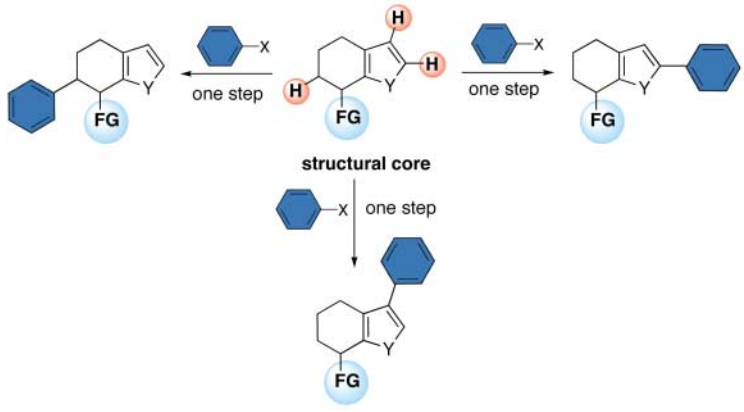

Fig. 4. Structural core diversification by means of C–H bond functionalization: Systematic functionalization of complex motifs provides direct access to a series of structural analogs.

cesses initiated by an oxygen-centered radical were also developed (*8*). Most notably, Barton and Beaton introduced the photolysis of a nitrite ester as a means for converting an isolated methyl group into an oxime in one step. This transformation formed the key step in the synthesis of aldosterone acetate from readily available corticosterone acetate (*9*). Despite its low yield, this synthesis was a landmark achievement in demonstrating the potential of C–H functionalization in the context of an important problem.

These early examples also show that, in a general sense, the functionalization of unactivated sp^3 bonds results in profound strategic advantages; the alternative methods include either a stepwise functional group shuffle (from an existing functional group to the distant unactivated position) or de novo synthesis, neither of which can match the efficiency of the direct functionalization process.

Intramolecular Transition Metal–Catalyzed Carbene and Nitrene Insertion

Analogous to radicals, carbenes can also serve as reactive intermediates for C–H functionalization. In contrast to free carbenes, the corresponding transition metal carbenoids readily available by decomposition of diazocarbonyl substrates offer more control over the reaction course. In particular, the introduction of $Rh_2(OAc)_4$ as a versatile catalyst led to the development of a powerful synthetic methodology with a wide substrate scope. The rhodium-dimer is thought to chaperone the carbene insertion into the C–H bond in a direct fashion, without forming a new C–M intermediate (Fig. 6, top) (*10*). Thus, readily available diazocarbonyl substrates can be converted in one step to cyclic ketones, lactones, and lactams by means of regioselective C–C bond formation at the alkyl site. A wide variety of C–H bonds can be functionalized in this manner, including sterically hindered sp^3 C–H bonds. Furthermore, an excellent level of stereo- and enantioselectivity can be achieved in many different structural contexts by the proper choice of a chiral dirhodium catalyst (Fig. 6A) (*11*).

These reactions are frequently applied to the synthesis of advanced intermediates and natural products (*12*). Several features make them attractive in this respect, including neutral reaction conditions, good functional group tolerance, and a high degree of stereoselectivity. They provide a unique and direct strategy for preparation of valuable cyclic products, one that is orthogonal to the alternative multistep routes.

C–N bond formation at an isolated alkyl site, achieved by transition metal–catalyzed nitrene insertion, was pioneered by Breslow (*13*) and subsequently developed into an attractive methodology by Du Bois (*14*). Although the detailed mechanism is a subject of debate, it can formally be viewed as a nitrene insertion, a process analogous to the carbene relative. Cyclization of readily available carbamate or sulfamate substrates was achieved with the use of a $Rh_2(OAc)_4$ catalyst, in the presence of a $PhI(OAc)_2$ oxidant and a MgO base (Fig. 6B). This mild process is regio- and stereoselective, allowing for the introduction of a nitrogen atom at a late stage of the assembly. The strategic advantages of both carbene and nitrene insertion reactions have recently been demonstrated in a highly complex context of an elegant synthesis of natural product tetrodotoxin (Fig. 6C) (*15*).

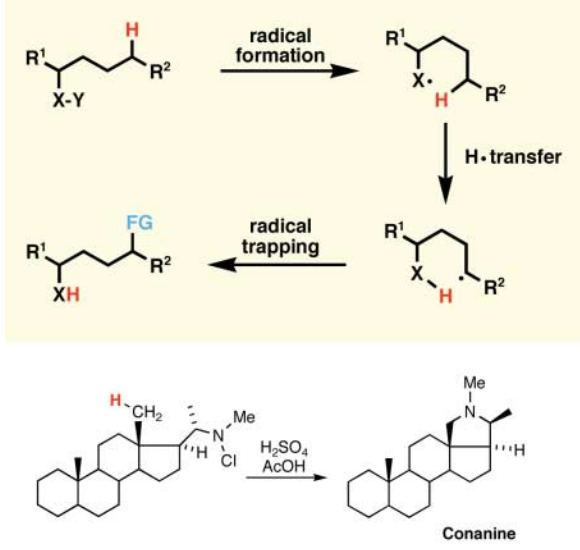

Fig. 5. Intramolecular radical reactions. Hydrogen atoms in red are those substituted in the depicted process. Me, methyl group.

C–H Functionalization by Means of Coordination-Directed Metallation

Directed metallation is another powerful approach for selective functionalization of C–H bonds in complex substrates applicable to a variety of different C–H bonds (sp^2 and sp^3), including those of isolated alkyls. It entails the use of a suitable heteroatomic function in the substrate to direct a metal complex to the vicinity of a distant C–H bond. The resulting metallacycle, usually a five- or six-membered ring, serves as a versatile intermediate en route to products containing new C–C or C–X bonds (Fig. 7).

In terms of structural complexity, one of the most advanced examples of directed metallation was carried out in the context of the synthesis of the antitumor alkaloid rhazinilam (*16*). The pivotal step involved selective dehydrogenation of the diethyl segment in intermediate **4**. This was achieved by the attachment of a platinum complex to the aniline nitrogen to form complex **5** and subsequently the reactive intermediate **6** (Fig. 7A). Thermolysis of complex **6** provided platinum hydride **7** as the major product through a sequence of C–H bond ac-

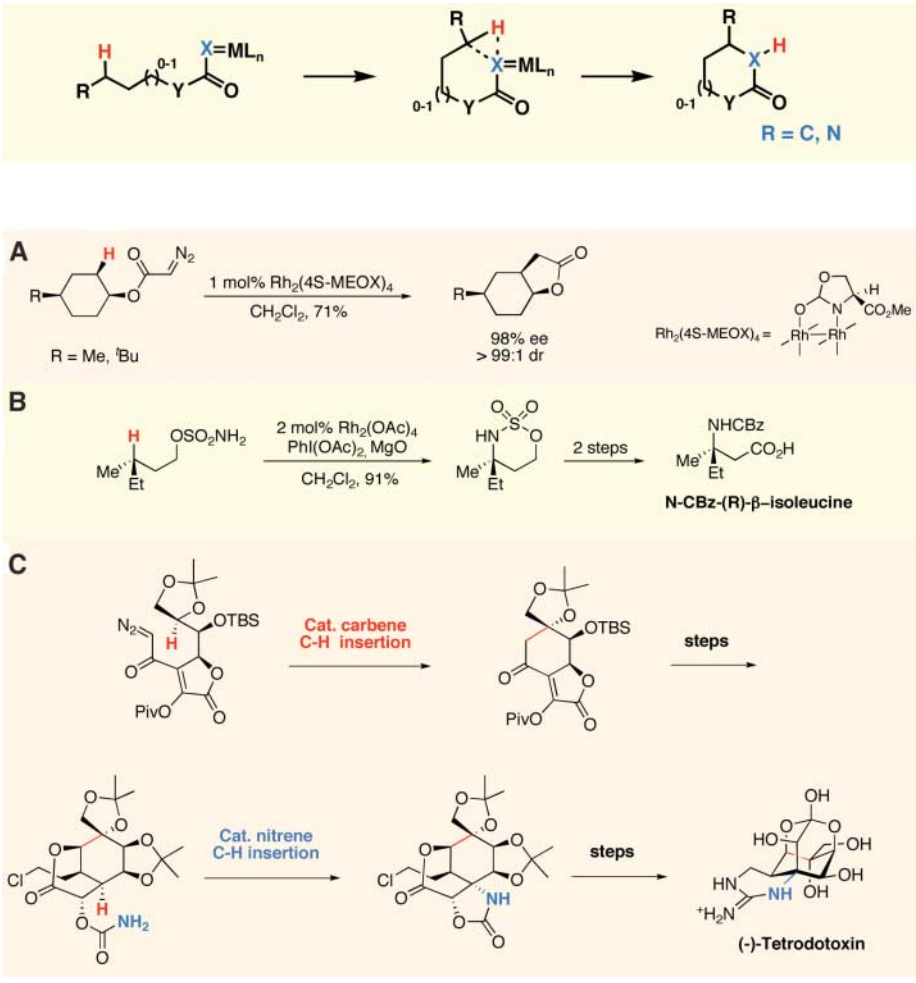

Fig. 6. (**A** to **C**) Intramolecular carbene and nitrene insertion into sp^3 C–H bonds. ML$_n$, general representation of a transition metal complex with a number (*n*) of ligands (L); ^{t}Bu, *tert*-butyl group; TBS, *tert*-butyldimethylsilyl group; Piv, pivaloyl group; CBz, benzyl carbamate; ee, enantiomeric excess; dr, diastereomeric ratio; (-) designates a levorotatory enantiomer.

tivation and β-hydride elimination. Notably, selective functionalization was achieved at the least reactive site, namely the isolated ethyl group, in the presence of notoriously reactive pyrrole and aniline rings.

Although this process was stoichiometric in platinum, it demonstrated the potential of C–H functionalization in synthesis of natural products and at the same time indicated that the transition metal chemistry developed for simple hydrocarbons [i.e., methane activation by Shilov chemistry (*17*)] was applicable to complex organic substrates. On a strategic level, it showed how C–H functionalization can give rise to novel and direct strategies for synthesis of complex natural products.

The versatility of palladium chemistry can be harnessed by both formation and utilization of palladacycles (*18*). Synthesis of the alkaloid teleocidine inspired the development of new C–C bond formation by means of transmetallation of palladacycle **8** with aryl- and alkenylboronic acids (*19*). Although the substrate scope is rather limited, this process represents a prototype for a direct arylation or alkenylation of unactivated sp^3 C–H bonds (Fig. 7B).

The directed platination and palladation approaches have also been used for selective oxygenation of isolated alkyl groups. Catalytic hydroxylation of α amino acids has been reported (*20*). For example, L-valine was converted to γ-lactone **9** in water in the presence of K_2PtCl_4 catalyst [1 to 10 mole percent (mol %)] and $CuCl_2$ oxidant (Fig. 7C). A number of substrates may be hydroxylated, including norvaline, leucine, isoleucine, *n*-butylamine, and valeric acid. Mechanistic study showed that the Pt(II) center cleaved the C–H bond, yielding a putative platinacycle intermediate, which underwent fast oxidation to a platinum (IV) intermediate, which in turn collapsed to the lactone and the platinum(II) catalyst. Thus, the direct functionalization of natural amino acids afforded valuable intermediates (γ-lactones) in one step without the use of organic solvents. Rooted in the Shilov platinum chemistry, this process represents an early example of selective hydroxylation of complex substrates by a simple transition metal catalyst. It differs conceptually from methods based on free radical chemistry (e.g., Fenton chemistry—oxidation with free hydroxyl radicals) or metal-oxo chemistry (P450 enzymes or small molecule mimics) (*21*).

Cyclopalladation of oximes has recently been re-examined and has formed the basis for a new catalytic process. Aliphatic oximes can undergo acetoxylation of the α methyl group catalyzed by $Pd(OAc)_2$ in the presence of $PhI(OAc)_2$ as the oxidant (Fig. 7D) (*22*). A minor alteration of the oxidant system also allows for formation of C–I bonds, as recently demonstrated in diastereoselective iodination of a methyl group under the direction of chiral oxazoline auxiliary (*23*). This is an active area of research that will continue to generate new catalytic protocols for both C–X and C–C bond formation directed by a variety of functional groups.

Coordination-directed metallation has also been the underlying mechanism for selective C–C formation at arene rings (sp^2 C–H bonds) in the ortho position to a suitable functional group. The key discovery in this area was made in the Murai group (*24*), which demonstrated the first efficient, catalytic, and selective coupling of an arene C–H bond and an alkene. Aromatic ketones may be alkylated exclusively in the ortho positions in the presence of a ruthenium catalyst under neutral conditions (Fig. 8A). This report attracted much interest and inspired the development of related reactions (*25*).

The likely mechanistic scenario involves the insertion of the low-valent ruthenium to the ortho-arene C–H bond affording a metallacycle intermediate (**10** in Fig. 8), which facilitates the subsequent C–C bond formation affording the product and the regenerated catalyst. The overall process provides a neutral alkylation method catalytic in the transition metal.

Substrates other than aromatic ketones, namely enones (*26*) and α,β-unsaturated esters (*27*), can be alkylated at the β position, whereas aldehydes can be converted to ketones by means of the insertion of alkenes into aldimine C–H bonds (*28*). In addition to alkylation, ortho-acylation occurs when a mixture of alkene and carbon monoxide is used (*29*). It was shown that the sp^2 nitrogen of imines and pyridines may also serve as the directing group, usually under the action of rhodium (I) complexes. Recently, Bergman and Ellman have reported the rhodium-catalyzed intramolecular alkylation of ketimines, affording new annulation methodologies for the formation of five- and six-membered cycles (Fig. 8B). This methodology allowed for straightforward and efficient access to a biologically active tricyclic analog of mescaline (*30*). A high degree of asymmetric control was also achieved in the presence of a chiral ligand (*31*).

The catalytic approach differs from traditional protocols on both a mechanistic and an operational level. For example, ortho-lithiation,

although a highly useful method for elaboration of arenes, requires a stoichiometric amount of strong base (butyl lithium), which has certain limitations with regard to the choice of suitable directing groups. It may also be problematic for substrates with sensitive functional groups. Similarly, electrophilic approaches do not provide access to the same products because the reactivity and regioselectivity preferences of Friedel-Crafts alkylation (electrophilic aromatic alkylation), dictated by the reaction mechanism, are completely different from those of the directed catalytic methods discussed above. For instance, product **11** shown in Fig. 8 would not be obtained under Friedel-Crafts conditions. Thus, the catalytic approach not only represents milder alternatives to standard ionic protocols but also unlocks a new scope of products inaccessible through the standard chemistries.

Catalytic ortho-arylation has also been developed for a variety of substrates, including aromatic imines, 2-aryl-oxazolines, -imidazolines, and -pyridines. Readily available haloarenes serve as arene donors in the presence of the ruthenium catalyst and a weak base (Fig. 8C) (*32*). The synthetic appeal of this process is readily apparent; the contiguous substitution patterns around the aromatic ring (e.g., 1,2,3-trisubtituted benzene derivative **12**) can be accessed in a highly efficient manner. Direct C–H arylation reactions offer a distinct advantage over standard cross-coupling reactions [e.g., Suzuki coupling (*33*)] in that they eliminate the need for functionalization of the substrates (such as the formation of a halide or a boronate ester) before C–C coupling. This seemingly small point carries important consequences in the synthesis of heavily substituted biaryl compounds.

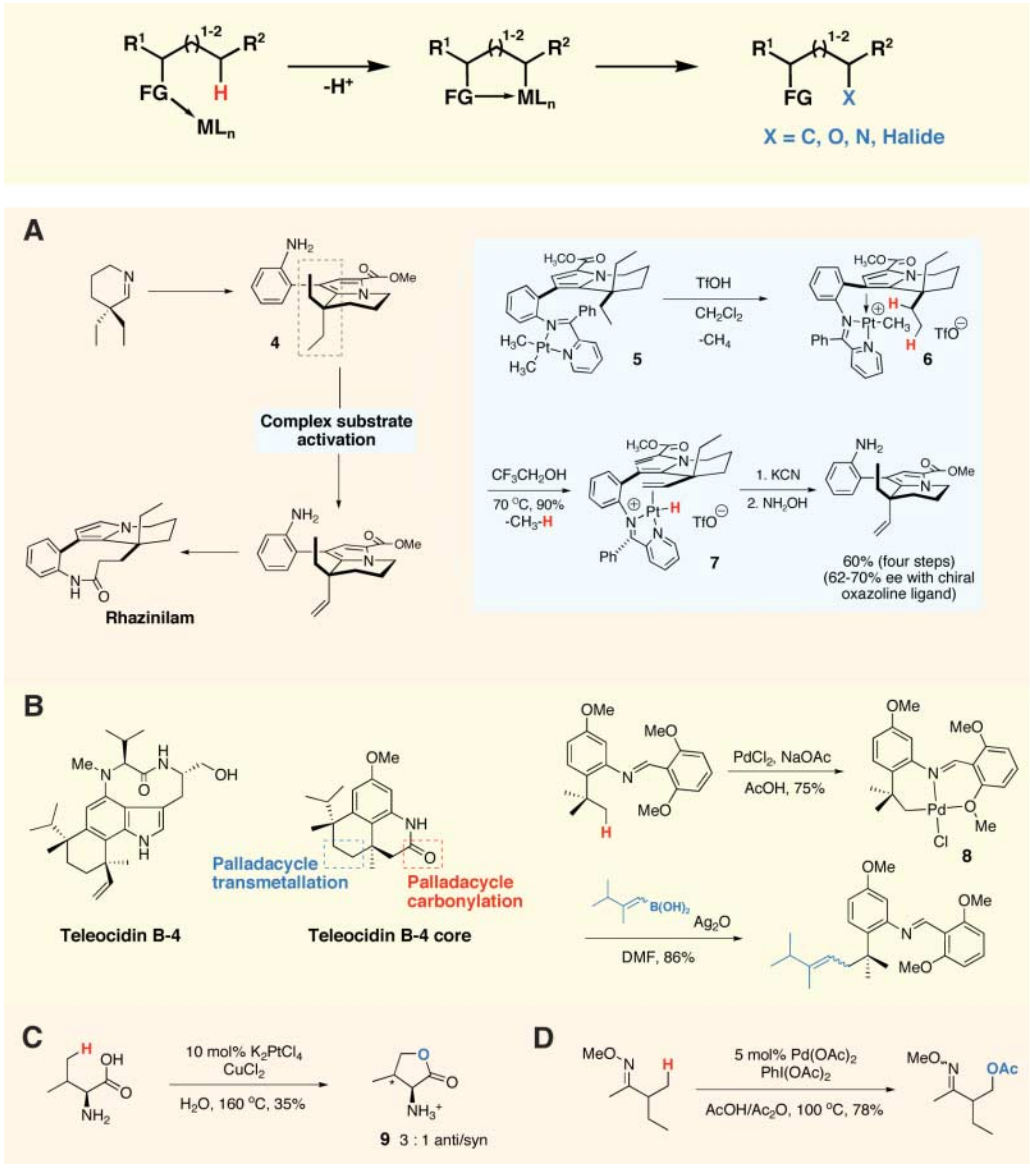

Fig. 7. (**A** to **D**) Functionalization of sp^3 C–H bonds by means of coordination-directed metallation. TfOH, trifluoromethanesulfonic acid; AcOH, acetic acid; Ac_2O, acetic anhydride; DMF, dimethylformamide; syn/anti, ratio of isomers with a pair of substituents on the same face (syn) and the opposite face (anti) of the lactone ring.

Directed metallation is a powerful approach that enables regioselective functionalization of C–H bonds in diverse structural contexts ranging from isolated alkyl groups to aromatic rings. The transition metal in cooperation with the directing group cleaves the targeted C–H bond, and the corresponding metallacycle serves as a versatile intermediate for either C–C or C–X bond forming processes. The availability of a variety of suitable metals—including electrophilic palladium and platinum salts or low-valent ruthenium, rhodium, and iridium complexes—lends sufficient flexibility for reaction design and development. This is an active area that will continue to generate new catalytic and selective C–H functionalization methods.

Other Approaches to Selective C–H Bond Functionalization

Aside from the intramolecular and directed methods, what other concepts and approaches may afford intermolecular and selective functionalization of C–H bonds in complex substrates? Can we generate relatively simple catalysts with programmable selectivities?

One such approach would require the catalyst to discern relative strength and stereoelectronic properties of C–H bonds. For example, sp^3 C–H bonds adjacent to heteroatoms, typically oxygen or nitrogen (α position of ether or amine) or an arene ring (benzylic position), are referred to as "activated," owing to their lower thermodynamic strength and higher reactivity in comparison to isolated alkyl C–H bonds.

For example, intermolecular carbene insertion reactions have been reported in neat hydrocarbons (*34*); however, in complex substrates, insertion occurs at activated positions. Davies has shown impressively broad scope for this reaction class, albeit with some limitation on the carbene precursor (*35*). Namely, α-aryl- and α-vinyl-diazocarbonyl compounds are required to disfavor carbene dimerization relative to C–H insertion. Otherwise, this method can substitute the α positions of ethers, amines, and carbamates, as well as benzylic and allylic positions. In a crude sense, the regioselectivity seems to be determined primarily by the C–H bond strength and secondarily by the steric hindrance (Fig. 9).

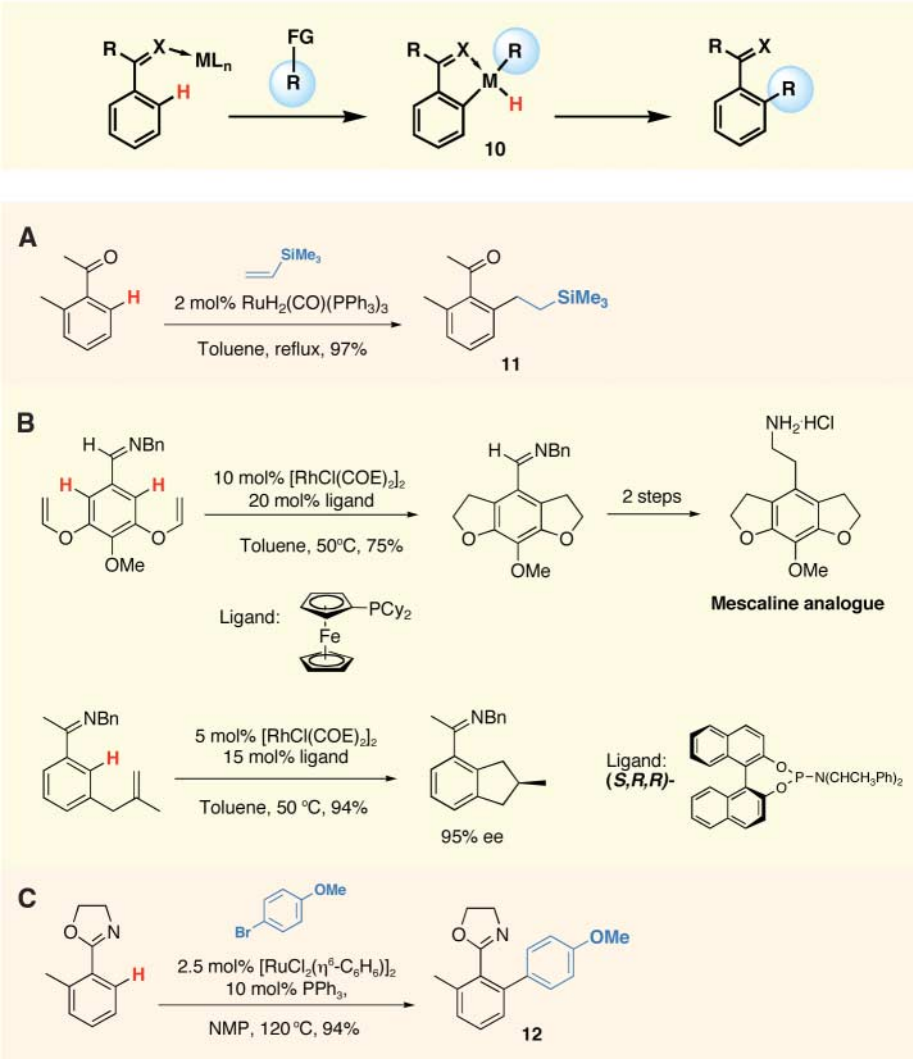

Fig. 8. (**A** to **C**) Functionalization of arene C–H bonds by means of coordination-directed metallation. Cy, cyclohexyl group; Bn, benzyl group; COE, cyclooctene; NMP, *N*-methylpyrrolidinone; PPh_3, triphenyl phosphine.

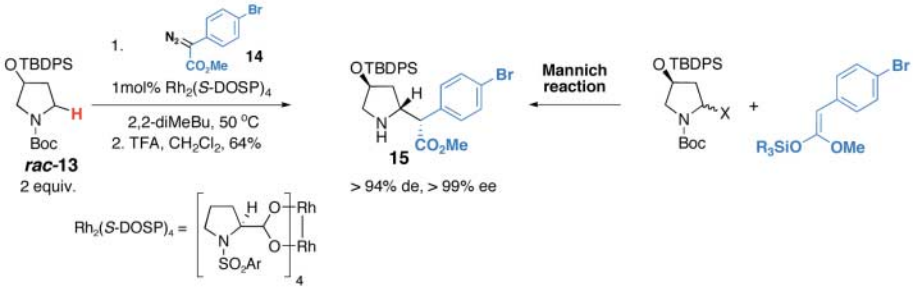

Fig. 9. Enantioselective intermolecular carbene insertion into activated sp^3 C–H bonds. R, alkyl group; TBDPS, *tert*-butyldiphenylsilyl group; Boc, *tert*-butyl carbamate; X, halide; de, diastereomeric excess.

Furthermore, the chiral dirhodium catalysts allow for excellent control of stereo- and enantioselectivity. This could be demonstrated by the kinetic resolution of a racemic pyrrolidine substrate **rac-13**. Coupling of **rac-13** with diazophenylacetate **14** afforded compound **15** as the major product with high diastereo- and enantioselectivity (Fig. 9) (*36*). This one-step process represents a highly attractive alternative to the traditional Mannich reaction (*37*). For the latter process, a regioselective oxidation of the corresponding pyrrolidine would be required before the C–C bond formation. Thus, carbene insertion with protected amines affords Mannich products; similarly, silylethers can directly lead to aldol products under neutral conditions. This method enabled efficient syntheses of pharmaceuticals and natural products.

The next key question in this context is whether a programmable selectivity can be achieved among unactivated sp^3 C–H bonds—i.e., within a long isolated alkyl group—in the absence of the suitable directing mechanisms discussed earlier, by the actions of a small transition metal catalyst. A recent report described selective borylation of terminal methyl groups in substrates containing a number of functional groups including ether, ketal, amine, and fluoride (Fig. 10) (*38*). It appears that the high selectivity is primarily governed by the sensitivity of the rhodium catalyst to steric hindrance. Furthermore, in cases where multiple methyl groups are present, a preference for the least electron-rich C–H bonds was observed. It is notable that a small metal catalyst can achieve such a high level of reactivity and selectivity, highlighting the potential of transition metal chemistry.

Selective targeting of internal isolated sp^3 C–H bonds in complex targets has hitherto been limited to enzymatic or biomimetic systems (*39*) equipped with a recognition element capable of arranging the C–H bond of interest and the reactive center in a proximal and favorable orientation. At present, it seems that the reactivity differences between isolated alkyl C–H bonds (e.g., two adjacent methylenes in the middle of a long alkyl group) are very small to tackle this problem in the absence of the molecular recognition element. For now, this general goal represents the ultimate chemo-, regio-, and stereoselectivity to be achieved and continues to serve as an inspiration for the future generations of scientists.

In the area of aromatic systems, the unique properties of transition metal catalysts may lead to regioselectivity preferences that are complementary to the standard ionic methods. A novel process for catalytic borylation of aromatics with pinacolborane or pinacoldiboron has recently been introduced. Two catalytic systems have been developed for this transformation, namely iridium (I) phosphine complexes (*40*) and iridium (I) bipyridyl complexes (Fig. 10) (*41*). Both methods exhibit an impressive substrate scope, including electron-rich and electron-poor arenes and heteroarenes. Regioselectivity at the benzene ring is strictly controlled by sterics, placing the boronate in the least hindered position. Hence, these methods not only allow for one-step preparation of areneboronates, but also afford isomers that are not readily available by means of halogenation or ortho-lithiation. The observed kinetic trends (faster rates with electron-deficient arenes) imply that the key step may involve either oxidative addition of the C–H bond to the iridium metal or σ-bond metathesis between the C–H bond and Ir–B bond.

Because heteroaromatics are indispensable core structures of pharmaceuticals, biological

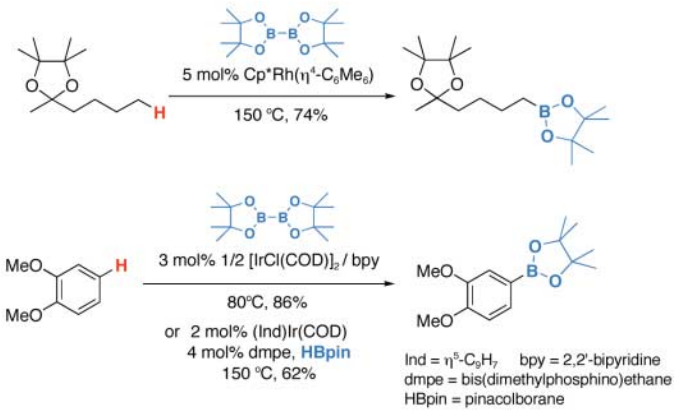

Fig. 10. Borylation of alkyl and aryl C–H bonds. COD, cyclooctadiene.

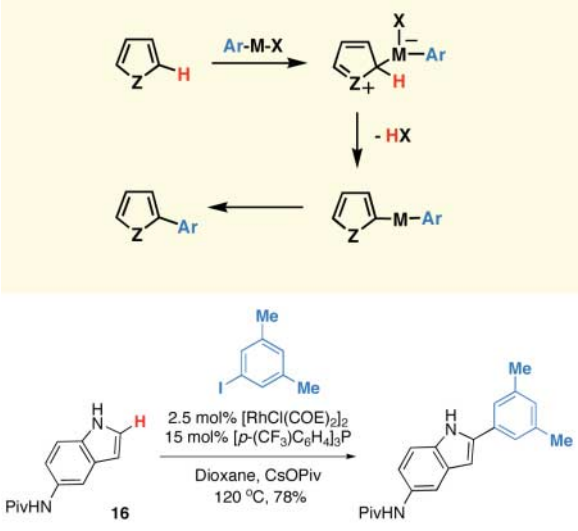

Fig. 11. Arylation of heteroarene C–H bonds. M, transition metal; Z, nitrogen, oxygen, or sulfur atom; Ar, aryl group; CsOPiv, cesium pivalate.

probes, and other functional synthetics, considerable attention is currently focused on catalytic functionalization of these compounds. After the early reports, several laboratories have been engaged in the development of new methods for arylation of electron-rich heteroarenes, such as furans, thiophenes, and (NR)-azoles (*42*–*44*). These protocols usually rely on a palladium catalyst in the presence of a weak base. Arylation of (NH)-azoles in a free form has been demonstrated. Fig. 11 illustrates an example of rhodium-catalyzed arylation of indole **16** (*45*). Notably, this catalytic system targets the C–H bond at the 2 position in the presence of two N–H bonds of relatively high acidity.

The experimental evidence suggests that these reactions proceed by means of an electrophilic metallation mechanism. However, in contrast to standard electrophiles (e.g., halogens and acyl halides), the transition metal catalyst prefers the cleavage of the C–H bond adjacent to the nitrogen atom, which in turn determines the final site of arylation. An alternative mechanistic possibility involves a Heck-type process. Although Heck coupling—which entails catalytic coupling between haloarene and alkene—may also be classified as catalytic C–H functionalization transformation, this important process has been extensively studied and reviewed (*46*).

Arylation of electron-deficient positions of heteroaromatic compounds has also been demonstrated, although with limited scope and efficiency (*47*–*49*). However, this is an active area of research, and advances in terms of substrate scope, catalyst efficiency, and operational issues may be expected in the coming years.

Conclusions

C–H bond functionalization is an area of rapid growth that will continue to push the limits of chemical reactivity to the extent that C–H bonds may soon be viewed as ubiquitous functional groups (*50*). Such an ability to transform a variety of C–H bonds unlocks entirely new perspectives in complex organic synthesis. The direct strategies for assembling molecules are readily apparent from a topological perspective and should lead to major simplification of synthetic sequences. Unlocking the reactivity of ubiquitous bonds will also affect the process of molecular design in many diverse areas of research, because novel synthetic processes not only affect how we make desirable materials but also what we make and study.

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