C–H Activation

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Abstract: Transition metal-catalyzed C–H activation has emerged as an increasingly powerful platform for molecular syntheses, with enabling applications to natural product synthesis, late-stage modification, pharmaceutical industries and material sciences, among others. This primer summarizes representative developments in C–H activation, including recent advances in asymmetric, photo-induced and electrochemical C–H activation. Likewise, strategies for applications of C–H activation towards the assembly of structurally-complex (bio)polymers and drugs in academia and industry are discussed.

Introduction

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The enormous progress in molecular syntheses has largely been enabled through transformative metal catalysis, allowing for the assembly of increasingly complex compounds.[1] For instance, the Nobel prize-winning palladium-catalyzed cross-couplings have found widespread applications in academia in industries (Fig. 1a).[2-4] Despite of indisputable advances, cross-couplings require two pre-functionalized substrates, thus resulting in lengthy syntheses and the formation of undesired stoichiometric by-products. In contrast, the selective activation of otherwise inert C–H bonds has the power to avoid pre-functionalizations, thereby minimizing the generation of often hazardous waste.[5-13] Thus, transition metal-catalyzed C–H activation, namely the inner-sphere C–H cleavage to form a C–TM bond, represents an environmentally-benign and economically-attractive strategy for organic syntheses (Fig. 1b). As a consequence, C–H activation has been recognized as a transformative tool.

The full control of chemo- and position-selectivities constitutes the major challenges for synthetically-meaningful C–H activations. Position-selectivity can, for example, be achieved by exploiting the substrate's electronic or steric properties as well as by chelation assistance. To this end, numerous mono- or bidentate directing groups have been devised for largely proximity-induced transition metal-catalyzed C–H activation,[7] while significant progress was made in remote C–H activation by σ-activation, template assistance or hydrogen-bonding linker.

Herein, we present concepts and strategies for synthetically-useful C–H activations, each being illustrated by selected representative examples. Notable applications of C–H activation to total syntheses, drug diversification, or peptide and polymer assembly are discussed, along with their limitations, current trends, future challenges and opportunities.

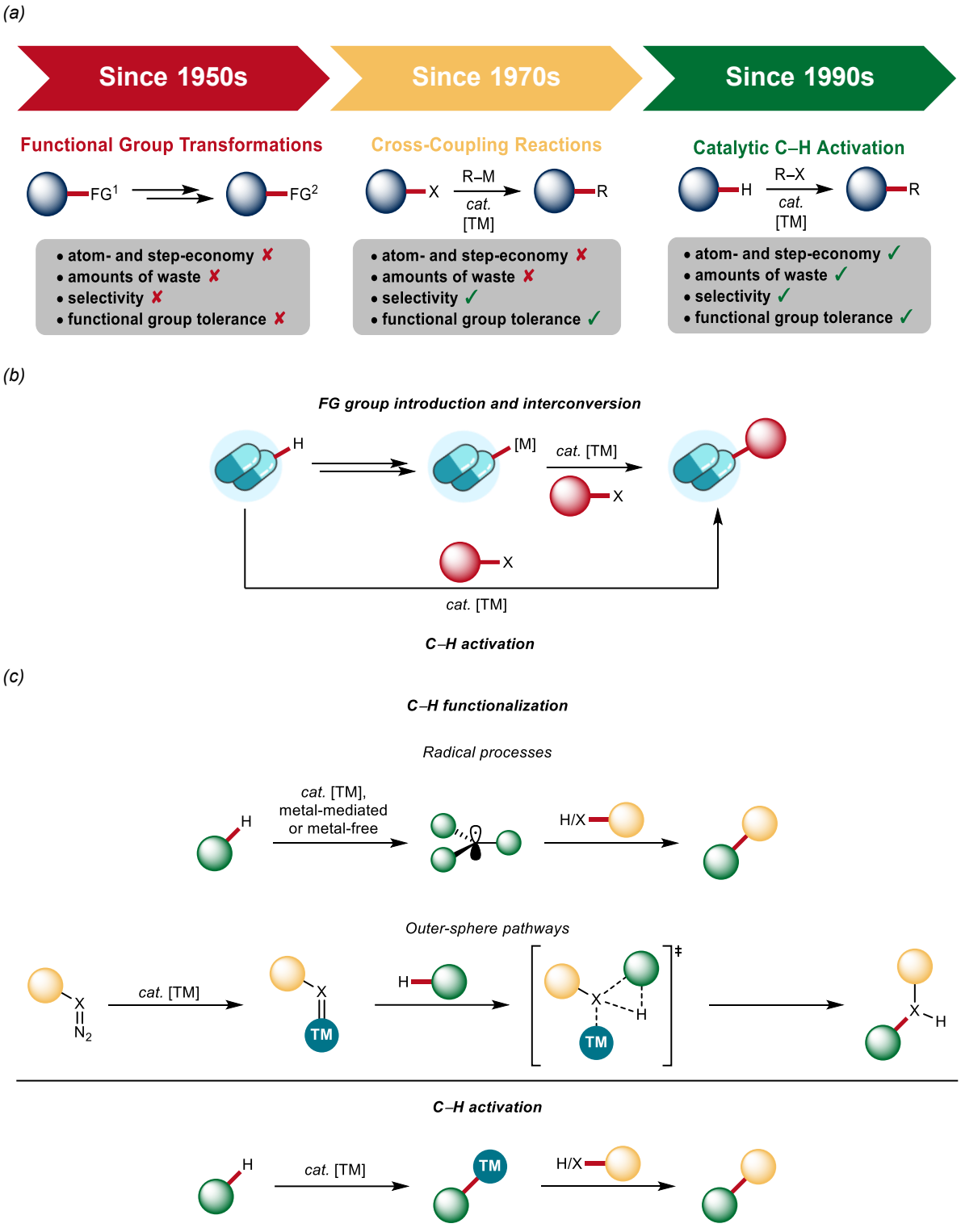

Figure 1. (a) The evolution of molecular syntheses from functional group interconversions to catalytic C–H activation; (b) Comparison of traditional functional group interconversion and C–H activation; (c) C–H Functionalization *versus* inner-sphere C–H activation.

2. Experimentation

The reactions described in this primer are typically conducted with organic chemistry equipment, including Schlenk flasks for air- and moisture-sensitive transformations. Since these transformations employ potentially toxic or otherwise harmful reagents, metal salts and organometallic complexes as well as flammable organic solvents, appropriate safety measures must be considered and the experiments should be conducted by practitioners with a proper training in experimental organic chemistry. For the characterization of organic and organometallic compounds a variety of different analytical methods, such as nuclear magnetic resonance (NMR) spectroscopy mass spectrometry, gas-chromatography coupled with mass spectrometry (GC-MS) and liquid-chromatography coupled with mass spectrometry (LC-MS) analysis, infrared (IR) spectroscopy, or X-ray diffraction, is employed. Furthermore, the characterization of heterogeneous catalysts and macromolecules requires a diverse set of analytical methods, including electron microscopy, solid-state NMR spectroscopy and gel-permeation chromatography, among others. For the elucidation of reaction mechanisms in C–H activation chemistry, numerous techniques have been established over the years, ranging from kinetic analysis *via in situ* IR and NMR spectroscopy for the detection of intermediates.

2.1 Stoichiometric Metallation and Formation of Metallacycles

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C–H activation by transition metal (TM) complexes is the inner-sphere cleavage of a C–H bond to form an organometallic compound with a C–TM bond. C–H activation has been realized in a stoichiometric fashion several decades ago, with important contributions by *Chatt*,[14] *Shilov*,[15] *Cope*,[16] and *Bergman*,[17] among others.[18] In contrast to a noteworthy study on the metallation of azobenzene with Cp_2Ni by *Dubeck*,[19] which arguably represents the first example of chelation-facilitated C–H activation, this approach typically proceeded through an oxidative addition of the C–H bond to an electron-rich 4d or 5d transition metal complex and were often showcased with simple hydrocarbons, such as naphthalene, and cyclohexane.

Proximity-induced C–H activation led to the formation of a metallacyclic intermediate, which represents a widely employed strategy for the selective activation of specific C–H bonds (Fig. 2a).[20,21] While directed C–H metalation was early observed for the activation of $C(sp^2)$–H bonds of azobenzenes and aryl phosphine

ligands,[19,22,23] a variety of directing groups were thereafter exploited.[7] Metallacycles can be efficiently generated *via* the activation of arenes and less frequently alkanes by the aid of strongly coordinating *N*-heterocyclic or weakly coordinating directing groups, such as ketones or esters.[24,25] Indeed, detailed studies on metallacycles derived from 4d, 5d and Earth-abundant 3d transition metals were performed and their role as key intermediates in catalytic transformations of C–H bonds was identified by means of experiment, computation, kinetics and spectroscopy (Fig. 2b).

Depending on the exact nature of the substrate distinct mechanistic pathways can occur for the key C–H activation process. Traditionally, C–H activation was proposed to occur *via* i) oxidative addition for electron-rich late transition metals, such as [Cp*Ir(PMe$_3$)], ii) *σ*-bond metathesis for early transition metals, for example with [Cp*$_2$ScMe], and iii) electrophilic substitution for electron-deficient late transition metals, such as iridium alkoxide complexes.[26,27] In addition, C–H activation with carboxylate or carbonate complexes can take place through a concerted process *via* formation of a six-membered cyclic transition state, coined *concerted metallation-deprotonation* (CMD) or *ambiphilic metal-ligand activation* (AMLA). Alternatively, a *base-assisted internal electrophilic substitution* (BIES) pathway is frequently viable with more electrophilic metals.[28]

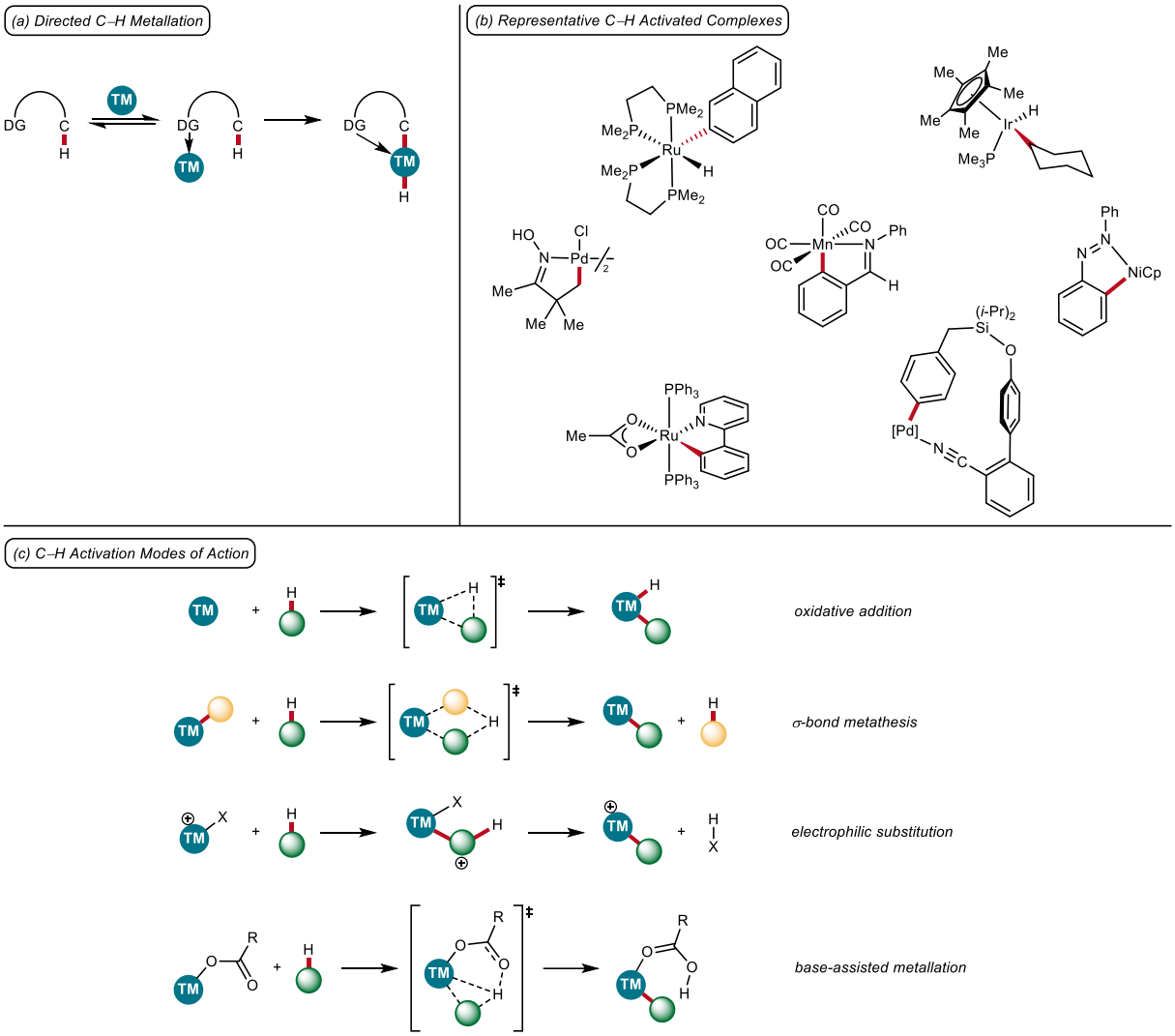

Figure 2. Stoichiometric C–H metallation. (a) Directed C–H metallation; (b) Representative metallacycles; (c) C–H Activation modes of action.

2.2 C–C Bond Formation

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Because C–C bond formation is a fundamental transformation in synthetic organic chemistry, C–C bond formation *via* C–H activation is used to prepare a wide variety of complex organic molecules starting from structurally simple starting materials. Actually, C–C bond formation *via* C–H activation has long been known. One of the pioneering examples of C–C bond formation *via* C–H activation was reported by *Murahashi* in

1955 and dealt with the cobalt-promoted C–H carbonylation of a Schiff base (Fig. 3a).[29] However, because the importance of C–H activation was not recognized at that time, it did not attract much attention. In fact, no such terminology existed at that time. Some pioneering works were reported from time to time, such as the palladium(II)-catalyzed Fujiwara-Moritani reaction,[30] the ruthenium(II)-catalyzed *ortho*-C–H ethylation of phenol with ethylene,[31] and the palladium(II)-catalyzed arylation of heteroaromatic compounds.[32] Meanwhile, in 1993, *Murai* reported one of the monumental landmarks in catalytic C–C bond formation *via* C–H activation. He found that a ketone can serve as a potent directing group in the *ortho*-C–H alkylation of aromatic ketones with alkenes using a ruthenium catalyst (Fig. 3a).[33] In this reaction, the five-membered ruthenacycle **1**, formed by the oxidative addition of a C–H bond to ruthenium(0) was proposed as a key intermediate. Subsequent DFT studies indicated that the rate-determining step (r.d.s.) is reductive elimination, and not C–H activation,[34] which was different from what was originally expected. Since the publication of *Murai's* paper, chelation-assistance has become the most powerful and reliable method for the *ortho*-C–H functionalization and huge numbers of C–C bond formation reactions that involve a chelation-assisted strategy have been reported.[6-8,35-39] The reaction patterns of C–C bond formation *via* C–H activation are very wide, and arylation, alkenylation, allylation, alkylation, alkynylation, cyanation, trifluoromethylation, carbonylation, as well as others can all be achieved *via* C–H activation (Fig. 3b). C–H activation is also applicable to annulation reactions to give cyclized products. In addition, various metal complexes in various oxidative states, including palladium, ruthenium, rhodium, and iridium, and even non-precious metals, such as manganese, rhenium, iron, cobalt, nickel, and copper, are known to show a high catalytic activity in a variety of C–C bond formation reactions that proceed *via* C–H activation. Furthermore, it is also known that various coupling partners, including electrophiles, nucleophiles, and radical species, are applicable to C–C bond formation *via* C–H activation. In these contexts, C–H activation is an attractive route in organic syntheses.

More than 99% chelation-assisted C–C bond formation reactions involve an *ortho*-selective transformation. In 2012, *Yu* reported an early example of *meta*-selective oxidative alkenylation with activated alkenes using a well-designed ether linkage as a directing template and a nitrile group as a directing group (Fig. 3c).[40] Computational studies indicated that the C–H activation step, which proceeds *via* a concerted metalation-deprotonation (CMD) pathway, is the rate- and regioselectivity-determining step and that the C–H activation with the nitrile-containing template occurs *via* a Pd-Ag heterodimeric transition state **2**.[41] Since then, a number of groups have designed various directing templates by adopting distance and geometry correlations for use in *meta*-selective C–H activation reactions.[42] This directing template strategy was also extended to *para*-selective C–C bond formation.[43] In 2017, *Yu* reported a new strategy for the *meta*-selective alkenylation of

3-phenylpyridine using a bi-functional metal-ligand template **3** (Fig. 3c),[44] in which the template can coordinate to two metal atoms; one of the metal sites functions to trap a substrate and the other metal site activates the proximal C–H bond in the substrate, as in **4**. Remarkably, only a catalytic amount of the ligand template was sufficient for this *meta*-selective C–H alkenylation to proceed successfully, suggesting that the reversible coordination between bi-functional metal-ligand template and the substrate takes place. Most of the *ortho*-selective reactions reported thus far proceeded through a five- or six-membered metalacycle. However, the success of the *meta*- and *para*-selective reactions suggests that ring size is not so important provided that a well-designed directing group is used. However, *meta*- and *para*-selectivity currently remains imperfect, although 100% *ortho*-selectivity has been reported. Further improvements are still required. Furthermore, several methods for *meta*-selective reactions utilizing non-covalent interactions, such as hydrogen bonding, Lewis acid-base pair, and ion pairs have been designed. However, all of these examples of non-covalent interactions involved C–H borylation, a subject that is beyond the scope of this chapter.[45] Applications of these new strategies for *meta*-selective C–C bond formation will likely be developed in the near future. It is also known that *meta*-selective C–C bond formation can be achieved by ruthenium(II)-catalyzed reactions with activated alkyl halides, such as benzyl halides, *tert*-alkyl halides, 2-bromo-2,2-difluoroacetates and related derivatives *via* a single electron transfer (SET) mechanism, in which an alkyl radical generated by SET attacks the benzene ring carbon at the *para*-position to the C–Ru bond to give **5** (Fig. 3c).[46,47] Another method for *meta*-selective C–C bond formation involves the Catellani-type reaction. The traditional Catellani reaction involves the use of an aryl halide as a starting substrate and the reaction is initiated by the oxidative addition of an aryl halide to a palladium(0) species.[48] However, the initial step in the C–H Catellani reaction involves *ortho*-C–H palladation with a palladium(II) complex (Fig. 3c).[49,50] The reaction proceeds through chelation-assisted *ortho*-C–H palladation, the insertion of norbornene (NBE), a second C–H activation at the *meta*-C–H bond, oxidative addition of an aryl halide, reductive elimination, β-carbon elimination, followed by protonation.

In 2016, *Nakao* reported an effective method for the direct *para*-selective alkylation of benzamide derivatives and aromatic ketones with alkenes using a nickel/Lewis acid (LA) cooperative catalytic system (Fig. 3d).[51] The coordination of a carbonyl group with methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) (MAD) enhances the reactivity of the substrate for an electron-rich nickel catalyst, and it was also assumed that the steric repulsion between a sterically bulky MAD and a sterically bulky NHC-ligated nickel catalyst resulted in *para*-selective alkylation, as in **6**.

Compared to chelation-assisted C–C bond formation that proceeds *via* the activation of C(sp^2)–H bonds in aromatics, heteroaromatics, and alkenes, fewer reports on chelation-assisted C–C bond formation *via* C(sp^3)–H activation have appeared because of the lower reactivity of these bonds. Nevertheless, many researchers have now focused on the functionalization of C(sp^3)–H bonds (Fig. 3e).[52-54] Similar to the case of the activation of C(sp^2)–H bonds, the activation of C(sp^3)–H bonds proceeds predominantly through a five- or six-membered metallacycle intermediate **7**, indicating that C–C bond formation takes place at the γ- or δ-positions to the coordinating heteroatoms. Similar to the case of the activation of C(sp^2)–H bonds, a wide variety of transformations using various transition metal complexes has been reported.

Asymmetric C–C bond formation has been a subject of great interest in the field of C–H activation (*vide infra*).[55,56] While noble transition metals, such as palladium, rhodium, and iridium complexes are typically used as catalysts in most of the asymmetric reactions that have been developed thus far, the use of inexpensive and sustainable 3d metals, such as nickel and cobalt is increasing.[57-59] The most challenging issue involves reactions involving C(sp^3)–H bonds (Fig. 3f).[60] *Yu* reported the palladium(II)-catalyzed enantio-selective β-arylation, alkenylation, and alkynylation of isobutyric acid derivatives.[61] The N-acetyl group is oriented on the top face of the palladium square plane due to steric repulsion from the *tert*-butyl group on the side chain. The 4-benzyl group on the oxazoline ring further shields the top face of the intermediate **8**. These combined steric interactions appear to reinforce the orientation of the methyl group, thereby controlling the stereochemistry of the C–H cleavage step.

The presence of a directing group is required for regio-selective C–C bond formation *via* C–H activation to be achieved, irrespective of the position of the C–H bond, as described above. A wide variety of directing groups that contain heteroatoms, such as N(sp^2), N(sp^3), O(sp^2), and S(sp^3) atoms as coordinating sites have been designed and are currently in use. Although these are powerful and reliable directing groups such reactions to proceed successfully, one serious concern is that some of them are not easily installed, nor are they easily removed or converted into more useful functional groups. In some cases, it is impossible to remove these groups. Consequently, a more readily removable directing group has been extensively used.[62] However, these reactions still require a minimum of two additional steps that involve the installation of a directing group prior C–H functionalization and the removal of a covalently attached directing group after the functionalization is complete. To overcome this drawback, researchers devised the concept of transient directing group (TDG) assisted C–H bond activation, which clearly reduces the step economic issue because the installation and removal of the transient directing group can occur *in situ* during the reaction (Fig. 3g). The use of a TDG strategy also has some obvious advantages over a covalently attached DG approach.[63-65]

While a variety of TDG strategies have been developed, the use of in-situ generated enamines or imines, which are formed by the condensation of a carbonyl compound, such as an aldehyde or ketone and an amine, is the most useful in organic synthesis. This methodology was recently applied to enantio-selective C–H phenylation,[66] atroposelective oxidative alkenylation[67] and alkynylation[68] reactions in which an amino acid is used as a chiral ligand (Fig. 3g). The *in situ* formation of an imine **9** is the key step for the reaction. C–C bond formation *via* C–H activation is now on the forefront of modern synthetic chemistry.

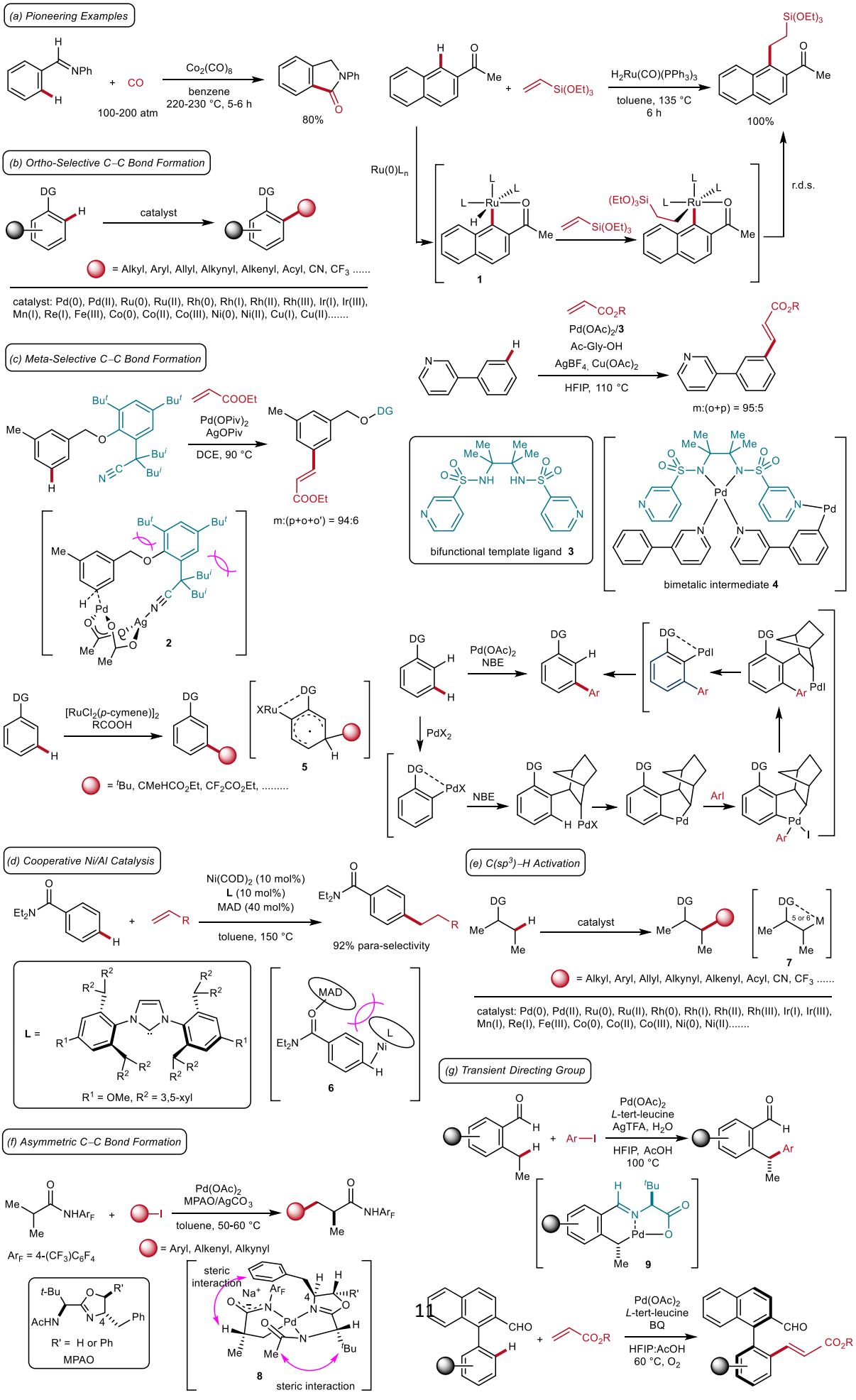
(a) Pioneering Examples
Co2(CO)8
benzene
220-230 °C, 5-6 h
100-200 atm
80%
H2Ru(CO)(PPh3)3
toluene, 135 °C
6 h
100%
(b) Ortho-Selective C–C Bond Formation
catalyst
= Alkyl, Aryl, Allyl, Alkynyl, Alkenyl, Acyl, CN, CF3 .....
catalyst: Pd(0), Pd(II), Ru(0), Ru(II), Rh(0), Rh(I), Rh(II), Rh(III), Ir(I), Ir(III), Mn(I), Re(I), Fe(III), Co(0), Co(II), Co(III), Ni(0), Ni(II), Cu(I), Cu(II).....
Ru(0)Ln
r.d.s.
1
(c) Meta-Selective C–C Bond Formation
Pd(OPiv)2
AgOPiv
DCE, 90 °C
m:(p+o+o') = 94:6
2
Pd(OAc)2/3
Ac-Gly-OH
AgBF4, Cu(OAc)2
HFIP, 110 °C
m:(o+p) = 95:5
bifunctional template ligand 3
bimetalic intermediate 4
[RuCl2(p-cymene)]2
RCOOH
5
= tBu, CMeHCO2Et, CF2CO2Et, ...
Pd(OAc)2
NBE
PdX2
ArI
(d) Cooperative Ni/Al Catalysis
Ni(COD)2 (10 mol%)
L (10 mol%)
MAD (40 mol%)
toluene, 150 °C
92% para-selectivity
L =
R1 = OMe, R2 = 3,5-xyl
6
(e) C(sp3)–H Activation
catalyst
7
= Alkyl, Aryl, Allyl, Alkynyl, Alkenyl, Acyl, CN, CF3 .....
catalyst: Pd(0), Pd(II), Ru(0), Ru(II), Rh(0), Rh(I), Rh(II), Rh(III), Ir(I), Ir(III), Mn(I), Re(I), Fe(III), Co(0), Co(II), Co(III), Ni(0), Ni(II).....
(f) Asymmetric C–C Bond Formation
Pd(OAc)2
MPAO/AgCO3
toluene, 50-60 °C
ArF = 4-(CF3)C6F4
= Aryl, Alkenyl, Alkynyl
R' = H or Ph
MPAO
steric interaction
8
(g) Transient Directing Group
Pd(OAc)2
L-tert-leucine
AgTFA, H2O
HFIP, AcOH
100 °C
9
Pd(OAc)2
L-tert-leucine
BQ
HFIP:AcOH
60 °C, O2

Figure 3. C–C bond formation *via* C–H activation. (a) Pioneering examples: C–H carbonylation (left) and C–H alkylation with alkenes (right); (b) Chelation-assisted *ortho*-selective C–C bond formation *via* C(sp^2)–H activation; (c) Chelation-assisted *meta*-selective C–C bond formation *via* C–H activation: template-strategy (left), a bifunctional template strategy (top right), ruthenium(II)-catalyzed reaction (bottom left), and Catellani-type reaction (bottom right); (d) *Para*-selective C–C bond formation using a Ni/Al cooperative catalytic system; (e) Chelation-assisted C–C bond formation *via* C(sp^3)–H activation; (f) Asymmetric C–C bond formation *via* C(sp^3)–H activation; (g) A transient directing group (TDG) strategy.

2.3 C–N Bond Formation

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Direct introduction of nitrogen-containing moieties into skeletal C–H bonds in a regio- or stereoselective manner has received special attention for the preparation of valuable amino compounds. Indeed, carbon-nitrogen bond-forming processes comprise more than half of chemical transformations used in medicinal chemistry, reflecting the omnipresence of the amino moiety in bioactive molecules.[69,70] Thus, it incited the development of diverse methods for direct C–H amination,[71] not only to avoid the use of prefunctionalized substrates but also to access more straightforward synthetic routes.[72]

In 2005, based on the oxidative cross-coupling procedure for C–C bond-formation, *Buchwald* reported a palladium-catalyzed intramolecular cross-dehydrogenative reaction to obtain carbazole products (Figure 4a).[73] An intermolecular version of the palladium-catalyzed regioselective C–H amination was reported by *Yu* and *Che* in 2006, using a chelation assistance.[74] Subsequently, various transition metal catalyst systems such as copper,[75,76] cobalt,[77] rhodium,[78] iridium,[79] nickel,[80,81] and silver[82] have been utilized for the C–H amination via oxidative coupling. As in the case of carbon-carbon coupling reactions, reductive elimination leads to the C–N bond formation releasing reduced metal species, although its energy barrier is often higher than that of C–C bond forming process due to the polarized metal-nitrogen bond.[83] While stoichiometric amounts of an oxidant are required to regenerate the active catalyst, the use of traditional chemical oxidants may suffer from the formation of (toxic) byproducts or undesired side pathways. To address this issue,

alternative oxidation procedures have been developed for the catalyst regeneration, such as electrochemical[84-89] and photocatalytic redox process.[90]

Instead of using the external oxidation system, electrophilic amine sources, usually possessing polarized N–Y bonds as an internal oxidant, have been utilized to construct a redox neutral catalytic cycle (Figure 4b). *Yu* and *Che* observed that a carbometalated palladacycle intermediate readily reacts with iminoiodinane to form a C–H amination product.[74] In 2010, *Hartwig* employed oxime esters as an electrophilic amino source for the palladium-catalyzed intramolecular C–H amination,[91] where oxidative addition of N–O bond onto the palladium(0) was proposed before the C–H carbometallation (Y = -OCOCF$_3$). *Miura* introduced chloroamine derivatives for the copper-catalyzed direct C–H amination of oxazoles.[92] The same amino source was also utilized for the rhodium(III)-catalyzed regioselective sp^2 C–H amination process, which was developed independently by *Glorius*[93] and *Yu*.[94] In 2012, *Chang* group successfully utilized organic azides for the chelation-assisted C–H amination by a rhodium(III) catalyst system, wherein gaseous N_2 is released as a sole byproduct.[95] The organic azides were then employed for the sp^2- and sp^3-C–H amination reactions with copper(I),[96] cobalt(III),[97] ruthenium(II),[98,99] rhodium(III),[100] and iridium(III)[101,102] catalyst systems. Other electrophilic amine sources such as *N*-fluorobenzenesulfonimide (NFSI)[103] and nitrosoarenes[104] were additionally employed for the C–H amination processes.

On the other hand, direct C–H insertion of putative metal nitrenoids has emerged as an effective strategy for the catalytic C–N bond formation (Figure 4c). In the seminal report by *Breslow*, a catalytic transfer of reactive nitrenes into the C–H bonds was shown to be mediated by Fe^{III}(TPP)Cl[105] or $Rh^{II}_2(OAc)_4$.[106] Others later reported analogous procedures by a range of catalyst systems such as copper,[107,108] ruthenium,[109,110] cobalt,[111] and manganese.[112,113] Mechanistic studies on the key insertion step of metal nitrenoids revealed that the C–H bond cleavage takes place via one of two manners: i) concerted C–H insertion, or ii) stepwise hydrogen atom abstraction and subsequent radical recombination.[114] More recently, *Chang* reported an iridium(III)-catalyzed selective γ-lactam formation using dioxazolones as a robust nitrene precursor, where the electronic property of ligands was found to be critical in suppressing the undesired Curtius rearrangement of the reactive acyl nitrene intermediate.[115] Further ligand modifications based on the computational analysis enabled chemodivergent C–H amination[116] and enantioselective lactam sysnthesis.[117] The same mechanistic framework was suggested to operate also in the cobalt[118] and ruthenium[119] catalysis.

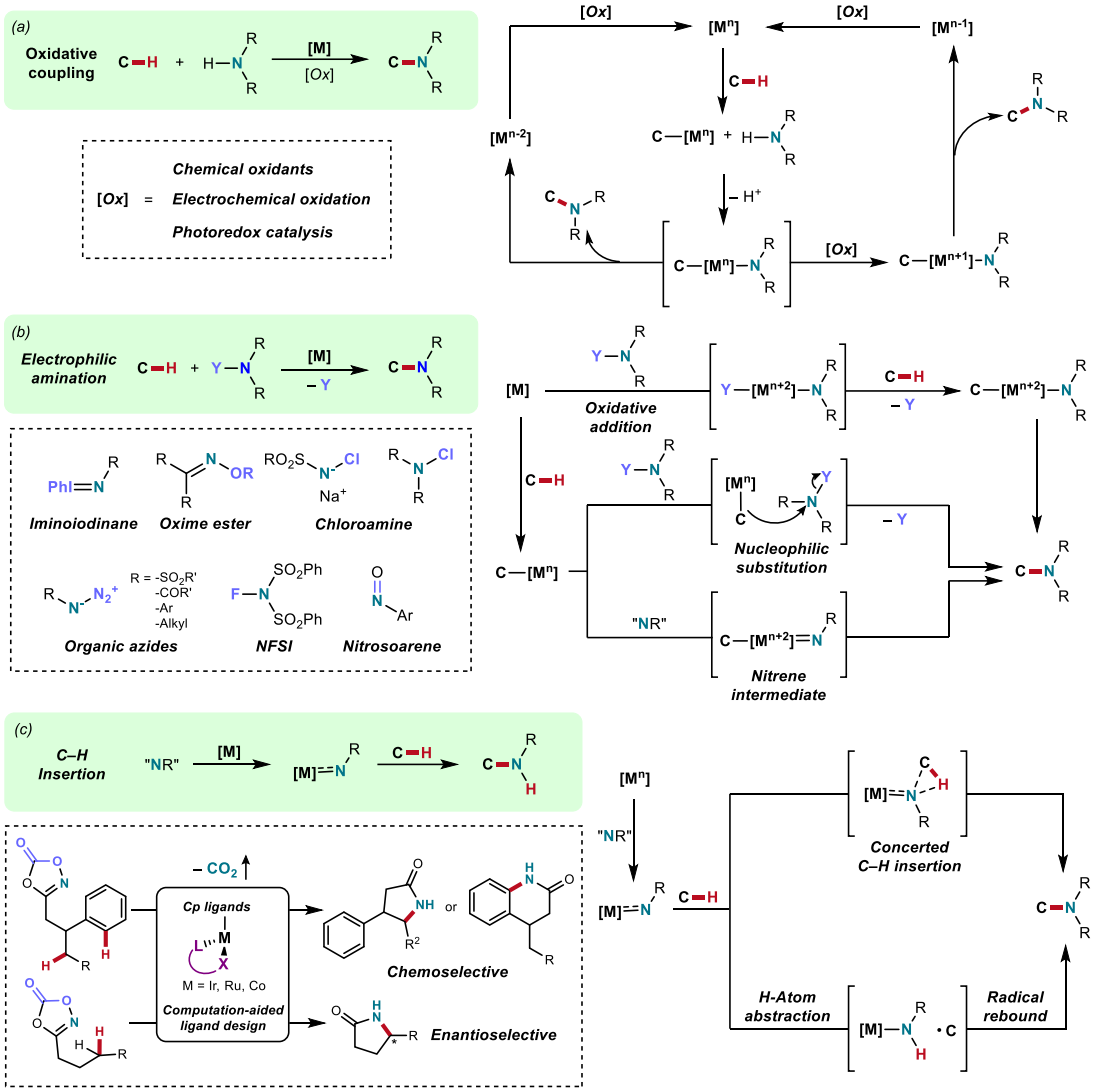

Figure 4. Representative approaches for transition-metal catalyzed direct C–H amination, depicted with proposed mechanistic pathways. (a) C–N bond formation *via* oxidative coupling with oxidation systems for catalyst regeneration; (b) Electrophilic amination using a range of amine sources; (c) C–H insertion of metal nitrenoid species controlled by ligand modification.

2.4 C–O Bond Formation

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Numerous key structural motifs in natural products and pharmaceutically active compounds can be accessed through C–H oxygenations.[120-122] While metal-mediated C–H oxygenations, even for the challenging transformation of methane have been established,[123] these C–H transformations often required stoichiometric amounts of toxic platinum salts.[124] Since the 1990s, a variety of catalytic C–O bond forming reactions have emerged. These approaches largely employ $Pd(OAc)_2$,[125-128] or [Ru(*p*-cymene)($O_2CR)_2$],[129-132] while Earth-abundant $Cu(OAc)_2$,[133,134] and $Co(acac)_2$[135] can likewise facilitate C–H oxygenations in select cases (Fig. 5a).[136] Typical O-coupling partners comprise *inter alia* alcohols, carboxylic acids and water.

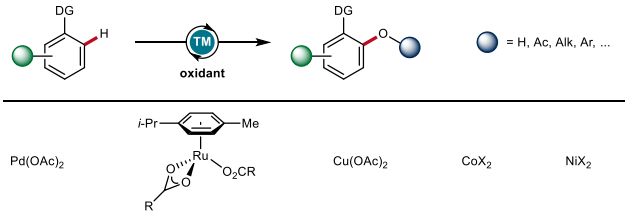
A critical aspect of direct oxygenations constitutes the choice of the oxidant, since an oxidation-induced reductive elimination manifold[137,138] is often key to an efficient catalyst regeneration and thus catalyst turnover. Typical oxidants comprise hypervalent iodine(III) reagents, silver(I) or copper(I) salts and peroxides.[136] The use of environmentally-benign molecular oxygen as the terminal oxidant has also been realized in a limited number of cases, particularly with the aid of co-oxidants, such as benzoquinone or *N*-hydroxyphthalimide.[139,140]

As to the catalyst's mode of action, mechanistic studies have provided strong support for palladium-catalyzed C–H oxygenations to typically proceed through a palladium(II/IV) regime.[141,142] Initial C–H cleavage is often facilitated by chelation assistance to form palladacyclic intermediate **12**. Oxidation of palladium(II) to palladium(IV) and subsequent reductive elimination generates the desired product and regenerates the catalytically competent palladium(II) complex.[127] Experimental and computational studies on complementary C–H hydroxylations by ruthenium catalysis were suggestive of a ruthenium(II/IV) mechanism to be operative (Fig. 5b).[129,143]

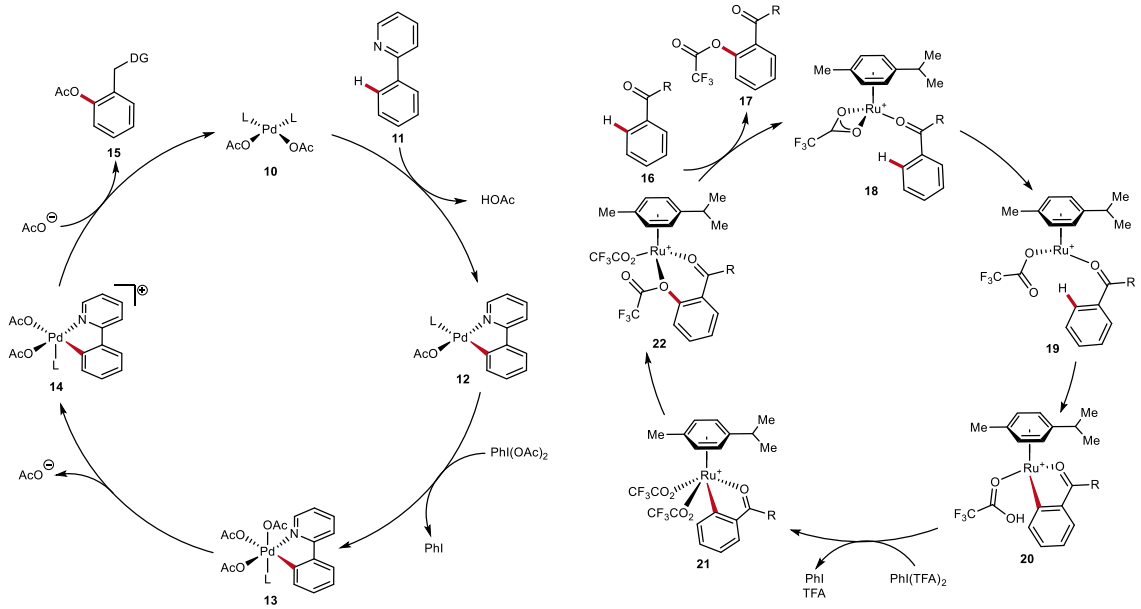
Whilst catalyzed C–H oxygenations enabled the synthesis of synthetically useful compounds, the required superstoichiometric amounts of potentially hazardous chemical oxidants were detrimental to the sustainable nature of the C–H activation approach. Over the last few years, the merger of electrochemistry and C–H activation has, in this context, gained considerable attention (see Box 3). The use of light or electricity as a sustainable, traceless oxidizing agent can circumvent the requirement for chemical oxidants.[144,145] In this context, electrochemical C–H alkoxylations by Earth-abundant cobalt and nickel catalysts were very recently put into practice, generating molecular hydrogen as the sole byproduct.[146,147] Detailed studies by experiment and computation provided strong support for a dual role of electricity.[148] Hence, electricity not only serves as the formal oxidant, but enabled also the oxidation-induced reductive elimination starting from cyclometallated

cobalt(III) complex **26** *via* a octahedral cobalt(IV) complex **27**. Finally, anodic oxidation reoxidizes cobalt(II) to the catalytically active cobalt(III), while cathodic protonreduction generates molecular H_2 (Fig. 5c).

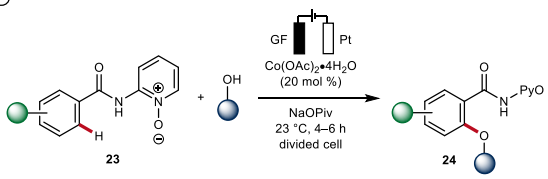
(a) C–H Oxygenations



(b) Proposed Mechanism



(c) Cobaltaelectro-Catalyzed C–H Alkoxylation



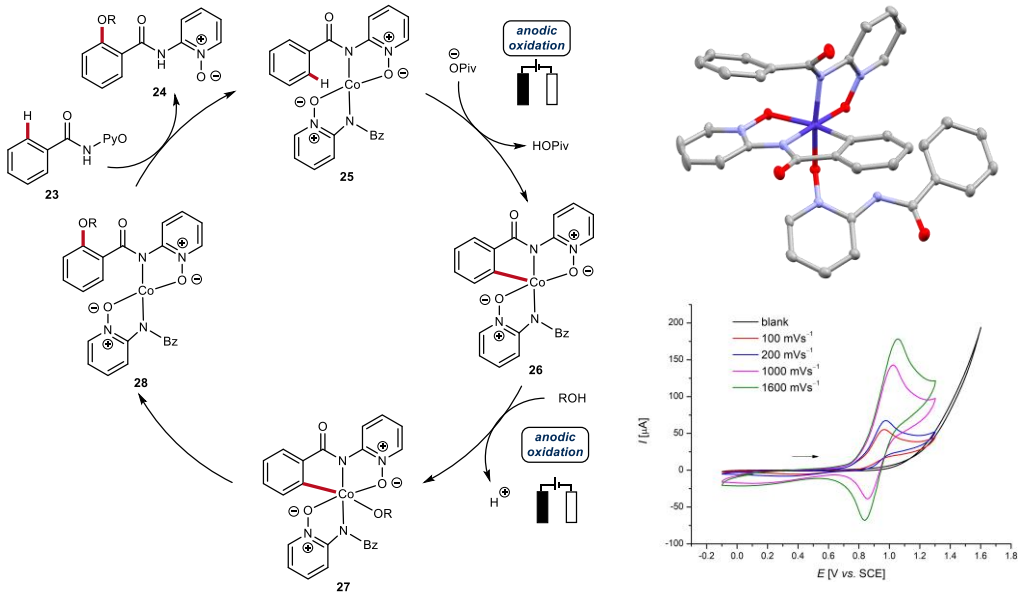


Figure 5. C–O bond formation *via* C–H activation. (a) General reaction and selected examples of typically employed catalysts; (b) Proposed catalytic cycles for palladium- (left) and ruthenium-catalyzed (right) C–H oxygenations; (c) Electrochemical cobalt-catalyzed C–H alkoxylations, proposed catalytic cycle and molecular structure of the catalytically active cobalt(III) species **26**.[148]

2.5 Miscellaneaous Bond Formations

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C–H borylation. Borylation of ubiquitous hydrocarbon C–H bonds is an extremely important reaction because of the wide applicability of organoboron compounds in constructing C–C and C–heteroatom bonds. A wide range of stoichiometric and catalytic examples of C–H borylation by thermal and photochemical processes are known since decades.[149-151] The catalytic borylation of arenes and alkanes to aryl- and alkylboronates by $Cp^*Re(CO)_3$[152] and $Cp^*Rh(\eta^4\text{-}C_6Me_6)$[153] using bis(pinacolato)diboron (B_2pin_2) as borylating reagent is reported (Figure 6a). Similarly, pinacolborane (HBpin) is used in the borylation of aromatic substrates employing $Cp^*Rh(\eta^4\text{-}C_6Me_6)$,[154] $Cp^*Ir(PMe_3)(H)(Bpin)$,[155] $RhCl(P^iPr_3)_2(N_2)$[156] and $[Cp^*RhCl_2]_2$ catalysts at elevated temperatures. Interestingly, the iridium(I) catalyst is outperformed with the support of constrained dipyridyl ligands, dtbpy, tmphen or with bisphosphine, and favored borylation of arenes with B_2pin_2 under mild conditions (Figure 6b).[157-159] Regioselectivity of the arene C–H borylation by iridium catalysis is generally governed by the sterics, whereas heteroaromatics borylation is controlled by the electronic factors. [160] Following a series of experimental and theoretical studies, a common iridium(III)/iridium(V) catalytic cycle is proposed with iridium(III) triboryl as the active species (Figure 6d).[161] The turnover-limiting oxidative addition of the arene C–H bond to iridium(III) triboryl leads to a hepta-coordinated iridium(V) hydride intermediate. Finally, the reductive elimination of the aryl boronate (C–B) product regenerates the active catalyst in the presence of B_2pin_2 or HBpin. Notably, for a large ligand or pincer-based catalyst, the study supports a M(I)/M(III) (M = Rh, Ir) catalytic path.[162,163]

Selective C–H functionalization of simple alkanes and methane represents arguably one of the most fundamental challenges. Particularly, the borylation of inert and nonpolar $C(sp^3)$–H bonds on n-alkanes, unactivated methylene, tetrahydrofuran, cyclopropanes with B_2pin_2 reagent has mostly been achieved

employing N-ligand coordinated Rh or Ir complexes.[164-167] The kinetically more inert C–H bond of methane was borylated with B_2pin_2 in cyclohexane solvent at 150 °C under 2800-3500 kilopascals of methane pressure.[168,169] Various precatalysts, $[Ir(COD)(\mu\text{-}OMe)]_2$, $(Mes)Ir(Bpin)_3$, $Cp^*Rh(C_6Me_6)$, $[Cp^*Ru(\mu\text{-}Cl)Cl]_2$ can be used for the reaction. Notably, the iridium complex needed the assistance of a phen-based or dmpe ($Me_2PCH_2CH_2PMe_2$) ligand for the efficient borylation of methane, though the dmpe-coordinated complex has shown improved chemoselectivity for the monoborylation.[170] Moreover, the ruthenium complex generally provided the highest ratio of mono- versus diborylated methane, *i.e.* CH_3Bpin and $CH_2(Bpin)_2$.

In addition to the noble metal catalysts in C–H borylation, the base metals are of significant interest due to their cost and environmental advantages as well as their distinct electronic features. The borylation of aromatic compounds has been reported employing Cp*Fe(NHC),[171] Fe_2O_3 nanoparticles[172] and heterobimetallic copper complexes,[173] however, with limited scope. A series of cobalt complexes ligated with pincer ligands are recently shown as active catalysts for C–H borylation (Figure 6c).[174-176] Generally, the more electron-rich cobalt center with electron-donating ligands, (^{iPr}PNP)Co($SiMe_3$), enhances the rate of borylation by facilitating the oxidative addition of the C–H bond, and is superior among others. Several five-membered heterocycles such as 2-methylfuran, thiophenes, benzofuran, indoles as well as pyridine and arenes were selectively borylated using B_2pin_2 under mild conditions. Detailed mechanistic studies revealed that the reaction operates *via* a cobalt(I)/cobalt(III) redox process, wherein the turnover-limiting C–H activation occurs at cobalt(I) boryl intermediate in the case of borylation of pyridines and arenes with B_2pin_2 (Figure 6e).[177] However, the *trans*-cobalt(III) dihydride boryl, (^{iPr}PNP)Co$(H)_2$(Bpin), is the resting state for C(sp^2)–H borylation of five-membered heteroarenes with HBpin as boron source, and the reductive elimination of H_2 from this complex is assumed as the turnover-limiting step.[178]

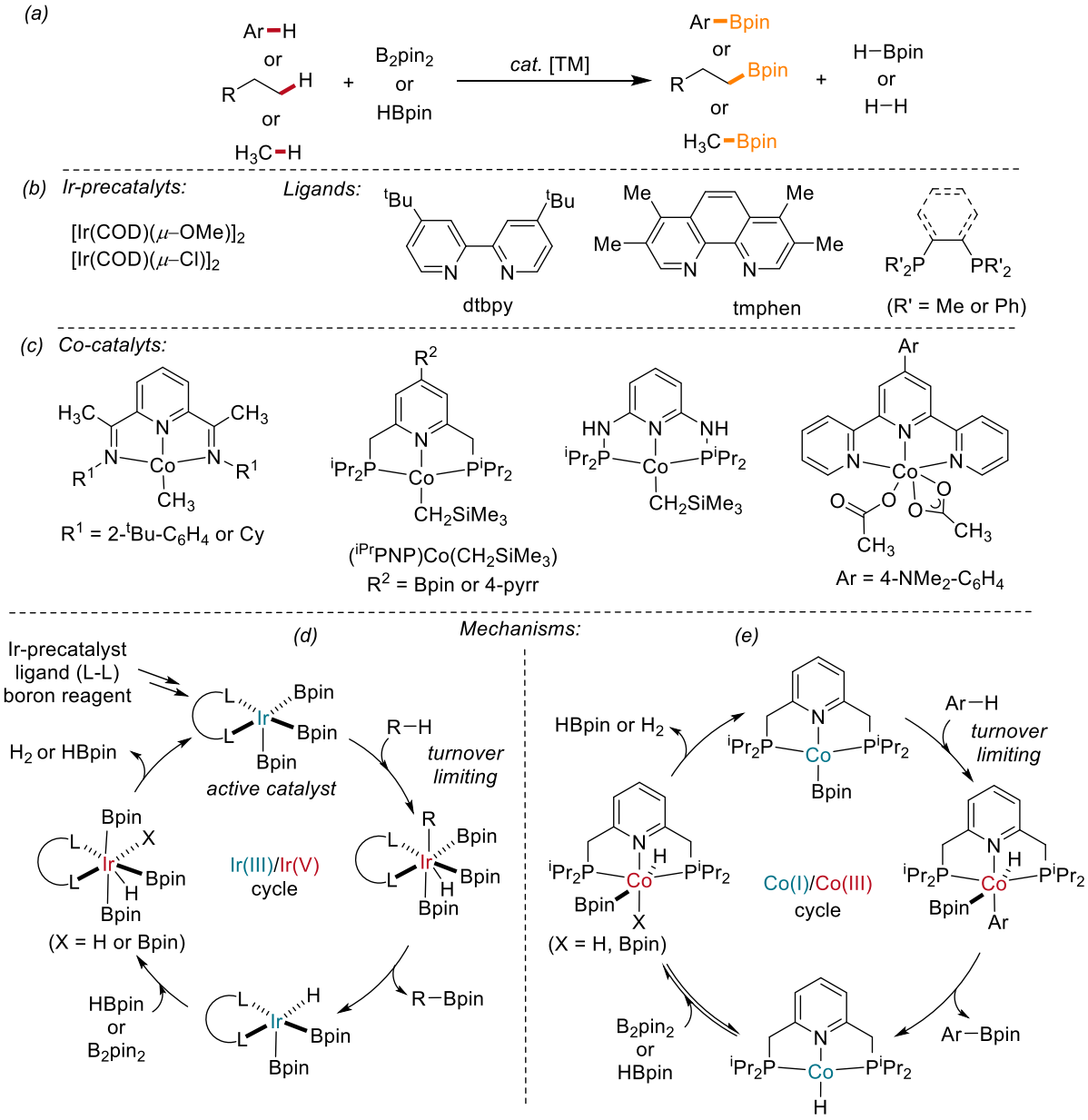

Figure 6. Borylation of hydrocarbon C–H bonds and mechanistic cycles.

C–H halogenations. Organohalides are a particularly useful group of compounds, extensively used as precursors in diverse organic transformations in the synthesis of pharmaceutical molecules, natural products and functional materials. Development in transition metal-catalyzed C–H halogenations has eradicated many earlier problems observed in traditional halogenations, such as stoichiometric metal salt byproducts, regioselectivity issues, over halogenations and low functional group tolerability. Among various metal catalysts used, palladium has dominated the field wherein it involves a C–H bond activation mode.[179] After

the seminal work by *Fahey* on selective *ortho*-chlorination of azobenzene with Cl_2 gas using $PdCl_2$,[180] a number of reports on stoichiometric and catalytic C(sp^2)–H and C(sp^3)–H bond halogenations has been demonstrated. Most of the methods proceed *via* oxidative C–H halogenation, utilizing the substrates bearing Lewis base directing groups that provide a high regioselectivity (Figure 7).[127,181,182] A diverse range of mild and efficient halogenating reagents like $CuCl_2$, NCS, NBS, $PhICl_2$, I_2/oxidant can be used.

Mechanistically, *van Koten* provided an early evidence of C–Cl reductive elimination from a palladium(IV) species in stoichiometric reaction.[183] Since then extensive studies have been performed that suggest a facile C–halogen bond formation from a high valent palladium(IV) species as the C–halogen reductive elimination is thermodynamically and kinetically disfavored from a palladium(II) species. A well accepted and general mechanism involves the precoordination of directing group on substrate to palladium(II), thereby promoting cyclopalladation *via* C–H activation (Figure 7).[16,184] The resulting palladacycle would oxidize to palladium(IV) possessing at least one halogen ligand, followed by C–halogen bond forming reductive elimination to form desired halogenated product and the active catalyst.

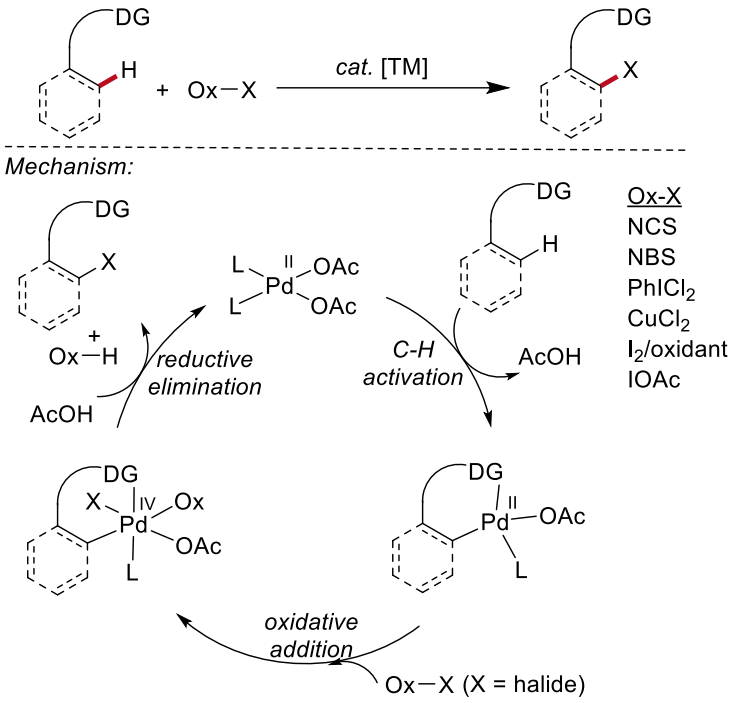

Figure 7. Halogenation of C–H bonds and catalytic cycle.

Box 1. (L. L. Schafer)

Early transition metal catalytic C–H activation reactions are limited to the alkylation of amines with simple alkene substrates (Fig. 8a). This hydroaminoalkylation reaction results in the addition of a C–H bond α-to the nitrogen across the alkene to result in the formation of a new $C(sp^3)$–$C(sp^3)$ bond in a 100% atom economic fashion. Early transition metals (from groups 3, 4 & 5) can mediate this reaction that only requires an alkene as a reaction partner, thereby further increasing the sustainability of alkylation strategies by avoiding the generation of activated substrates. Also, early transition metal catalysts require no co-catalysts or additives thereby facilitating product isolation. Early transition metals are comparatively inexpensive and more abundant than most late transition metals and are used extensively on industrial scale in the polymer industry but are typically overlooked for selective organic synthesis. However, these rarely investigated metals show much promise for the synthesis of selectively alkylated amines and N-heterocycles.

One of the drawbacks of early transition metals is their oxophilic nature which means that these metals have limited functional group tolerance. As such, early transition metals are not well suited for late-stage functionalization strategies, but are best applied toward the assembly of selectively alkylated amine and N-heterocyclic building blocks that can be incorporated into convergent synthetic strategies. Stoichiometric variants of the hydroaminoalkylation reaction have been extensively explored,[185] and it is only within the past decade that catalytic variants have become prevalent.

Early transition metals are easily oxidized and consequently these metals promote reactivity in a mechanistically distinct way that avoids redox reactions and instead relies upon proton-shuttling mechanisms (Fig. 8b).[186] These very electrophilic metal centers form highly polarized metal-element bonds and readily bind a variety of donors, thus promoting associative reaction mechanisms throughout the catalytic cycle. First, an intramolecular C–H activation event forms an intermediate strained metallaziridine (**29**) that can undergo alkene insertion to give a metallacycle (**30**). The use of catalysts with sufficient steric accessibility can promote protonolysis of **30** with incoming amine substrate to generate a diamido metal complex (**31**) that can undergo a subsequent C–H activation event to release the desired product and regenerate the catalytically relevant metallaziridine **29**. This mechanistic profile was initially proposed, based upon deuterium labelling studies, in one of the first disclosures of this reaction in 1980.[187] It was not until *Herzon* and *Hartwig* in 2007[188] showed that the strategic selection of aryl amine substrates that are more prone to metallaziridine formation[189] resulted in high yielding catalytic reactions. These early stage results set the stage for early transition metal organometallic chemists to exploit ligand design strategies to realized intra-[190-192] and

intermolecular enhanced reactivity that reduce reaction temperatures from 140–165 °C to as low as room temperature reactions[193] and increase the substrate scope to include a broad range of silylated amines,[194] alkyl amines[195] and N-heterocycles[196] for reactivity with unactivated alkenes, conjugated alkenes[197] and allenes.[198] Further mechanistic investigations using computational approaches[199] as well as experimental tools such as kinetic isotope effects, deuterium labelling, reaction kinetics and the isolation of organometallic reactive intermediates have confirmed that different early transition metals mediate this transformation using the same mechanistic profile.

N-Methyl aniline derivatives are the preferred amines for catalyst development efforts using all early transition metals. If terminal alkenes are used, these reactions proceed with the preferential formation of the branched products as predicted based upon the electronic effect of the preferential accumulation of electron density on the least substituted carbon during the alkene insertion step.[200] To date, racemic products are prevalent as only limited success has been realized in enantioselective catalysis.[201-203] One of the advantages of early transition metals that do not engage in redox chemistry is their compatibility with aryl halide containing substrates (Fig. 8c).[204] Tertiary amine derivatives can be used as substrates in combination with highly reactive and electrophilic scandium cationic catalysts (Fig. 8e).[205,206] In this case the proposed mechanism relies upon the dative N-metal bond to access a metallaziridine type intermediate. Primary amine containing products can be accessed using N-silylated amine substrates[207] and α-silylated amine substrates can be used to impose steric influences over regioselectivity to preferentially access linear hydroaminoalkylation products.[208]

Initial catalyst development efforts focused on the use of unactivated terminal alkene substrates, although internal alkenes, including unactivated linear internal alkenes, can be used to substrates in hydroaminoalkylation reactions, although harsh reaction conditions are typically required.[209,210]

As in late transition metal chemistry, pyridine can be used as a directing group in early transition metal/rare earth chemistry to realize Csp^2–Csp^3 bond formation upon the direct alkylation of pyridine with alkenes (Fig. 8f),[211] including enantioselective variants and reactions with gaseous ethylene substrates.[212,213]

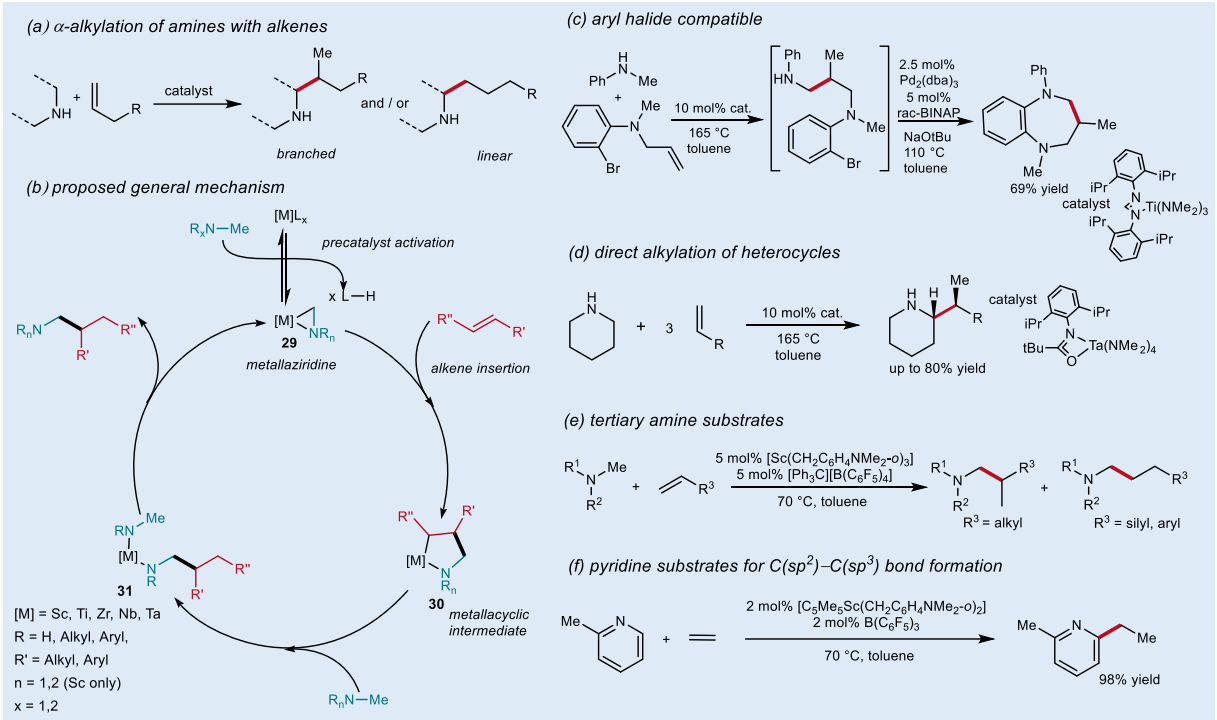

Figure 8. (a) General hydroaminoalkylation scheme; (b) Proposed simplified mechanism; (c) One-pot synthesis of 1,5-benzodiazepines; (d) Diastereoselective heterocycle alkylation; (e) Tertiary amines in hydroaminoalkylation; (f) Pyridine in hydroaminoalkylation.

2.6 Commonly employed computational methods

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The design of highly effective and selective catalysts for C–H activations of chemically and biologically available molecules requires an atomistic level understanding of the mechanisms and controlling factors of the targeted reactions. This requires state-of-the-art analytical, including computational, approaches. Recent developments in computational methodology,[214] and their application to catalysis,[27,215,216] were extensively reviewed. Therefore, here, we are limited to mentioning the computational approaches, which are broadly applicable to C–H activation and functionalization.

Today, the existing "gold-standard" of computational methods, CCSD(T),[217,218] allows to calculate properties of molecules with highest (*sub*-kcal/mol and 0.001 Å errors) accuracy. However, the application of these as

well as the recently extended DLPNO–CCSD(T) method[219] to system with more than 75 atoms, or complex C–H activation reactions, is not practical. Therefore, the use of methods that can provide high accuracy at lowest possible cost is an unavoidable compromise. The Kohn−Sham (KS) density functional theory (DFT)[220] is one of such approaches. Currently, numerous DFT functionals were reported, which often yield reasonably accurate results. However, a majority of these functionals fails to accurately describe long-range *dispersive interaction*, which is viewed as an attractive interaction originating from the response of electrons in one region to instantaneous charge density fluctuations in another, and can be critical in C–H activation.

In the literature, numerous dispersion correction (DC) approaches have been developed,[221,222] among which the semiclassical pairwise correction schemes (for example, *Grimme's* Dn schemes,[214] where n = 3 and 4) augmented by short covalent-bonding regime corrections (using the Becke-Johnson method[223]) are found to be more practical (referred to as Dn(BJ)) for studies on C–H activation. Currently, the B3LYP functional with Dn(BJ) corrections is one of the most widely utilized approaches by the organometallic community. Other commonly applied approaches are the Minnesota-family functionals,[224] and the doubly-hybrid functionals.[225] However, all of these methods have several limitations. For example, the Dn(BJ) schemes (1) make use of element-specific parameters that are precomputed in the gas-phase. This keeps constant the calculated dispersion interaction energy of two atoms or molecules no matter which material separates them, and (2) solely depend on the molecular geometry, which limits the modeling of all atoms in a system in their true electronic structure. The Minnesota-family functionals show a strong grid dependency and slow convergence with respect to the one-particle basis set expansion. The double-hybrid approaches are computationally demanding for the large systems.

Solvent effects are critical in chemical reactions. Existing computational solvation methods are classified as explicit and implicit models. Broadly used continuum solvation models (such as the polarizable continuum models CPCM or IEFPCM, and Solvation Model based on Density (SMD) approach)[226] are computationally economical, but fail to account for the local fluctuations in solvent density around a solute. Furthermore, these models are neglecting effects like hydrogen bonding or reorientation, thus introducing uncertainties in the studied reactions. Therefore, the use of explicit or implicit/explicit hybrid approaches, that directly include a small number of solvent molecules into the calculations but treats the bulk solvent by a continuum model, is a reasonable alternative.

The inclusion of *relativistic effects* in computational catalyst design for C–H activation is vital, too, especially for catalysis with third-row transition metals.[227,228] While the direct application of the Dirac equation for these

reactions is not practical, the use of (a) relativistic effective core potentials (such as SDD[229] and Lanl2dz[230]), and (b) Douglas-Kroll-Hess (DKH) and zeroth-order regular approximation (ZORA) scalar relativistic approximations is common.[231]

In large catalytic systems, the existence of weak and dispersive interactions often results in multiple conformers of large catalytic systems. This may critically impact the selectivity and reactivity of C–H activation reactions. Therefore, the *full conformational analysis* of large catalytic systems is absolutely necessary. For this reason, the "molecular dynamic (MD) then quantum mechanical (QM)" approach seems to be more practical: this approach allows to identify the energetically most favorable conformers of a system by MD simulations, and then improve their structure and energy by applying more accurate methods. In cases of bioinspired and enzymatic catalysts, where the size of the systems is too large, the direct use of QM methods may become computationally prohibitive, and the use of the hybrid QM/MM[232] or/and ONIOM[233,234] approaches is recommended.

Photocatalytic C–H activation is another fast-developing C–H functionalization strategy. The well-established time-dependent-DFT (*i.e.* TD-DFT) method,[235] allowing to study electronic and photo-absorption spectra of the catalyst and substrate with a reasonable accuracy, is a well-suited computational method to investigate photocatalytic (as well as electrocatalytic) processes. Since the reactions initiated from the excited state of the super-molecule may involve multiple lower-lying electronic states of the reaction intermediates, one should use the DFT-Dn(BJ) scheme with caution and validate the results against multi-determinant approaches (for example, CASPT2[236]) when that is necessary.

In perspective, the increase of power (system software and hardware) of classical computers, and the improvement of computational methodologies, allowing to fully account for all possible factors impacting the catalytic processes,[237] will further advance chemical sciences, particularly, selective C–H activation and functionalization. The rapid development of Quantum Computers and the effective transfer of popular computational software from classical to quantum architecture is going to revolutionize the field of computational sciences, and will significantly advance their predictive power leading to more life-changing discoveries.

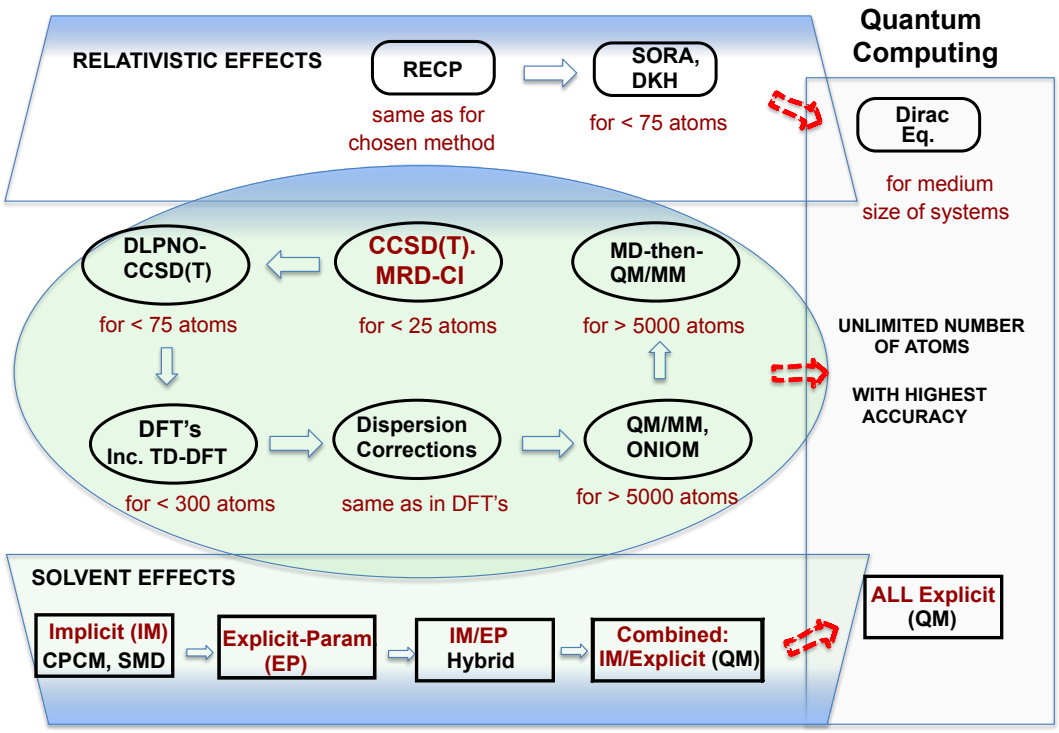

Figure 9. Schematic presentation of the utilized computational approaches in the catalytic C–H bond activation studies with their limitations and future extensions.

3. Applications

3.1 Rational Reaction and Catalyst Development

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The ultimate goal of theoretical studies of catalytic reactions is to predict and guide the design of more efficient, green, and selective processes, particularly, for catalytic C–H activation and functionalization of chemo- and bioavailable substrates. Factors such as stability, solubility, and synthetic accessibility of substrates, and practicality of the targeted products necessitate a close collaboration between experimentalists and theoreticians. To address the challenging problems of catalytic C–H activation chemistry, it is vital to in-depth understand the mechanism of the targeted process, and to elucidate the roles of each participating component (such as additive, base, solvent, substrate, among others) of the reaction. Today, the available computational tools allow for exploring catalytic reactions in varying degrees of

sophistication and enable (a) the identification of the nature of catalytically active species and short-lived intermediates, (b) establishing rate- and selectivity-controlling transition states, (c) the understanding of the roles of additive, base, solvent, and ligand, (d) exploring chirality transfer mechanisms in asymmetric C–H functionalization, (e) identifying the impact of unanticipated weak interactions between various components of catalysis on the selectivity of the reaction, and more.[238]

As an example, recently *Perez* and *Maseras*[239] have reported the quantitative descriptor-based alkane nucleophilicity (QDEAN) model, which reproduces the relative reactivity of alkane C−H bonds. The developed model has enabled the analysis of the reactivity of numerous alkane C−H bonds towards *in situ* generated metal carbene electrophiles.

Musaev and *France*[240] have used widely accessible descriptors (Fig. xx) to deconstruct electronic and steric effects in the $[Rh_2(esp)_2]$-catalyzed β-carbonyl ester carbene insertion into $C(sp^3)$–H bonds and developed a chemical-space map and general reactivity model that predicts more efficient carbonyl R-substituents for the C–H insertion.

These and numerous other examples demonstrate the critical importance of the quantum computation for the design of catalytic C–H activation reactions. Unfortunately, the presence of competing reaction pathways makes the computational prediction of the desired (productive) reaction pathway even more challenging. In this case, recent advances in automated reaction path search methods (for example, double-ended and automated transition state search methods) combined with commonly utilized quantum chemical techniques are proven to be extremely useful.[241-244] As an example, recently, *Sawamura*, *Maeda* and coworkers[245] have shown the utility of the ARIF method[243] for designing highly enantioselective and site-selective catalytic borylations of remote $C(sp^3)$–H bonds γ to the carbonyl group in aliphatic secondary and tertiary amides and esters. The predictions from quantum computation were vital for modularly assembling a chiral C–H activation catalyst containing an iridium center, a chiral monophosphite ligand, an achiral urea-pyridine receptor ligand, and pinacolatoboryl groups.

Undoubtedly, the integration of quantum computational approaches with machine learning algorithms[246,247] is a promising direction in rational reaction design, and may, in the near future, make the *in silico* (within a very short time limit and without generating an organic waste) design of more effective and highly selective C–H activation and functionalization reactions a reality.

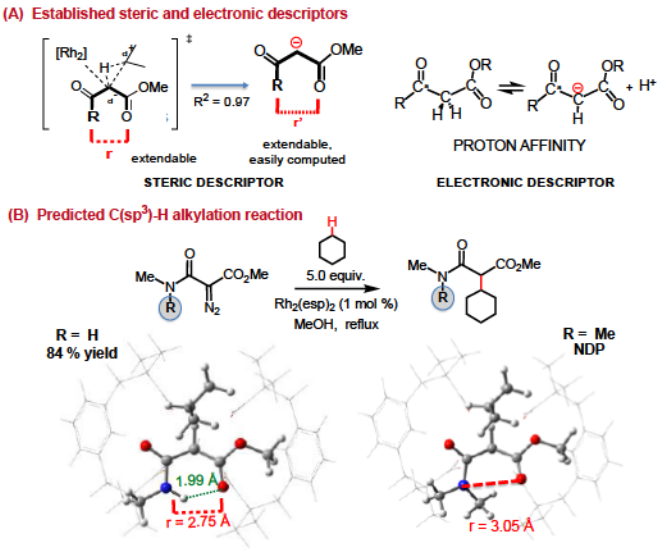

Figure 10. The $[Rh_2(esp)_2]$-catalyzed β-carbonyl ester carbene insertion into the C(sp^3)–H bond. (a) Established steric and electronic descriptors; (b) the predicted C(sp^3)–H alkylation reaction by the secondary amides.

3.2 Asymmetric C–H Activation

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With the continuously expanding importance of chiral molecules beyond the pharmaceutical industry and encompassing agrochemical industries, material sciences, and flavors, the design of innovative and sustainable asymmetric protocols is highly appealing. C–H activation strategies offer unique opportunities for the synthesis of enantiopure molecules, not only accelerating known synthetic routes towards known scaffolds, but even more importantly paving the way towards previously inaccessible chiral architectures.[248] Accordingly, considerable efforts devoted over the last decade to develop this research field has fructified in the design of a large diversity of asymmetric C–H activation protocols and approaches affording high-value-added chiral molecules in a single step from relatively simple precursors.

The pioneering elegant illustration of the potential of the stereoselective C–H activation, intramolecular chiral imine-directed Fujiwara-Moritani reaction furnishing a key precursor of lithospermic acid, was reported as early as 2005 by *Bergman* and *Ellman*.[249] Following this work and during the last 15 years, the field of

asymmetric C–H activation has progressively evolved from an uncharted research area[250] to a mature and comprehensive toolbox.

During the first years of asymmetric C–H activations, a majority of catalytic systems have been targeting direct metallation of aromatic C–H bonds.[251] C-stereogenic compounds could thus be obtained *via* directing group-controlled desymmetrization type reactions, when a chiral palladium complex, initially precoordinated by a chelating motif present on a prochiral carbon, was able to differentiate between two aromatic motifs. Although this approach was initially used to convert simple symmetric substrates, such as diaryl-2-pyridylmethanes[252,253] and diphenylacetic acid derivatives,[254] advanced applications followed, allowing, for example, syntheses of chiral diarylmethylamines *via ortho*-[255] or *meta*-C(sp^2)–H activation.[256,257] Asymmetric desymmetrization approach is also the strategy of choice to prepare various original heteroatom-stereogenic molecules,[258] including phosphinamides,[259] silanes[260] and diaryl sulfoxides.[261] Other scaffolds, such as indanes bearing all-carbon quaternary stereocenters,[262] dibenzazepinones,[263] dibenzosiloles[264] and dibenzophosphole oxides[265] can be constructed from well-designed substrates bearing a preactivated C–X bond (X = OTf, Br for example) *via* a conceptually closely related strategy, implying initial insertion of a chiral palladium catalyst into C–X bond followed by the stereoselective metallation of one the prochiral aromatic-motifs.

The stereoselective C(sp^2)–H activation approach turned out to be a unique tool to access axially chiral compounds.[266] Indeed, the direct functionalization of a biaryl precursor in *ortho*-position to a Ar–Ar linkage allows increasing the rotational barrier of a biaryl motif, thus delivering atropostable products. While using chiral sulfoxide motif as a traceless directing group, this approach is rather general allowing the assembly of a diversity of atropoisomerically pure compounds[267] and a diversity of atropisomeric biaryl *N*-heterocycles may be accessed *via* rhodium-catalyzed enantioselective reactions.[268] Recently, *Shi* has demonstrated that the axially C–C and C–N chiral aldehydes may also be accessed via this strategy while using amino-acid ligands, *via in situ* generation of a transient chiral imino-directing group.[269] Remarkably, pushing even further the sustainability concept, electrocatalyzed version of this asymmetric C–H activation reaction could be achieved, thus obviating the use of external chemical oxidants and further limiting undesired byproducts and waste formation.[270] An alternative route towards the synthesis of the axially chiral biaryls, C–H direct stereoselective arylation, although conceptually very appealing, remains extremely challenging as illustrated by its scarcity. Although the proof-of-concept work was published in 2012,[271] more general illustrations of such reactions allowing the synthesis of the axially chiral terphenyls featuring two perfectly controlled chiral axis[272] and atropisomeric (hetero)biaryls[273] were reported only recently.

In parallel to the above-mentioned stereoselective C(sp^2)–H activation reactions, the synthesis of chiral products *via* achiral C–H activation followed by stereochemistry-generating migratory insertion has become a truly synthetically useful tool.[248] The initial portfolio of chiral complexes promoting such stereoselective transformations, including rhodium(I) and iridium(I) complexes, was considerably expanded while proving the exceptional efficiency of chiral Rh(III)Cp*-derivatives.[274,275] During these transformations, the directed C–H activation of a simple aromatic substrates deliver stereogenic metallacyclic intermediates, prompt to react, via a migratory insertion, with a diversity of coupling partners, including allenes, alkynes, olefins, and diazocompounds, thus delivering a large panel of, often cyclized, products. This approach may also astutely be applied for enantioselective hydroacylations.[276] Remarkably, Earth-abundant 3d-metals, such as cobalt, nickel, and iron, coordinated by chiral ligands, are also potent catalysts for such asymmetric transformations,[57,277] as beautifully illustrated by *Yoshikai* in the context of cobalt-catalyzed hydroarylation of ketones and olefines[278] or by *Ackermann* in the iron-catalyzed C–H alkylation of (aza)-indoles.[277]

C–H functionalization of aliphatic substrates is intrinsically more challenging and has remained less developed compared to the activation of aromatic and vinylic substrates.[12,279] The initial efforts towards asymmetric C(sp^3)–H functionalization mainly concerned intramolecular palladium-catalyzed reactions.[52,55] Diversity of compounds including indolines,[280] indanes,[281] and cyclopropane-containing tetrahydroquinolines,[282] dihydroquinolones and dihydroisoquinolones,[283,284] and others could thus be build up from well design substrates bearing a preactivated C–X bond. The oxidative addition of palladium(0) species thus allows preinstallation of a chiral palladium-catalyst, hence being perfectly placed to differentiate two stereotopic CH_2 motifs. Remarkably, a diversity of ligands, such as chiral NHCs, diphosphines, monophosphines, and TADDOL-derived phosphoramidites can be used to realize such transformations. The development of directing group-controlled intermolecular asymmetric C(sp^3)–H activation has been clearly propelled by the discovery by *Yu* of the exceptional potential of the amino-acids ligands.[60,285] Indeed, following the pioneering example of the direct C(sp^3)–H alkylation of 2-isopropylpyridine achieved using palladium in combination with cyclopropyl-derived N-Boc protected amino-acid,[252] such ligands have rapidly established themselves as uniquely potent. Over the years, the complexity of aliphatic substrates undergoing stereoselective C–H activation has dramatically been increased, ranging from rather activated small cycloalkanes,[286,287] and benzylic substrates to flexible linear aliphatics.[288] In parallel to the ligand design, various coordinating groups, including bicoordinating ones, have emerged as appealing tools to reach highly enantio- and regio-selective transformations. Remarkably, the maturity of this field is further illustrated by a possibility of addressing not only the most common β-position, but also more challenging α-[289] and γ-

sites.[245,290] Interestingly, while very different metals, including palladium, ruthenium, rhodium, iridium, cobalt, iron, amongst others, are able to promote C(sp^2)–H activation delivering chiral products, the field of asymmetric C(sp^3)–H activation continues to be strongly dominated by the use of palladium-complexes. The development of more sustainable alternatives based on chiral 3d-metals is thus highly appealing.[291,292] In addition, complementary strategies, in terms of reactivity and regioselectivity, towards asymmetric C(sp^3)–H functionalization have been discovered by *Davies*, based on rhodium(II)-catalyzed outer-sphere type mechanism involving carbenoid insertion type reactions.[293-296]

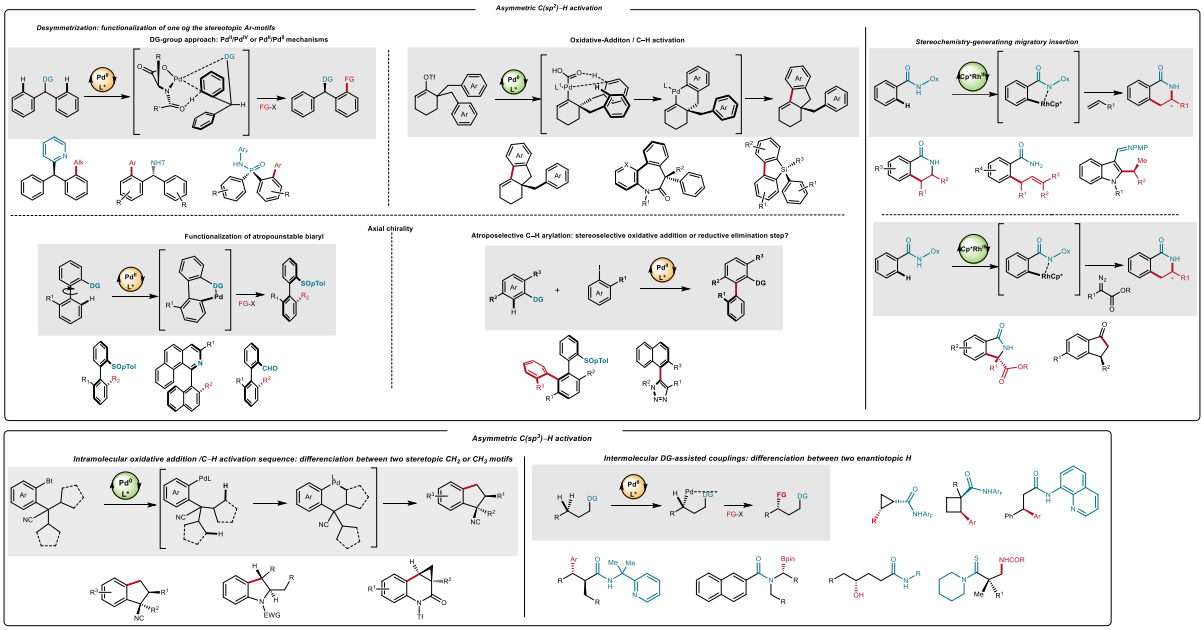

Figure 11. Asymmetric C–H Activation.

3.3 C–H Activation in Total Synthesis

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Recently, the terms C–H activation and C–H functionalization have been used interchangeably.[297,298] However, in rigorous terms, the mechanism of the former involves a primary organometallic step where insertion of a metal center into a C–H bond occurs to form a C–M bond, whereas the latter doesn't adhere to

such a requirement and therefore encompasses both processes.[299] In this section, we will present the applications of C–H functionalization in complex molecule synthesis (total synthesis). Early examples of C–H activation in the context of total synthesis, such as those spearheaded by *Sames*, involved the stoichiometric use of high-valent transition metals such as platinum[300] or palladium[301,302] (Fig. 12a). These processes were made enthalpically feasible through the formation of relatively stable metallocycles by virtue of directing groups inherent, or appended, to the substrates. Over the past two decades, myriad processes employing sub-stoichiometric amounts of metal complexes have been disclosed for the directed activation and functionalization of unactivated C–H bonds to form C–C,[303-306] C–O,[307-309] C–N[310-312] and C–Si[313,314] bonds, which have found utility in the elegant total syntheses of a wide range of natural products (Fig. 12b).

Over the last decade, undirected C–H functionalization methods utilizing either substoichiometric amounts of transition metal complexes or metal-free conditions have begun to emerge as powerful tools for the formation of C–X[315-317] and C–B[318,319] bonds (where X is halogen), which have also been profitably applied to natural product total synthesis (see Figure 12c for illustrative examples). These emerging methods leverage the steric or electronic subtleties inherent to the substrate, or employ rational catalyst design in order to override those preferences. Recent developments in the field of catalytic undirected C(sp^3)–B bond formation of saturated heterocycles[320] are of great promise for the future of complex molecule synthesis, as the conditions employed for these transformations are highly functional group tolerant and versatile, as the resulting borylated products can be elaborated to incorporate other groups at a later stage.

In many respects, over the last five years, history has begun to repeat itself in the context of C–H functionalization: some of the oldest C–H functionalization methodologies known to the chemist – radical reactions[321] – and to mother nature – enzymatic processes – are being revisited with a modern twist that now allows for better reactivity and selectivity profiles and have therefore begun to be applied in the arena of natural product synthesis. There has been a recent surge in radical C–H functionalization methodologies which, in contrast to their ancestral variants, are mild and selective enough to be applied to complex molecules. In part, this is possible because of the relative ease with which one can now generate highly reactive radical intermediates, using mild visible light,[322,323] photoredox,[324,325] or electrochemical[326] processes (Fig. 12d). One key advantage to radical methodologies is their different selectivity profiles which allow for the functionalization of tertiary, over stronger secondary or primary, C–H bonds, an otherwise difficult task to effect *via* C–H activation due to high barriers for insertion. Likewise, there have been sophisticated advances in biocatalysis in recent years, facilitating exceptional regio- and stereocontrol in the synthesis of a variety of complex natural products (Fig. 12d).[303,327-329] As new generations of chemists strive toward more efficient,

selective, environmentally-friendly, and transition metal-free tools for C–H functionalization – not unlike the shift from the application of stoichiometric transition metal-mediated to catalytic variants – these emerging methodologies will become the centerpiece of many more syntheses.

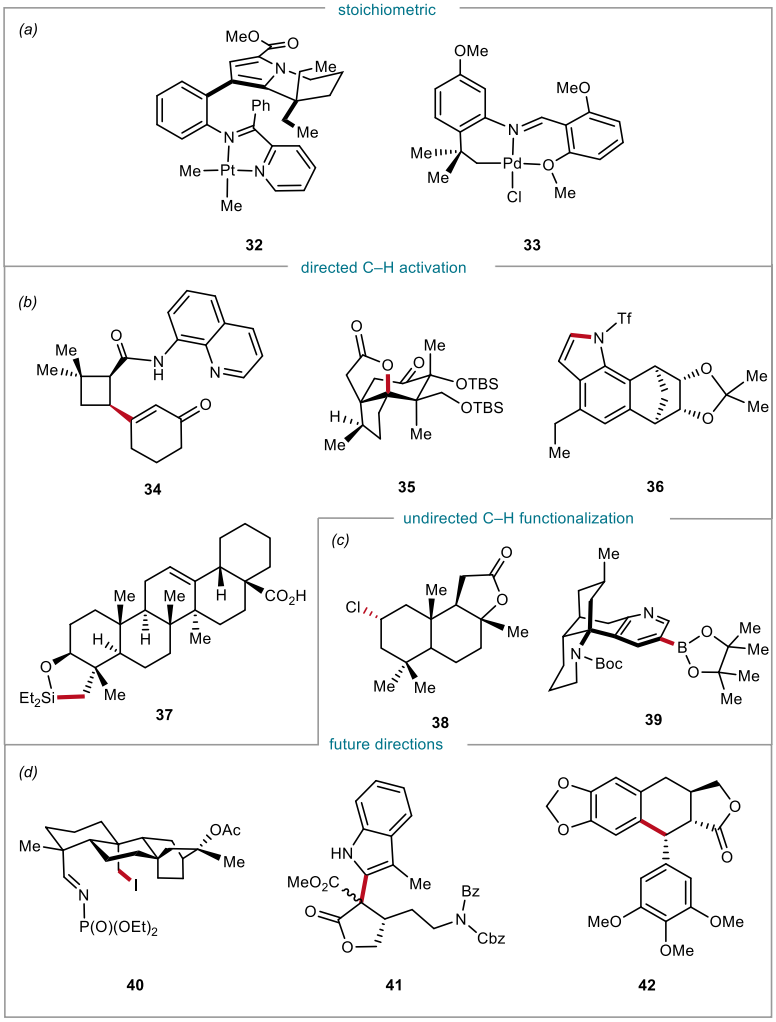

Figure 12: Key intermediates in the synthesis of selected natural products generated by C–H functionalization. (a) Stoichiometrically-derived platinum and palladium metallacycles in the synthesis of Rhazinilam (**32**) and Teleocidin B4 (**33**) by *Sames*; (b) Directed C–H functionalizations: C–C formation *via* C(sp^3)–H activation in the total synthesis of (+)-Psiguadial B by *Reisman* (**34**); C–O formation *via* C(sp^3)–H activation in the total synthesis of (+)-Pseudoanisatin by *Maimone* (**35**); C–N formation *via* C(sp^3)–H activation in the formal synthesis (±)-*cis*-trikentrin by *Sarpong* (**36**); C–Si formation *via* C(sp^3)–H activation in the formal synthesis of Hederagenin by *Hartwig* (**37**); (c) Undirected C–H functionalizations: C–Cl formation *via* radical C(sp^3)–H chlorination in the total synthesis of Chlorolissoclimide by *Alexanian* and *Vanderwal* (**38**);

C–B formation *via* C(sp^3)–H activation in the total synthesis of Complanadine A by *Sarpong* (**39**); (d) Future directions of C–H functionalization: C–I formation *via* radical C(sp^3)–H iodination in the total synthesis of (−)-Isoatisine by *Baran* (**40**); metallaphotoredox-mediated C(sp^3)–C(sp^2) coupling in the total synthesis of (+)-Gliocladin C by *Stephenson* (**41**); chemoenzymatic C(sp^3)–C(sp^2) coupling in the total synthesis of (−)-Podophyllotoxin by *Renata* (**42**).

3.4 C–H Activation on Macromolecules

3.4.1 C–H Activation on Peptides

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With over 70 peptide therapeutics approved as new chemical entities as of 2020, and hundreds earlier in the drug development pipeline, the efficient synthesis and modification of peptides is a key challenge for synthetic chemists.[330] While C–H activation has enabled the rapid and selective synthesis of unnatural amino acid (aa) building blocks,[331-333] arguably its greatest potential lies in the selective activation of C–H bonds in peptides. Analogous to post-translational modification, this approach allows step-economic late-stage peptide diversification[334,335] and includes the macrocyclization/stapling of peptides, which often leads to improved drug-like properties over the linear peptide precursors.[336]

The palladium-catalysed C2(sp^2)–H activation of tryptophan (Trp), first applied to peptides by *Albericio* and *Lavilla* in 2010,[337] is the most investigated peptide C–H activation. Selectivity relies on the inherent reactivity of Trp at C2, it can be carried out under aqueous conditions, and has been used successfully for peptide macrocyclisations.[338-340] This method has been carried out on peptides attached to solid phase peptide synthesis (SPPS) resins,[341] and has even been used for the selective arylation of Trp residues in a protein using a heterogenous palladium nanoparticle biohybrid as catalyst.[342] In a similar fashion a gold-catalysed Trp C2(sp^2)–H selective activation and alkynylation was reported in 2016 by the groups of *Hansen*[343] and *Waser.*[344] The potential utility of this method was demonstrated by the alkynylation of a protein (horse heart apomyoglobin) in water/acetonitrile solvent, albeit requiring superstoichiometric loading of the gold catalyst.[343]

The native backbone assisted palladium-catalysed phenylalanine (Phe) $C_\delta(sp^2)$–H selective and Trp C2(sp^2)–H selective activation and olefination of peptides has been reported by *Wang*.[345,346] This methodology is restricted to Phe or Trp at the peptide C-terminus, but can be used to effect macrocyclizations on SPPS resins.

To date the only example of C4(sp^2)–H activation of Trp in peptides is the triflate directed olefination reported by *Wang* in 2020. The methodology is currently restricted to N-terminal *N*-triisopropylsilyl (TIPS) protected Trp residues, and has been used successfully for the synthesis of indole bridged macrocycles by olefination.[346]

Although the bulk of C–H activation in peptides has involved palladium catalysis, there has been promising recent progress using auxiliary (2-pyridyl or 2-pyrimidyl) directed Trp C2(sp^2)–H activation. Ruthenium,[347,348] manganese,[349,350] cobalt,[351] and rhodium[352] have been successfully employed in peptide modification. Notably the auxiliaries can be removed tracelessly, and enable activation at any position in a peptide, while the change in catalyst removes the requirement for stoichiometric silver salts (a limitation of some palladium-catalysed C–H activations) in the case of ruthenium, cobalt and manganese catalysis. Ruthenium catalysis is particularly promising having been demonstrated to be compatible with water as a solvent and in SPPS.[347,348]

The selective C(sp^3)–H activation methods for peptides developed to date rely on the activation of specific C–H bonds through cyclic or bicyclic palladium intermediates. *Yu* first reported the $Pd(OAc)_2$ catalysed $C_\beta(sp^3)$–H activation of Ala at the N-terminus of peptides in 2014. Selectivity occurred through native backbone assistance, allowing selective acetoxylation and arylation at the β-carbon without requiring an exogenous directing group.[353] N-terminal leucine (Leu), Phe, 2-aminoisobutyric acid and 1-amino-1-cyclobutanecarboxylic acid have also been determined to be successful substrates, and macrocyclizations using this method can be successfully carried out on peptides still attached to SPPS resins, making it a powerful tool for the synthesis of peptides.[354,355]

The use of exogenous auxiliaries for C(sp^3)–H activation has proven to be a useful tool for peptide modification. When the C-terminal aa does not have a free NH (proline[356] or N-methyl-Ala[357]), aminoquinoline (AQ) directed $C_\beta(sp^3)$–H activation is possible thus enabling arylation.

In the sole example of C(sp^3)–H activation of an internal aa reported to date, *Ackermann* used triazole, a peptide isostere found in many peptidomimetics, to selectively activate the $C_\beta(sp^3)$–H on Ala on its N-terminal

side, allowing arylation. A modification of this methodology also allows the activation of Ala and Phe at the N-terminus of peptides.[358-360]

The picolinamide (PA) auxiliary has been used by *Shi* to selectively activate and silylate the $C_\gamma(sp^3)$–H of valine (Val), isoleucine (Ile), *t*BuO-threonine (*t*Bu-Thr), *tert*-leucine (Tle) or aminobutyric acid when at the *N*-terminus of peptides.[361] Subsequent extension by *Chen* allowed this activation to be carried out in aqueous solvent, making it compatible with peptides containing polar aas.[362]

Recently, *Shi* reported the $C_\gamma(sp^3)$–H arylation of Tle at the C-terminus of short peptides (≤3 aa) in modest yields, the first example in peptides where $C(sp^3)$–H activation occurs through a weak 6 membered ring transition state, allowing selective arylation at the γ-carbon without the requirement of an exogenous directing group.[363] A further auxiliary-free approach to $C_\beta(sp^3)$–H activation was reported by *Ackermann* in 2020. The $C_\beta(sp^3)$–H activation of Ala at the N-terminus of peptides (≤4 aa) was demonstrated where an adjacent asparagine (Asn) participates in a 5,6-fused bicyclic palladacycle.[364]

While promising developments – such as the first examples of selective C–H activation on proteins, the increasing diversity of metal catalysts employed, the ability to carry out reactions in water and the development of SPPS compatible methodologies – are already beginning to make their mark on peptide synthesis, many challenges remain to be overcome before the true potential of C–H activation can be realised for peptide synthesis. As summarised in Figure 13, the library of C–H bonds which can currently be selectively targeted in peptides represents only a fraction of the C–H bond types present in peptides, and existing C–H approaches often lack substrate tolerance, especially for thiols (e.g. cysteine), restricting their application.

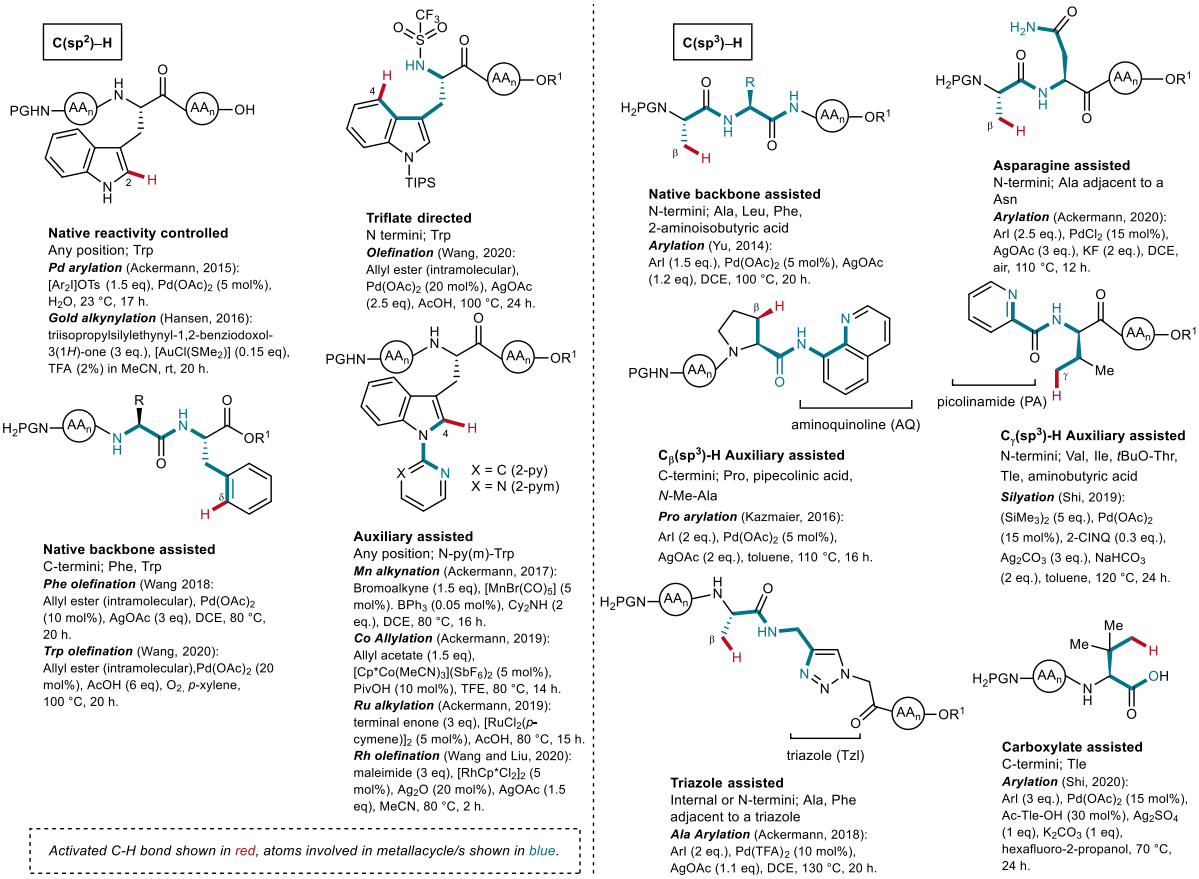

Figure 13. Summary of the peptide C–H bonds currently accessible through C–H activation with representative experimental procedures and mechanism of selectivity indicated. AA_n = amino acid chain, R = Amino acid side chain, R^1 = alkyl group, PG = protecting group.

3.4.2 C–H Activation for the Preparation of Conjugated Polymers

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Direct arylation polymerization (DAP) results in the “greener” synthesis of organic electronic materials that have a broad range of applications including plastic semi-conductors, opto-electronic devices and organic photovoltaics.[365] The solubility of the resulting functional macromolecules ensures that they can be easily processed and allows for alternative electronics manufacturing methods including inkjet printing, spray coating and roll-to-roll printing. By exploiting C–H functionalization routes, rather than traditional cross-coupling approaches, such as Suzuki, Kumada, Stille and Negishi reactions, aryl–aryl coupled products can

be obtained with fewer stoichiometric by-products. Furthermore, the reduced need for activated transmetallating agents reduces the cost of the starting materials. Most importantly, these approaches reduce the amount of potentially contaminating by-products that can be trapped in these materials, which are known to impact the performance of these conjugated materials.[366] These strategies have been exploited in the synthesis of linear polymers, brush polymers,[367] hyperbranched,[368] and porous[369] materials.

The first report of DAP by *Lemaire* in 1999 exploited palladium catalysis in the synthesis of thiophene oligomers (Fig. 14a).[370] The directing effect of the heteroatom containing thiophene is critical for promoting this reactivity, resulting in a common alternative abbreviation for this class of polymerization reactions, namely DHAP (direct (hetero)arylation polymerization). This initial report of DAP proposed a Mizoroki-Heck-type coupling mechanism, although more intensive mechanistic investigations on palladium-catalysed DAP has revealed the critical role of CMD C–H activation pathways. These mechanistic insights have been leveraged to help control coupling regioselectivity and unwanted crosslinking in the synthesis of poly(3-hexylthiophene), the most studied semiconducting polymer for plastic electronics applications.

This early result preceded significant advances in the field by a decade and since 2010 DAP has become an explosive area of research for the assembly of conjugated organic materials.[371] Various functional groups can be incorporated to tune the electronic properties of the materials while alkyl substituents can be incorporated into the building blocks to enhance solubility.[372] By combining dibrominated units with unfunctionalized units electron rich “push” monomers can be conjugated to electron deficient ”pull” monomers (Fig. 14b).[373] For example benzothiadiazole, carbazole, diketopyrrolopyrrole, napththalenediimide, isoindigo, thienoisoindigo and thienothiadiazole can be incorporated to access materials with diverse electronic properties.[374,375] This strategy has yielded materials with long conjugation lengths and tunable band gaps to target applications ranging from Organic Light Emitting Diodes (OLEDs),[376] Organic Field Effect Transistors (OFETS)[377] to Organic Solar Cells (OSC).[378] This is a rapidly evolving field with new contributions emerging weekly.

Advances in developing improved reaction conditions and the identification of optimized catalysts has rendered this approach suitable for the synthesis of conjugated materials ranging from small oligomers to high molecular weight polymers of more than 100 000 kg/mol.[379] Recently improved sustainability has been realized using DAP by using copper catalysts.[380] Furthermore, costs can be further reduced through the use of emerging methods that use dichlorinated monomers rather than dibromide precursors.[381] New classes of

heteroaryl units are being explored as DAP substrates to offer yet further modified electronic and responsive properties for advanced applications.

An attractive alternative synthesis of conjugated materials employs oxidative cross-coupling polymerizations of unfunctionalized monomers (Fig. 14c). Indeed electrochemical and chemical oxidative cross-coupling have been long known for the preparation of polyarenes, although controlled polymerizations remain a challenge.[382] For example poly(thiophene) can be prepared using oxidative cross-coupling with oxygen as the terminal oxidant, although modest yields, low molecular weights and high dispersities have been reported.[382] Improvements have been realized by using monomers that feature directing groups, such as ester substituents, to promote C–H activation.[372] These approaches have been explored using alternative heterocycles, such as azoles.[383] Synthetic advances in oxidative cross-coupling reactions may provide the breakthrough required to make this approach competitive with DAP for the synthesis of conjugated polymers.

C–H activation *via* the Catellani reaction[49] can be exploited in the synthesis of rigid ladder polymers (Fig. 14d)[384] that display high thermal stability and high porosity. These materials have found application as porous materials for gas separations.[385] More recent advances explore the incorporation of functionality and substituents to modify functional properties in the resultant materials.[386]

C–H activation can be used to generate reactive organometallic initiators for insertion polymerizations of alkenes. Using this approach end-capped functionalized oligomers and polymers can be accessed (Fig. 14e) using both early and late transition metal catalysts.[387] By using rare earth alkyl precatalysts thiophene,[388] methoxy-substituted arenes[389] and N-heteroaromatic groups[390] can undergo C–H activation to generate an active catalyst initiator suitable for alkene polymerization. More recent contributions have featured this approach in the preparation of a variety of block co-polymers.[391]

An emerging area of materials chemistry explores the use of C–H activation reactions to efficiently access functionalized monomers that can then be used in the preparation of responsive materials. Amine/aniline functionalized materials have been prepared using hydroaminoalkylation and ring-opening metathesis polymerization (Fig. 14f)[392] to access materials with dynamic associations resulting from hydrogen bonding and pi-pi stacking non-covalent interactions. These associating polymers offer access to distinctive materials with unique physical properties.[393] Alternatively, C–H activation can be used in an intermolecular fashion to generate co-polymers, such as acetophenone derivatives with silylated dienes.[394] Post-polymerization modification by C–H activation of various alkene terminated oligomers or polymers can be used to install boryl,[395] alcohol[396] or ketone functionalities.[397]

A diverse array of C–H activation reactions are powerful strategies for polymerization reactions. These flexible synthetic route results in reduced waste generation offer green synthetic approaches to make functional materials for green energy applications and beyond.

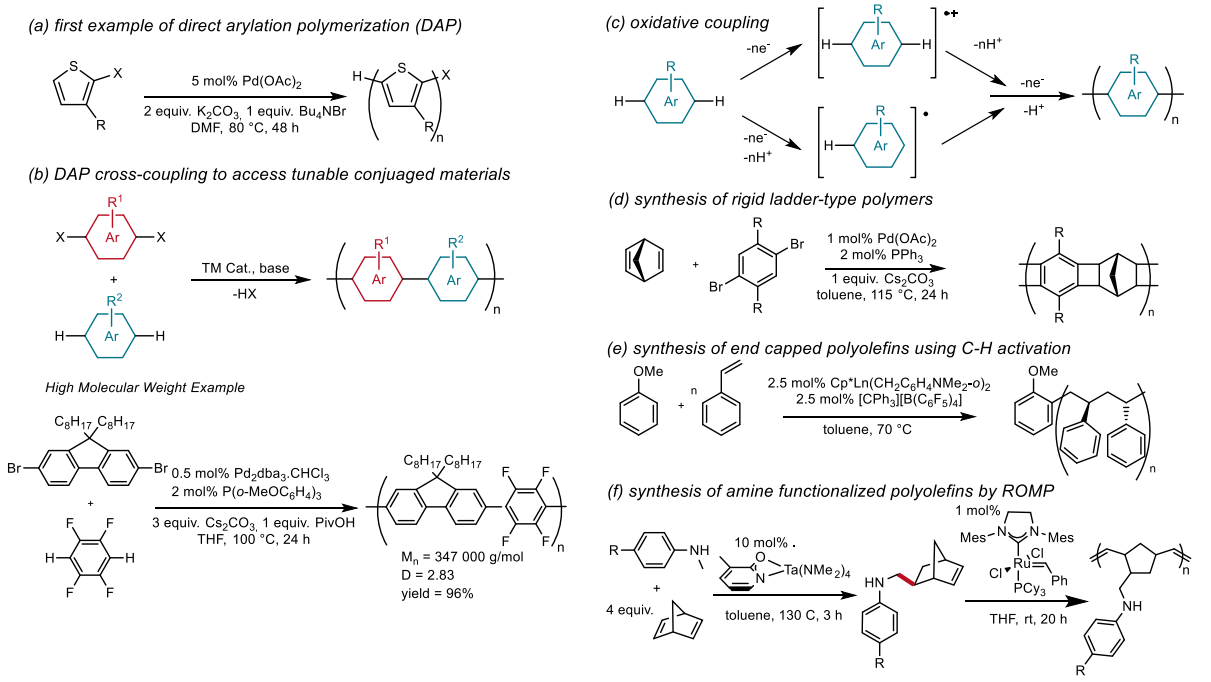

Figure 14. (a) DAP for the synthesis of conjugated materials as first disclosed by *Lemaire* in 1999;[370] (b) DAP as a generalized route to the synthesis of donor/acceptor conjugated materials with tunable bandgaps, including a specific optimized example by *Ozawa* to realize high molecular weight material;[379] (c) oxidative coupling as a promising strategy for assembling conjugated polymers; (d) Catellani type reactions for the synthesis of rigid ladder polymers; (e) C–H activation used to make initiators suitable for chain transfer polymerization; (f) C–H activation for the efficient synthesis of new monomers suitable for ROMP.

3.5 Late-Stage Diversification for Pharmaceutical Developments

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Late-stage functionalization (LSF) has emerged as an attractive strategy for the diversification of lead compounds in drug development, not only because of its step reducing and atom economic nature but also

as a means of accessing previously synthetically challenging compounds.[398,399] The theoretical scope of such C–H functionalization chemistry is immense and current capabilities only scratch the surface of this intriguing field of research.[400] A multitude of mechanistic manifolds allows for selective C–H functionalizations, herein however we will focus entirely on activation using transition-metal catalysis. Two manifolds have mainly found practical applications in drug discovery. 1) Directed C–H activation which takes advantage of the presence of Lewis basic sites to direct and insert a metal into a C–H bond, forming a metallacycle and 2) Non-directed C–H activation where selectivity is guided to certain C–H bonds by either catalyst control or inherent substrate reactivity. Below we discuss selected examples and their utility in drug discovery.

The C–H activation strategy which takes advantage of designed directing groups (DGs) has pioneered the field of LSF. Identification of Lewis basic sites or derivatives thereof within the parent compounds has allowed regioselective functionalization in close proximity to those groups, utilizing a plethora of transition metals (Fig. 15).[6,7,141,401-403] In 2011, the introduction of a *N*-pentafluorophenyl sulfonyl directing group enabled in a straighforward and predictable way an access to a multitude of analogues of *Celecoxib*.[404] This divergent methodology allowed for iodination, arylation, methylation, carbonylation, carboxylation and olefination using a palladium(II) reaction manifold. Interestingly enough the pyrazole directing group did not compete in a productive way with the anionic sulfonamide, further evidence for selectivities in systems containing competing DGs are found in the computational study carried out by *Norrby* and co-workers.[405] Moving this manifold outside of ortho activation of aromatic motifs is most commonly done by utilizing either the Catellani reaction[406] or typically *σ*-activation mechanisms which render *meta*- and/or *para*-functionalization opportunities.[407,408] In 2020, *Johansson* and *Ackermann* showcased that it is indeed possible to design a catalytic system that takes advantage of vast number of inherent directing groups, i.e. no designed directing groups, allowing for the direct insertion of a methyl group into C–H bonds of both complex natural products as well as marketed drugs.[409,410] The strategy took advantage of a an environmentally benign cobalt(III) catalyst together with a boron based methyl source, which renders this methodology very functional group tolerant. High-Throughput-Experimenation (HTE) allowed for the identification of robust reaction conditions, functional group tolerance screen and ranking of different directing groups, thus making the prediction of regiochemical outcome of complex molecules easy. Using this approach, e.g. complete selectivity for the C–H bonds proximal to the pyrazole core of non-prefunctionalized *Celecoxib* was observed with an Earth-abundant cobalt catalyst. Selective directed activation of C(sp^3)–H in LSF applications continue to be rare. In contrast, *Gaunt* has elegantly designed a ligand-enabled palladium(II)-catalysed γ-C(sp^3)–H arylation.[411] The presence of a tertiary amine directs activation to the γ-C(sp^3)–H bond and produces arylated products

using simple arylboronic acids as coupling partners. *Trimipramine* was thereby smoothly arylated in a single step.

The most widely used non-directed C–H activation is arguably the iridium-catalyzed C–H borylation, largely developed by the groups of *Ishiyama/Miyaura/Hartwig*, *Smith/Maleczka* and *Hartwig* (see Section 2.5).[157-159,412] It has become widely used because of its large scope including heteroaromatics and the fact that the resulting aryl boron species are extremely versatile in downstream functionalizations such as Chan-Lam *N*-arylations, oxidations, fluorinations, alkylations, perfluoroalkylations, and arylations. The *Hartwig* group has elegantly showcased the utility of iridium-catalyzed borylation in several different tandem borylation/functionalization processes. In an LSF example of a *c-Met* kinase inhibitor, borylation occurred selectively in the 4-position of the benzoxazole, resulting in a quick SAR exploration of that specific position.[413] The regio-complementarity to both directed C–H activation, radical addition (Minisci) and electrophilic aromatic substitution makes this method very useful in drug discovery programs accessing new functionalized aromatic moieties. Very recently this chemistry has been further expanded to C(sp^3)–H activation and an impressive functionalization of dehydroabietic acid was disclosed.[320]

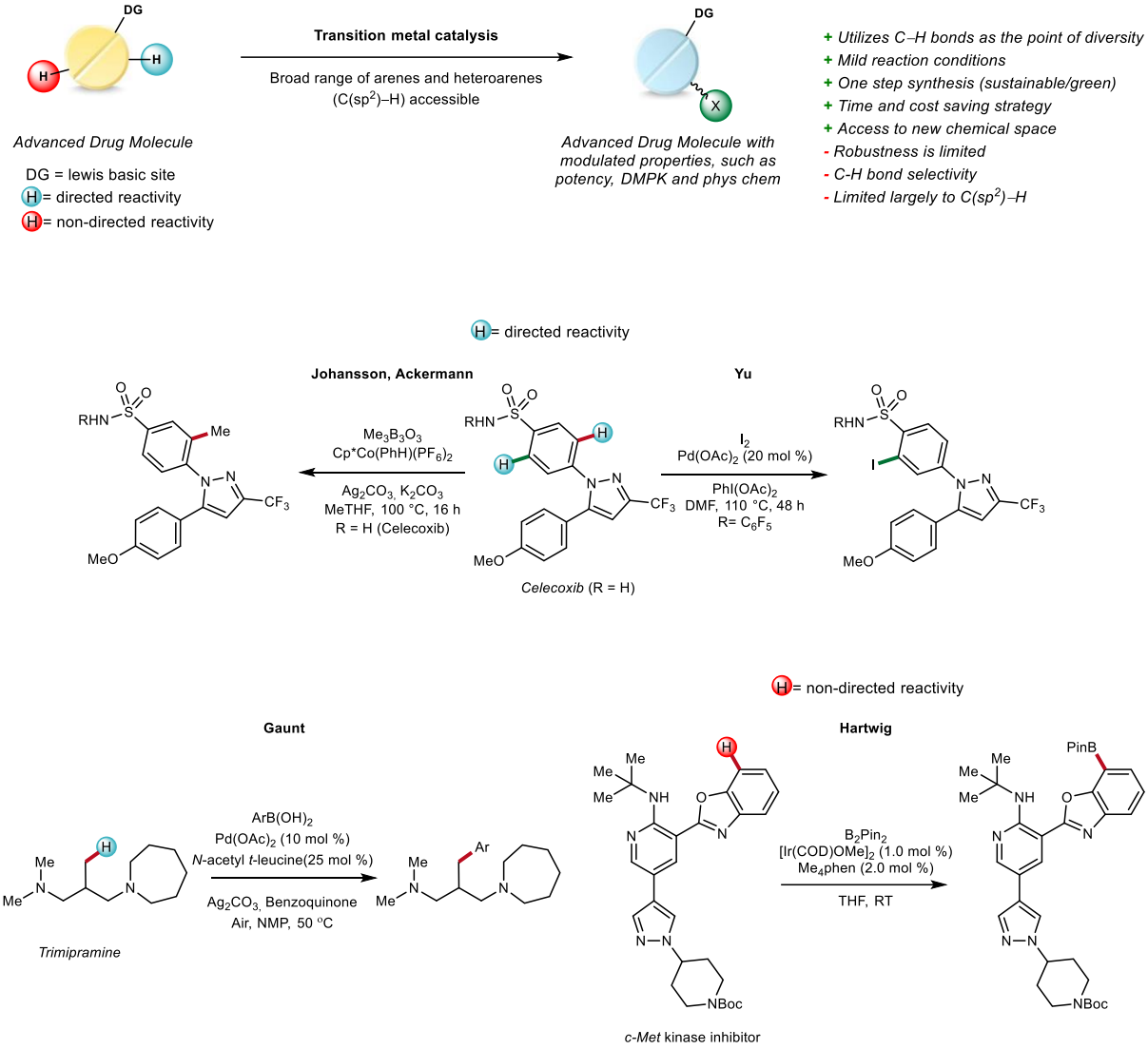

Figure 15. Late-stage diversification in drug discovery. Transition metal-catalyzed C–H activation enables the diversification of pharmaceuticals exploiting directing group assistance or the substrate's innate reactivity.

4. Reproducibility and Data Deposition

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For the reproduction of experimental results, a comprehensive description of all procedures, materials and techniques are of prime importance. Especially for procedures beyond the realm of classical batch synthesis protocols, such as flow-, photo- or electrochemical reactions, a detailed description of the employed reaction

setup, including photos if necessary, is absolutely required to ensure reproducibility. Furthermore, the suppliers of commercially obtained materials should be noted. This information, along with full sets of analytical data of synthesized compounds, is typically available in the corresponding publications or their associated supplementary materials. The emergence of dedicated journals, such as *Organic Syntheses* or *Nature Protocols*, further assists to ensure the reproducibility of novel synthetic protocols, providing a platform for the publication of validated, in-depth and step-by-step descriptions of experimental operations. Characterization data of organic and organometallic compounds, such as NMR, MS and IR data, are not necessarily deposited in dedicated data repositories, but instead published as supplementary information along with the respective scientific contributions. It should be noted that the *Beilstein Journal of Organic Synthesis*, *Synthesis* and *Synlett* offer a platform for the deposition of primary data. Crystallographic data obtained from X-ray diffraction measurements are deposited with the *Cambridge Crystallographic Data Centre* (CCDC). With regard to data to support computational studies, the current situation appears rather more diverse. Although calculated energies and geometries are typically included in the supplementary information files, in some cases a deposition of coordinates as separate files is opted for.

The rise of big data analysis methods[414,415] that exploit published experimental data has recently induced a considerable impetus for the dissemination of additional data – especially on unsuccessful experiments. However, a general consensus in terms of data deposition for subsequent reuse was not yet reached, but is highly desirable.

5. Limitations and Optimizations

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We have discussed a plethora of bond forming reactions that originate from activation of a C–H bond. There are some inherent obstacles in C–H activation processes and by identifying and presenting the strategies applied in each section we have highlighted some general limitations but also how these, to some extent, can be turned into opportunities. Finally, we will briefly showcase how High-Throughput Experimentation (HTE) and artificial intelligence (AI) can accelerate the development of new C–H activation processes and aid the optimization of existing ones.

1) Selectivity is key in all organic transformations and also applies when the targeted site of functionalization is a C–H bond. The omnipresence of C–H bonds makes selectivity an important factor that can be difficult to achieve. This also includes regioselective processes and desymmetrizations where multiple equivalent C–H bonds are present. Depending on the operating mechanistic manifold this can be controlled by *inter alia* the careful choice of metal, ligands, additives, or steric effects. Specifically, in the case of C(sp^3)–H bond activation there are opportunities to render chiral products stereoselectively. This area is still in its infancy and suffers from the need of screening of chiral additives, such as chiral ligands, and chiral acids/bases, among others.[58,251] Considering aromatic substrates, another selectivity issue relates to moving directed C–H bond activation beyond the realm of *ortho*-functionalization to access *meta/para*-functionalized products, which has proven difficult, especially in the absence of "designer" directing groups.[40,47,406,416-424] The ultimate goal is to design selective processes to be able to functionalize any given C–H bond.

2) In all intermolecular C–H activations, a careful consideration of a suitable coupling partner has to be taken. In the most desirable case, this coupling partner is also a reactant containing yet another C–H or Het–H bond.[425] The lack of prefunctionalization is foremost an advantage. However, when there are competing C–H bonds available, a directing group can enhance the selectivity. Furthermore, heteroatom based nucleophiles are still, to a large extent, limited to various protected derivatives, such as activated azides, whereas more practical reagents, including unprotected basic amines, are very difficult to employ.[11] In the area of C(sp^2)–C(sp^3) formations, both strongly electrophilic (e.g. alkylhalides) as well as nucleophilic (e.g. alkyl grignards) reagents are still predominantly used.[6,426,427] A shift to less reactive substrates, such as alkylboronates, would be expected to improve both the selectivity and synthetic applicability of this very important transformation.

3) The oxidation state required for a metal to render a bond-forming reaction catalytic most commonly requires expensive and toxic metal oxidants in stoichiometric amounts as additives. The need for an external oxidant is a disadvantage, as the reduced oxidant generates waste, an exception being when dioxygen can

be applied. More recently however, applications of photo- and electro-chemistry have proven to be sustainable and efficient ways to avoid stoichiometric external oxidants.[428-431]

Box 2.

While constantly searching for more sustainable and innovative catalysis manifolds, recently considerable attention has been focused on the possibility of merging the C–H activation field with visible-light photocatalysis. Accordingly, several conceptually unique catalytic systems have been designed, benefiting in various manner from the unique reactivity accessible *via* photocatalysis.[428,432,433] In a notable report concerning such dual catalysis, the photocatalysis has been astutely used to complete a reoxidation step within a "classical" C–H activation reaction, as elegantly illustrated by palladium-catalyzed intramolecular oxidative C–H/C–H coupling disclosed by *Rueping*.[434] While using iridium-based photosensitizer under visible-light irradiation, the targeted indole synthesis occurring *via* a palladium(0)/ palladium(II) catalytic cycle, was completed in the absence of an external chemical oxidant, thus further improving the sustainability of the overall transformation.[435] During the following years, the generality of this approach was greatly expended and implementation of the photocatalytic cycle as a "green" reoxidation mode turned out to be compatible with the diversity of C–H activation protocols, including palladium,[90] rhodium,[436] ruthenium[437] and cobalt-catalyzed[438] transformations.

The synergistic combination of C–H activation and photocatalysis also unlocks the door towards truly mild direct functionalization protocols. The synergistic action of metal-catalyzed C–H activation and photocatalysis allows the simultaneous generation of a metallacyclic intermediate together with a highly reactive radical partner, thus allowing molecular transformations under exceedingly mild reaction conditions. Such an approach turned out to be particularly appealing for biaryl synthesis,[439-441] as well as direct acylations.[442,443]

An elegant combination of C-H activation and photocatalysis was likewise disclosed by *Ackermann*[444] and *Greaney*[445] while studying remote ruthenium-catalyzed *meta*-selective alkylation of phenyl-pyridine derivatives occurring at room temperature. In this case, the *in-situ* generated ruthenacycle is photoactive and thus the overall transformation does not require an external photocatalyst.[446] The portfolio of dual catalytic systems has also been complemented with undirected transformations, mainly involving direct arylations of arenes[447] and heteroarenes[448,449] – even with Earth-abundant 3d transition metals – as well as modern versions of Sonogashira-Hagihara-type reactions.[450,451]

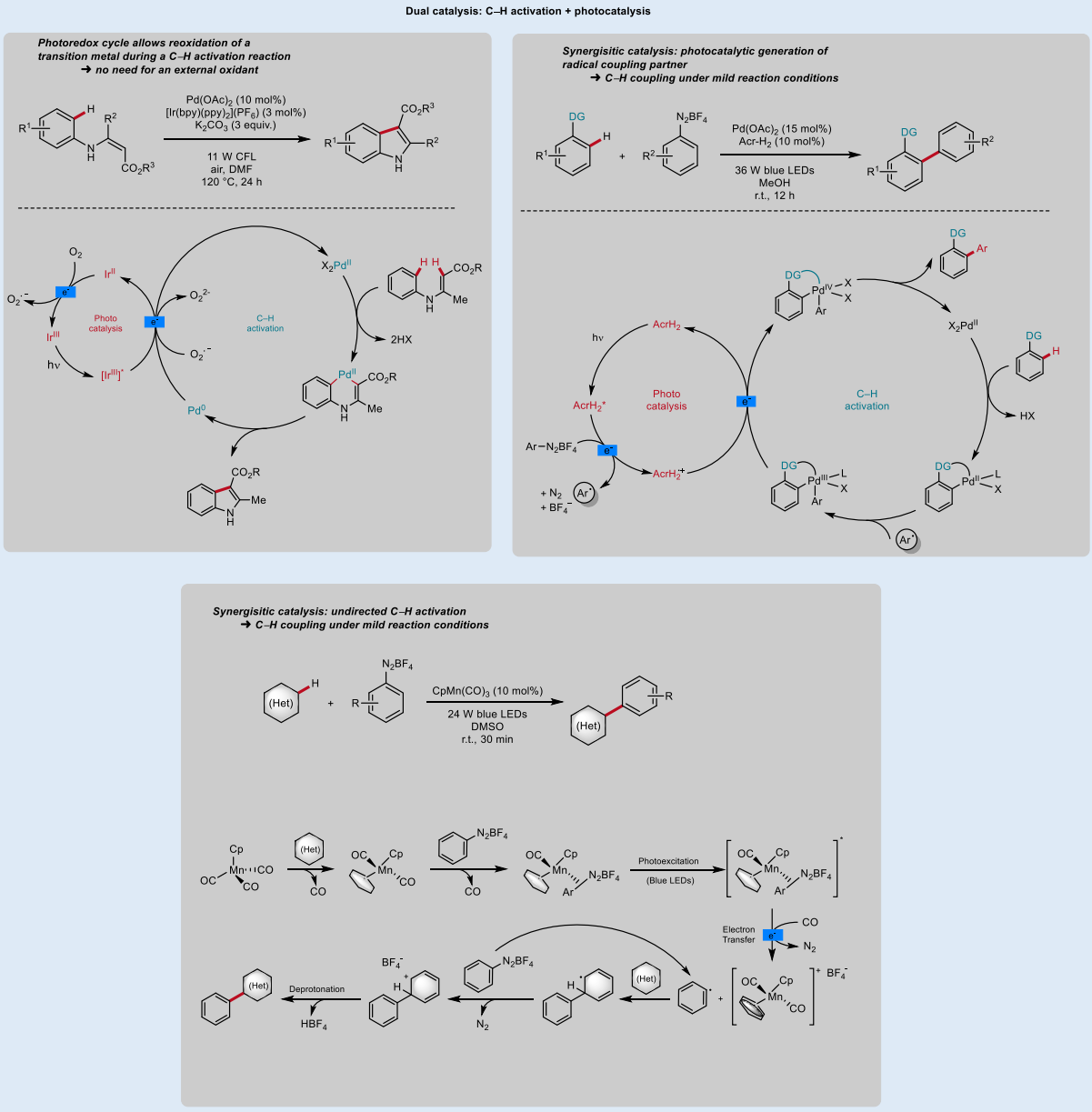

Figure 16. Photocatalysis and C–H Activation.

Box 3.

While C–H activation chemistry has undoubtedly revolutionized the toolbox of synthetic chemistry, oxidative transformations continue to heavily rely on overstoichiometric amounts of expensive and potentially toxic copper(II) or silver(I) salts as well as highly reactive hypervalent iodine compounds as the oxidant. These features compromise the sustainable nature of the C–H activation approach. Electrochemistry has very

recently undergone a renaissance in molecular syntheses and has gained considerable momentum as an environmentally-benign toolbox.[144,145] In particular, the merger of electrochemistry and transition metal-catalyzed C–H activation has enabled various oxidative C–H activations with H_2 as the sole stoichiometric byproduct, thereby significantly improving the overall sustainability (Fig. 17a).[452-455] To this end, 4d, 5d as well as Earth-abundant 3d metals were employed for *inter alia* nitrogenations,[84-89,456-458] oxygenations[146,147] and alkene, alkyne or allene annulations[459-461] *via* metallaelectro-catalyzed C–H activation (Fig. 17b).[462-464] In addition to oxidative reactions, redox-neutral transformations can likewise benefit from electrochemistry due to facilitated single-electron transfer (SET) processes. Indeed, nickelaelectro-catalyzed C–H alkylations were very recently achieved under exceedingly mild conditions of ambient temperature (Fig. 17c).[465] Despite this undisputable progress, metallaelectro-catalyzed C–H activation is still in its infancy. The merger of electrocatalytic C–H activation with photocatalysis,[466,467] the use of electro-flow-catalysis[468,469] as well as the design of novel hybrid metal catalysts bears enormous potential and will likely provide a significant stimulus for the development of highly efficient and sustainable approaches in C–H activation chemistry.[470]

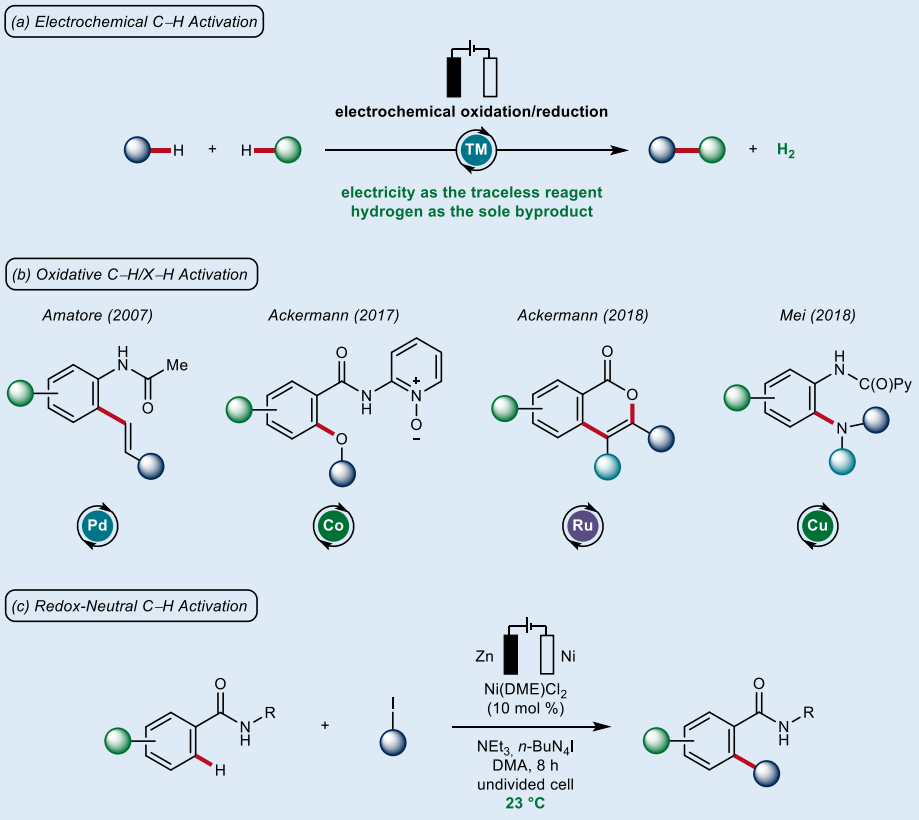

Figure 17. Electrochemical C–H Activation. (a) General strategy for improved resource-economy; (b) Representative examples of oxidative C–H/X–H activations; (c) C–H alkylations under nickelaelectrocatalysis.

Historically, new methodologies have been developed by combining mechanistic knowledge and then, by careful considerations, optimizing these processes by changing a number of parameters, including directing groups, coupling partners, metals, bases, additives etc. The use of high-throughput-experimentation has allowed more extensive studies to be undertaken, including screening of hundreds, if not thousands of conditions simultaneously. *Ackermann* and *Johansson* recently showcased that an HTE campaign was instrumental in developing a methodology, which took benefit of both an environmentally-benign catalyst as well as a boron-based methyl source, allowing for the late-stage functionalization of several complex marketed drugs and natural products. In addition, the HTE data obtained provided direct access to information regarding directing group strength and reaction robustness.[409]

Another emerging area is the use of artificial intelligence/machine learning to predict C–H site selectivity as well as providing quantitative likelihood (reactivity) of success of C–H functionalizations in structurally more complex molecules.[471] Such tools will be indispensable for the future of medicinal chemistry and process chemistry in order to prioritize among targets compounds to make, but also to predict the regiochemical outcome.

6. Outlook

During the last decade, transition metal-catalyzed C–H activation has been recognized as an increasingly viable tool for the assembly of compounds of interest to *inter alia* medicinal chemistry, drug discovery and material sciences. While considerable advances have been achieved with the aid of late 4d and 5d transition metals, the use of Earth-abundant, less toxic metal catalysts has recently received significant momentum. Likewise, the merger of transition metal-catalyzed C–H activation with photochemistry and, very recently, electrochemistry has enabled the development of novel molecular transformations under exceedingly mild reaction conditions, thus providing considerable impetus for environmentally-sound molecular syntheses.

Box 4. (T. Rogge, N. Kaplaneris, L. Ackermann)

Although C–H activation has found wide-spread application in industry and in academia (*vide supra*), a number of significant challenges remain. The development of novel and highly selective transformations under mild reaction conditions, in particular with the aid of less toxic Earth-abundant 3d transition metal catalysis, is of key importance in C–H activation chemistry. In this context, advances in protic solvent-tolerant C–H activations in a bioorthogonal manner will have tremendous impact on *in vitro* and *in vivo* studies. Furthermore, efforts to increase the power of the C–H activation approach by the merger of resource-economical electro- or photochemistry with C–H activation, by employing green solvents[472] or by the still underdeveloped application of heterogeneous, and thus reusable, transition metal catalysts[473] will likely attract significant attention. In addition, the development of novel approaches for enantioselective C–H activation[248] holds enormous potential for the synthesis and late-stage diversification of compounds of interest to medicinal chemists.

The application of data science and machine learning approaches in organic synthesis has recently been demonstrated for the prediction of reaction outcomes and optimization of reaction conditions.[474-477] The adaptation of these approaches for C–H activation chemistry will arguably provide a considerable stimulus for the development of novel transformations through a rational catalyst design, while simultaneously reducing the number of reactions required to be experimentally evaluated.

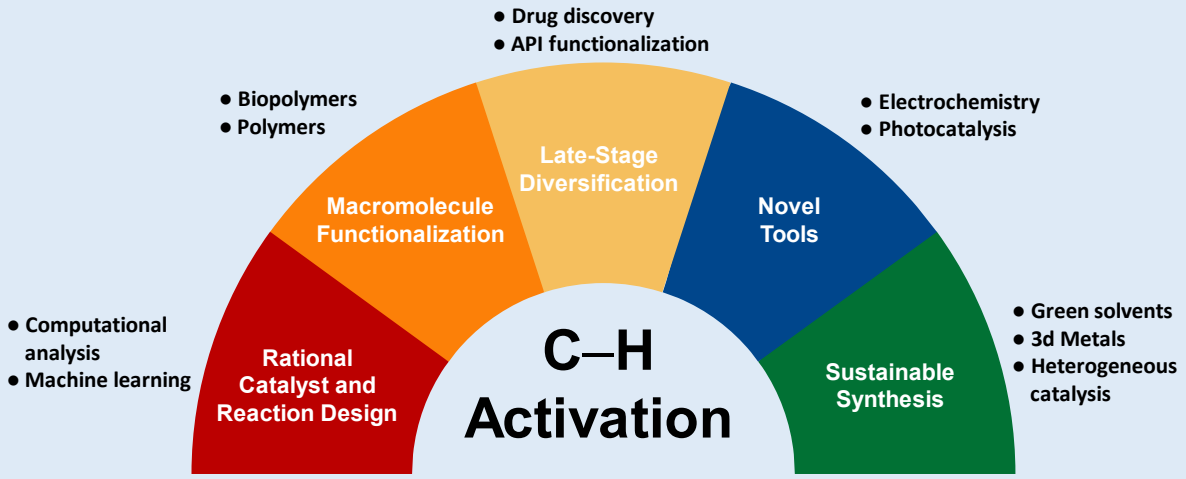

Figure 18. Challenges and priorities for the next years.

6.1 Early Transition Metal Catalysis

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Early transition metal-catalyzed C–H alkylation is attractive due to its atom economy and the use of simple alkene feedstocks. This is a growth area of research with opportunities for enhanced reaction and catalyst development, asymmetric hydroaminoalkylation, catalyst controlled regioselectivity, and the incorporation of hydroaminoalkylation as a key step in the synthesis of more complex N-heterocycles.

6.2 Large Scale Industrial Applications

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Intriguingly, the application of C–H activation in process chemistry is still in its infancy. This is partially due to the fact that introductions of halides/pseudohalides along with downstream coupling reactions are well studied and offer reliable access to target compounds. Having said that, many C–H activations, e.g. directed metalation, offer regiocomplementary products to “classical chemistry” and as such will be irreplaceable transformations towards any new molecule.[401,402,478] A number of processes on kg scale have been generated over the last 10 years, including both directed[479-481] as well as non-directed C–H activation.[417] The main inherent advantages include positive impact on environmental factor (e-factor) and process mass intensity (PMI), while overall atom- and step-economy needs to be analyzed for every individual case. In the near future, we can foresee that C–H activation in process development and manufacturing will develop dramatically, foreseen improvements include catalyst robustness,[482-484] removal of stoichiometric oxidants by either photo-[428] or electrochemistry,[430,431] use of 3d metals[6,431] to make processes more environmentally sustainable and the extended use of High-Throughput Experimentation (HTE)[485] to fine-tune conditions.

Highlighted References

Key references (5-10% of total references) with a single sentence description, highlighting the significance of the work.

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Author Contributions

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Competing Interests

The authors declare no competing financial interests.

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