

C–H Activation: Toward Sustainability and Applications

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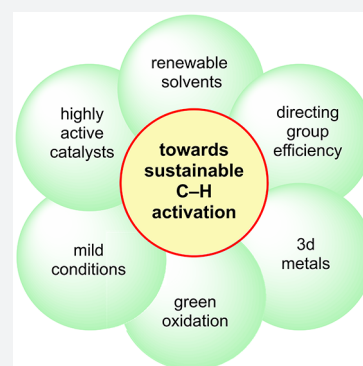
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ABSTRACT: Since the definition of the “12 Principles of Green Chemistry” more than 20 years ago, chemists have become increasingly mindful of the need to conserve natural resources and protect the environment through the judicious choice of synthetic routes and materials. The direct activation and functionalization of C–H bonds, bypassing intermediate functional group installation is, *in abstracto*, step and atom economic, but numerous factors still hinder the sustainability of large-scale applications. In this Outlook, we highlight the research areas seeking to overcome the sustainability challenges of C–H activation: the pursuit of abundant metal catalysts, the avoidance of static directing groups, the replacement of metal oxidants, and the introduction of bioderived solvents. We close by examining the progress made in the subfield of aryl C–H borylation from its origins, through highly efficient but precious Ir-based systems, to emerging 3d metal catalysts. The future growth of this field will depend on industrial uptake, and thus we urge researchers to strive toward sustainable C–H activation.



1. INTRODUCTION

Sustainability is achieved when the needs of the present can be satisfied without compromising those of the future. In recent years, the ideals of sustainability have emerged as a dominant theme in organic chemistry, with a view to the technology transfer of novel reactions from the lab bench to process plant. The ideal sustainable transformation eliminates the use of scarce materials and materials which, through their production or disposal, represent an environmental hazard or burden. The design of “environmentally friendly” chemistry goes hand-in-hand with economic transformations.^{1,2} For instance, the use of catalytic reactions, mild conditions, and limiting step-count and waste typically results in cost savings and cycle-time reduction. As society seeks to counter resource scarcity and address the climate emergency, legislative restrictions on the use of materials perceived to be hazardous or highly polluting are increasing.^{3–5} In 1998, Anastas and Warner defined the “12 Principles of Green Chemistry” as “design rules” to make chemical processes more sustainable (Figure 1). Nowadays, transformations are evaluated numerically using parameters such as *atom economy*, *E factor*, *process mass intensity*, and many others.^{6–17} More recently, enormous efforts have been made to develop the science of “lifecycle assessment”—the quantitative metrics by which the total mass and energy inputs and waste outputs of a given chemical transformation are evaluated for their environmental impact.^{18–21} Since then, industrial chemists have led the charge by compiling important guides on reagent and solvent selection.^{22–28}

In comparison to the more established cross-coupling reactions, C–H activation removes the requirement for prefunctionalization of both partners; as such, C–H activation

The 12 Principles of Green Chemistry

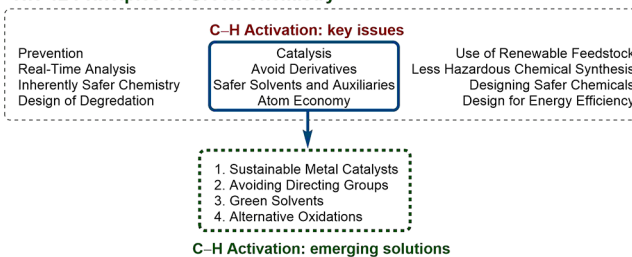
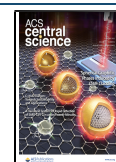


Figure 1. C–H Activation: sustainability trends.

has long promised a means to decrease step-count and hence mass intensity of chemical processes (Scheme 1).²⁹ That said, the selective cleavage of unactivated C–H bonds remains an active and comparatively difficult area of academic research. Consequently, the use of precious metal catalysts in high loadings, stoichiometric metal-based oxidants, high temperatures, and directing group manipulations are often required. Until now, practical and economic considerations have presented the major barriers to industrial application; sustainability considerations are likely to dominate in the years to come.

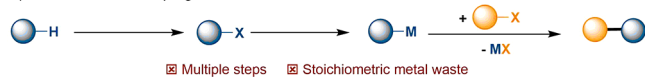
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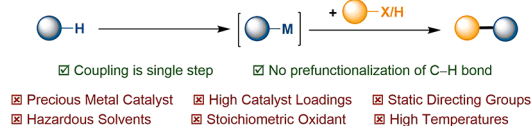


Scheme 1. C–H Activation: Intrinsic Opportunities

A) Traditional Cross-Coupling



B) Typical C–H Activation/Functionalization



A great body of work has already sought to address many of these limitations. Reviews on the subtopics of mild, efficient, and undirected C–H activation have been published, as well as those addressing the use of more sustainable solvents, nonprecious metals, and alternative oxidative systems, but to our knowledge there has yet to be a thematic overview from the perspective of sustainability.^{30–40} In this Outlook, we highlight noteworthy examples in areas where C–H activation faces its greatest sustainability challenges. Naturally, many transformations we have chosen span several such categories; most present at least one unsustainable aspect. The question is not whether these

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reactions are objectively green but rather in which ways do they represent an advance in sustainability. Our aim is to provide a cross-section that informs the reader of the fast-growing research lines in pursuit of sustainable, and thereby applicable, C–H activation.

2. NEXT GENERATION METAL CATALYSTS

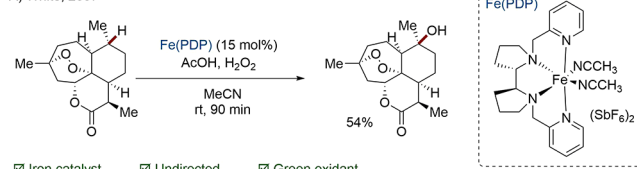
C–H Activation and functionalization has relied heavily on the ability of precious transition metals to affect diverse catalytic steps. The sheer cost and price volatility of these elements disincentivizes large-scale applications. Even if resource scarcity does not inhibit future use, the supply of such materials may become subject to geopolitical risk.⁴¹ In addition, the low abundance of precious metals contributes to a significantly higher carbon footprint in their extraction.⁴² To initiate a move away from wasteful precious metal chemistry, many groups are now focused on developing alternative 3d metal systems and recoverable, heterogeneous catalysts.

2.1. Adopting 3d Metals. The 3d metals are generally viewed as inexpensive and less toxic, decreasing the impact of higher catalyst loadings.³⁸ Promoting their uptake by the synthetic community depends heavily on expanding the range of chemistry which can be accomplished by these metals.

A well-known example of a 3d complex is the Fe-centered White–Chen catalyst, which is able to oxidize unactivated C(sp³)–H bonds. In the breakthrough work, it was discovered that the rigidity afforded by the pyrrolidine–pyridine (PDP) ligand conferred a high degree of regioselectivity based on subtle electronic differences. The original catalyst system favored oxidation of tertiary C–H bonds to alcohols over oxidation of methylene units to ketones (Scheme 2A).^{43,44} In a later study, a more substituted PDP complex was disclosed which reverses

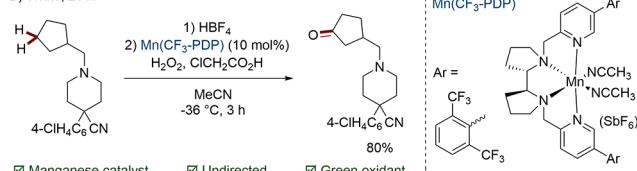
Scheme 2. PDP-Mediated Alkane Oxidations

A) White, 2007



Iron catalyst Undirected Green oxidant

B) White, 2019



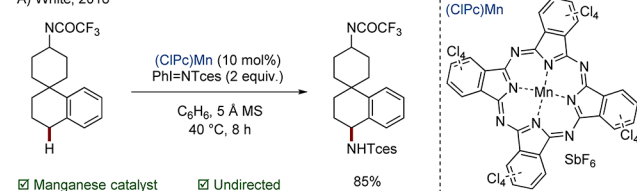
Manganese catalyst Undirected Green oxidant

this trend by restricting substrate access to the metal center.⁴⁵ Great efforts have been made to broaden the scope of this chemistry to molecules representative of biologically active compounds, for example, by coordinating problematic functionality with a Lewis acid.^{46–48} In one recent paper, interchange of the Fe center for Mn results in tolerance of basic nitrogen, halogens, and heterocyclic moieties (Scheme 2B).⁴⁹

The related nitrenoid chemistry, based on electron-rich porphyrin (Por) and phthalocyanine (Pc) ligands, has likewise seen intense development.^{50,51} White's 2012 FePc system was notable for selective, intramolecular allylic C–H amination over the aziridination favored by earlier Rh systems.⁵² The group of Che used an NHC–PorFe catalyst for the preparation of saturated nitrogen heterocycles from alkyl azides.⁵³ Recently, a highly functional group tolerant PcMn analogue was disclosed for intermolecular, benzylic C–H amination; multiple late-stage derivatizations of biologically active compounds were exemplified (Scheme 3A).⁵⁴ In parallel, the group of Zhang has led the development of the corresponding PorCo systems. Chiral amidoporphyrin ligands have enabled impressive enantioselective aminations, including the first intermolecular example in

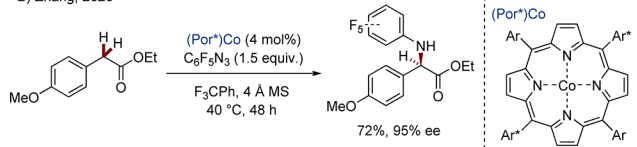
Scheme 3. Porphyrin/Phthalocyanine-Mediated Amination and Amidation

A) White, 2018



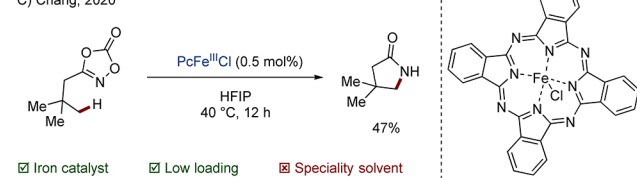
Manganese catalyst Undirected

B) Zhang, 2020



Cobalt catalyst Undirected Speciality solvent

C) Chang, 2020

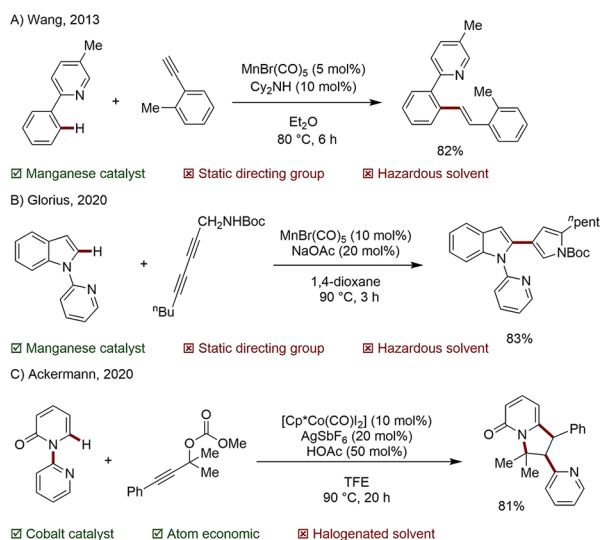


Iron catalyst Low loading Speciality solvent

2020 (Scheme 3B).⁵⁵ In the same year, Chang extended the concept to intramolecular amidation for the preparation of γ -lactams from dioxazolones (Scheme 3C).⁵⁶ The PCFe system is remarkable for its high activity, activating even primary alkyl C–H bonds at a catalyst loading of just 0.5 mol % (TON was 47 000 for benzylic C–H bonds).

3d Metals are now well-established in reactions involving the insertion of C–C double and triple bonds. Early research on Mn-catalyzed C–H aromatic alkenylation was conducted by Wang and co-workers. High regio-, chemo-, and stereoselectivity were achieved, and *anti*-Markovnikov *E*-configured olefins were obtained in high yields using the simple $\text{MnBr}(\text{CO})_5$ catalyst (Scheme 4A).⁵⁷ Shortly afterward, an imine directing group was harnessed to provide a Mn-catalyzed route to 3,4-disubstituted isoquinolines.⁵⁸

Scheme 4. Mn- and Co-Catalyzed C–H Functionalizations

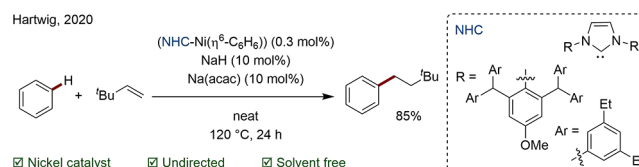


Glorius and co-workers later accomplished a highly selective synthesis of 1,3-enynes, pyrroles, and furans using $\text{MnBr}(\text{CO})_5$ as a catalyst (Scheme 4B).⁵⁹ Significantly, Rh- and Ru-based catalysts normally used for coupling 1,3-diynes were not successful in this transformation. Co has likewise emerged as a competent metal in C–H addition chemistry. In a recent example, Ackermann and co-workers reported a selective domino C–H activation, pyridine migration-annulation sequence catalyzed by a pentamethyl cyclopentadienyl (Cp^*) Co complex (Scheme 4C).⁶⁰ Likewise, this reaction could not be accomplished by Rh or Ru, underlining the potential of 3d metals to serve not only as more sustainable alternatives, but in many cases offering contrasting reactivity. Until now, however, undirected Mn and Co examples of this type have been elusive.

In contrast, Hartwig and Nakao have pioneered a Ni/NHC-catalyst system for the atypical, *anti*-Markovnikov hydroarylation of alkenes with arenes (Scheme 5). The authors demonstrate the presence of stabilizing, noncovalent interactions in the transition state between the bulky ligand and substrates. This chemistry is all the more remarkable for the high catalyst TON of 183, translating to a loading of just 0.3 mol %.⁶¹

The 3d metals have the potential to match and surpass the chemistry of the precious transition metals, but it is likely that further success will depend heavily on advanced ligand design so that these metal centers can participate in a wider range of elementary steps. The environmental impact of ligand syntheses

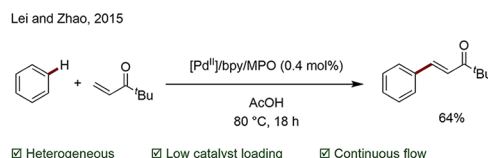
Scheme 5. Ni-Catalyzed Undirected *anti*-Markovnikov Addition of Alkenes to Arenes



can bear an outsize influence on the environmental burden of a process.⁹ Finding efficiencies in the multistep preparation of ligands represents an additional practical barrier to be overcome if such chemistry is to achieve mainstream appeal.

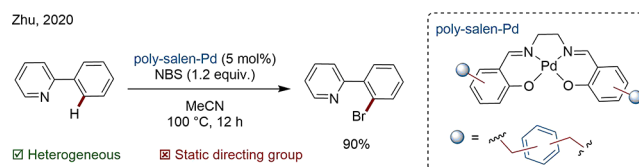
2.2. Heterogeneous Systems. The use of heterogeneous catalysts has warranted attention owing to the ease of removal and recycling of the catalyst.^{62,63} Provided metal leaching is sufficiently low, such systems can render the use of precious metals more sustainable. The group of Glorius reported several examples of direct arylation of (hetero)aryls using simple Pd/C, followed by the first undirected C–H thiolation of electron-rich heteroarenes by Pd/ Al_2O_3 .^{64–67} In 2015, Lei and Zhao disclosed a system for the catalysis of the Fujiwara–Moritani reaction involving bipyridine bound Pd on mesoporous organosilica (MPO). Kinetic experiments demonstrated a superior catalytic activity relative to the corresponding homogeneous system, a longer lifetime of the catalyst owing to the prevention of Pd(0) aggregate formation, and the means to perform the reaction in continuous flow mode (Scheme 6).⁶⁸

Scheme 6. Fujiwara–Moritani Reaction Catalyzed by Pd on Silica



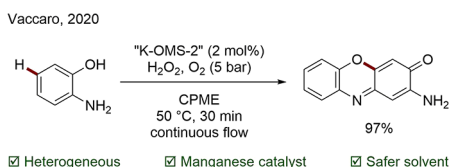
Zhu and co-workers developed a salen-based, hyper-cross-linked polymer-supported Pd catalyst to carry out C–H bromination and chlorination. The catalyst exhibited superior activity in comparison to homogeneous $\text{Pd}(\text{OAc})_2$ under the same conditions. Only trace Pd leaching was detected, confirming the suitability of poly salen as support material (Scheme 7).⁶⁹

Scheme 7. C–H Bromination Catalyzed by Pd Supported on a Salen-Based, Hyper-Cross-Linked Polymer



Vaccaro and co-workers reported the use of a Mn based heterogeneous catalyst for the oxidative coupling reaction of 2-aminophenols, *O*-phenylenediamines, and pyrogallol in continuous flow (Scheme 8).⁷⁰ Notably, this catalyst showed minimal leaching and low contamination of the product, which was readily purified by crystallization upon cooling of the CPME reaction solution, avoiding mass and solvent inefficient

Scheme 8. Oxidative Coupling of Aminophenol Catalyzed by Heterogeneous Mn-Based K-OMS-2

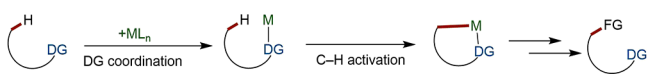


chromatography. (This solvent is regarded as process-friendly owing to its hydrophobicity, high boiling point, and low tendency to form peroxides.) The solvent could be recovered by distillation and reused, contributing to a very small E factor of 1.4 under continuous flow conditions versus 19 in batch.

3. AVOIDING AND REPLACING STATIC DIRECTING GROUPS

Most of the time, C–H bond activation is enabled by directing groups (DGs) that are covalently linked to the substrate (Scheme 9). A wide variety of functional groups with Lewis basic

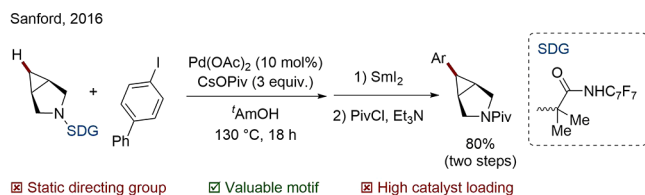
Scheme 9. Directing Group Mode of Action



properties, for instance, monodentate amides, pyridines, esters, or imines, as well as bidentate DGs, have been utilized.⁷¹ This coordination expedites C–H activation since it increases the local concentration of substrate in the proximity of the catalyst as well as controlling regioselectivity.

Unfortunately, for most valuable substrates, existing functionality is not suitable for the facilitation of directed C–H functionalization, and an existing functional group must be converted to a DG. Removal of the DG is often less trivial than is commonly admitted, but is crucial to obtain products of genuine utility. For example, Sanford was able to demonstrate a Pd-catalyzed C(sp³)–H arylation of bicyclic amines, which represent an important class of medically relevant compounds, with successful and efficient DG removal (Scheme 10).⁷² In later

Scheme 10. Arylation of Bicyclic Amines with Removable DG



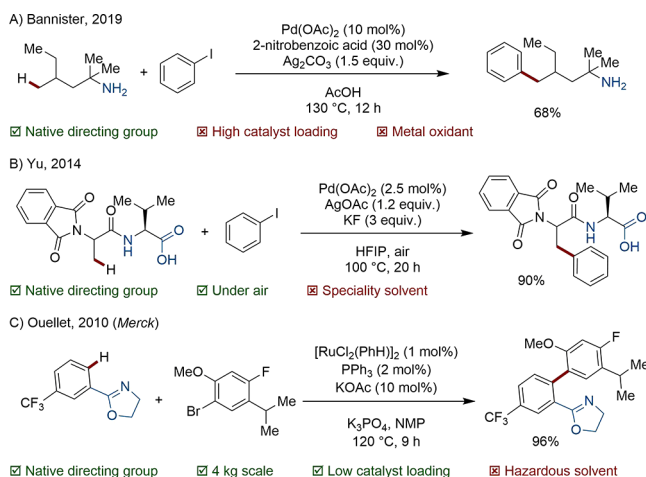
work, it was found that the addition of picolinic or quinaldic acid as ligands improved the reactivity of the system and expanded the scope to the valuable tropane and homotropine cores.⁷³

For high value-structures, it is perhaps possible to make an exceptional case for so-called static directing groups (SDGs). At best, the installation and removal of covalent SDGs negate the step and atom economy potential of C–H activation—at worst, final removal of the DG is either not possible, requires harsh conditions, or offers low yields. Since SDG removal is likely to be the final step, this represents a disproportionate resource burden on a synthesis. SDGs arguably represent the single largest barrier to the uptake of C–H activation by industry, conflicting with the

Green Chemistry principle of avoiding derivatives. For fundamental research, SDGs are a necessary evil; realistically, chemistry of this design is unlikely to find applications unless high product value and a lack of alternative methodology are evident.

3.1. Native Directing Groups. In many cases, so-called native functionality, where a Lewis basic site is already present, can be harnessed as a DG. For instance, Bannister and co-workers reported the utilization of primary amines as a native directing group (Scheme 11A).⁷⁴ Yu accomplished the site-

Scheme 11. Native Heteroatom Directed C(sp³)–H Arylation

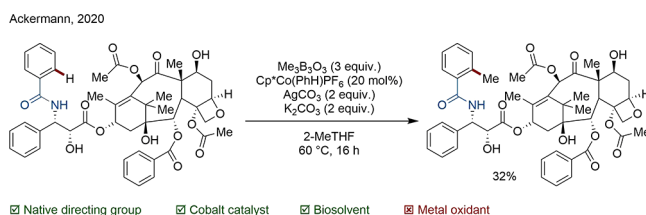


selective C(sp³)–H functionalization of *N*-protected di-, tri-, and tetrapeptides by making use of bidentate N,O coordination (Scheme 11B).⁷⁵ In Merck's kilo-scale synthesis of Anacetrapib, Ru *ortho*-coordination is helpfully provided by a neighboring oxazoline which forms part of the final active pharmaceutical ingredient (Scheme 11C).⁷⁶

In a high-profile example of native functionality exploitation, Ackermann recently published a Co-catalyzed methylation of a number of bioactive compounds.⁷⁷ The addition of a methyl group is widely recognized to have an outsize influence on biological activity and physicochemical properties. In this work, a catalytic system was identified that could transfer a methyl group to C(sp²) and C(sp³) centers coordinated by a range of Lewis basic moieties including *N*-containing heterocycles, amides, amines, ketones, and aldehydes. The reaction was then applied successfully to the late-stage functionalization of 22 biologically active compounds, although several required isomeric separation. A highlight of this work was the selective monomethylation of paclitaxel, which contains some 47 C–H bonds (Scheme 12).

Of course, natively directed C–H functionalizations are highly substrate specific and cannot offer a general strategy for

Scheme 12. Co-Catalyzed C–H Methylation of Paclitaxel

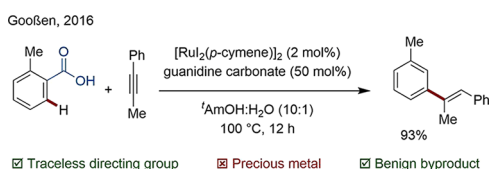


functionalization of each and every C–H bond, especially for advanced synthetic intermediates.

3.2. Traceless Directing Groups. Recently, attention has been drawn to the replacement of preinstalled SDGs by more step-economic alternatives. These strategies allow for the use of less functionalized substrates. Consequently, a rapid increase in value and diversity from simple substrates can be achieved. As a special case of SDGs, traceless directing groups (TsDGs) are commonly pre-existing coordinating groups that can be engineered in the C–H bond functionalization of the substrate and subsequently removed from the product without an additional step.⁷⁸

Among the most used TsDGs are carboxylic acids. In particular, the use of benzoic acid derivatives is convenient, since they are often inexpensive and commercially available. In 2016, Gooßen accomplished a regioselective C–H hydroarylation of internal alkynes with benzoic acid derivatives using a Ru-based catalyst (Scheme 13).⁷⁹ Facile liberation of carbon

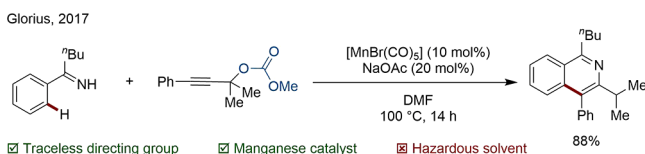
Scheme 13. Regioselective C–H Hydroarylation with Internal Asymmetric Alkynes



dioxide (CO₂) revealed the product. In the same year, Zhao published a similar method to convert lignin-derived 4-hydroxybenzoic acid into the corresponding *meta*-substituted alkenyl arene.⁸⁰

Although removal of the DG can still be achieved in one pot, often synthesis of the starting material is required. For instance, Glorius accomplished a Mn-catalyzed annulation with perfect regioselectivity owing to the presence of a carbonate-based TsDG on the alkyne (Scheme 14).⁸¹

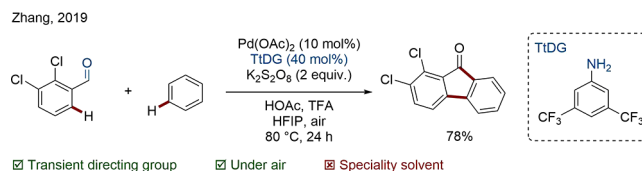
Scheme 14. Regioselective Annulation Using a Carbonate TsDG



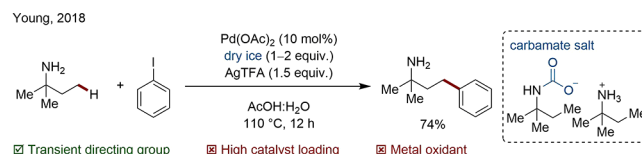
3.3. Transient Directing Groups. In the transient directing group (TtDG) strategy, DGs are installed as well as removed in situ. Often the TtDG can be added in catalytic amounts, rendering this process in theory more resource and step economic.⁸² The most common TtDGs are imines formed by the condensation of amines and carbonyls; examples of phosphonites and enamines are also known. Zhang exploited the monodentate and commercially available TtDG 3,5-bis-(trifluoromethyl)aniline for the synthesis of 9-fluorenones in a cross-dehydrogenative coupling (CDC).⁸³

Young and co-workers have reported protocols in which cheap and abundant CO₂ was used as a TtDG. The group applied this strategy to the C(sp³)–H γ -arylation of primary and secondary aliphatic amines (Scheme 16) and later to the C(sp²)–H arylation of primary and secondary benzylamines.^{84,85} The formation of a carbamate TtDG was suggested

Scheme 15. Pd-Catalyzed CDC Using an Aniline TtDG



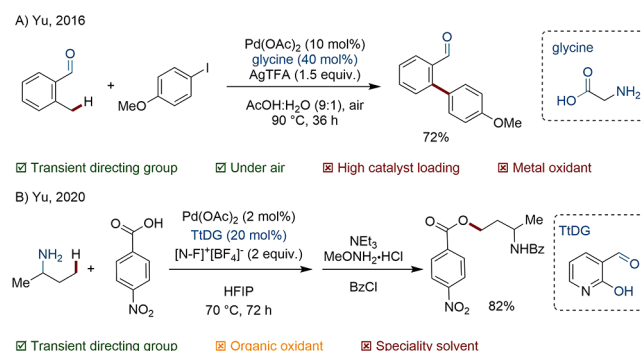
Scheme 16. C(sp³)–H Arylation Using a Carbamate TtDG



based on mechanistic investigations in which the corresponding carbamate salt, prepared from a reaction of the amine with dry ice, was converted to the coupled product without additional CO₂.

Bidentate TtDGs are now common. Yu utilized unfunctionalized glycine for the C(sp³)–H β -arylation of aliphatic ketones and C(sp³)–H γ -arylation of benzylic aldehydes (Scheme 17A).⁸⁶

Scheme 17. Bidentate TtDG Mediated C(sp³)–H Arylation and Alkylation

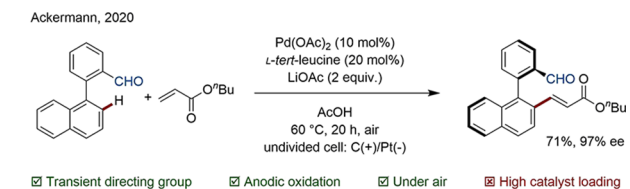


The same group likewise utilized 2-hydroxynicotinaldehyde as a TtDG group for the oxygenation of free amines (Scheme 17B).⁸⁷ In comparison to earlier protocols, the protection and deprotection of the amine were not necessary, and a one-step coupling was thus enabled. The same TtDG was also applied in the fluorination of free amines.⁸⁸ Sorensen and co-workers utilized a commercially available orthonitrolic acid as a TtDG for the C–H *ortho*-methylation or fluorination of benzaldehydes.⁸⁹ [N–F]⁺ salts were used either as the oxidant or as an electrophilic fluorine source.

Expansion of the concept to chiral TtDGs gives access to comparatively step and atom economic enantioselective C–H functionalizations. Among common chiral DGs are amino acids, amino amides, or chiral amines that form imine intermediates. Chiral amino acids are often utilized in combination with Pd; examples for the generation of molecules with central, axial, and planar chirality have been reported. Recently, Ackermann accomplished the synthesis of enantioenriched chiral biaryl and *N*-aryl pyrroles using simple *L*-tert-leucine as a chiral TtDG (Scheme 18).⁹⁰

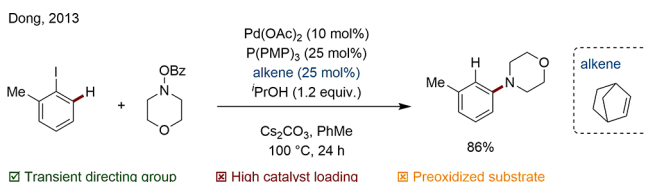
Finally, Catellani reaction variants represent noncondensation examples of TtDG mediated processes. *ortho*-Directed

Scheme 18. Atroposelective C–H Activation



amination of aryl iodides was achieved by Dong following an oxidative addition–carbopalladation directed C–H activation process (Scheme 19).⁹¹

Scheme 19. Transient Norbornene-Directed Amination

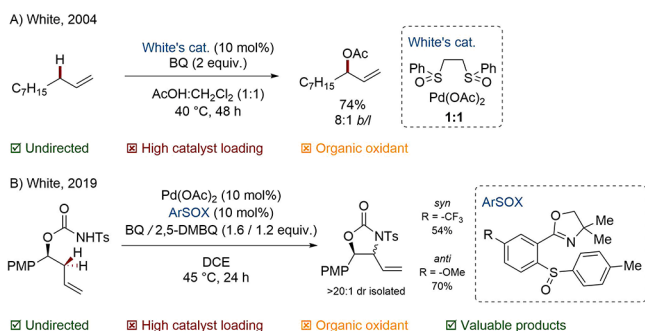


Nevertheless, a common criticism of TtDG reactions is the requirement for high metal catalyst and organic cocatalyst loadings, which mainstream applications will need to address.

3.4. Undirected C–H Activation. The area of undirected C–H activation, in which electronic and steric factors determine regioselectivity, is an exciting but incredibly challenging subfield. Unfortunately, in the absence of highly active catalysts, harsh conditions and high metal loadings are typical. Problematically, reactions often do not run to completion or give product mixtures which may require challenging separations.³²

The group of White was instrumental in developing the direct functionalization of allylic C(sp³)–H bonds, presenting an alternative to the Tsuji–Trost reaction, which requires an allylic leaving group. Initial work in 2004 revealed that under Wacker oxidation conditions the presence of DMSO led to linear allylic acetates from terminal olefins. The adduct of Pd(OAc)₂ and a simple disulfide ligand, which gives the alternative branched products, became known as White's catalyst (Scheme 20A).^{92,93}

Scheme 20. Pd-Catalyzed Allylic Functionalization

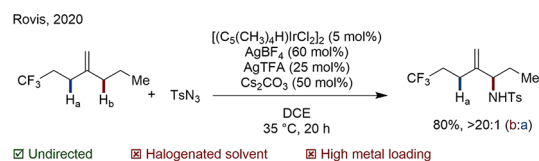


Since then, White and others have intensely developed this subfield, with related systems enabling intermolecular allylic amination, alkylation, and Heck-type arylation, and applied them to the synthesis of natural products.^{94–98} Furthermore, an array of methods now exist for highly regio- and stereoselective transformations.^{99–102} In one example, medically relevant *anti*- and *syn*-1,3 amino alcohols were prepared using complementary aryl-sulfoxide oxazoline (ArSOX) ligands

(Scheme 20B).¹⁰³ Unfortunately, most systems of this type require high Pd loadings and multiple equivalents of benzoquinone (BQ) type oxidants, presenting considerable scope for sustainability improvements.

Cp* complexes of the Group IX metals were later harnessed by Tanaka, Cossy, Blakey, Glorius, and others to accomplish related allylic C–H arylations, aminations, and arylations.^{104–111} A common weakness of these transformations is found in the product regioselectivity in the absence of nearby coordinating groups or strong electronic bias. For this reason, Rovis' 2020 work, in which allylic amination is guided by very subtle electronic effects via the σ -framework, is all the more remarkable (Scheme 21).¹¹² Despite the value of the products

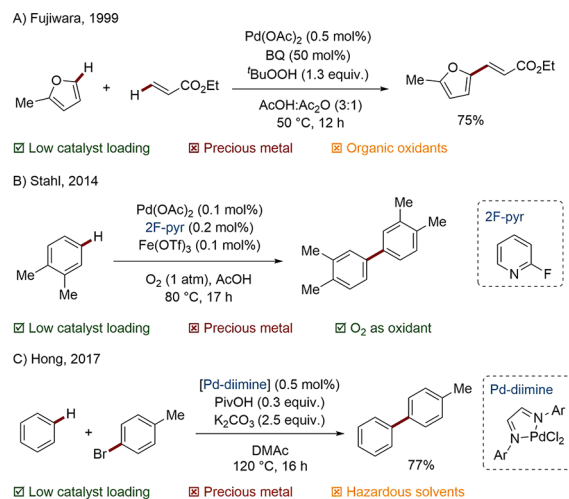
Scheme 21. Rh-Catalyzed Allylic Functionalization



obtained, once again such chemistry is blighted by the high loading of transition metals required as catalyst and oxidant as well as frequently environmentally hazardous solvents, such as 1,2-dichloroethane (DCE).

Other precious metal systems are known with significantly better efficiency. In 1999, Fujiwara published an oxidative Heck reaction giving styrene-type products with catalyst loadings as low as 0.2% (Scheme 22A).¹¹³ Since then, Stahl was able to show

Scheme 22. Low-Loading Pd-Catalyzed Examples of Undirected C–H Activation

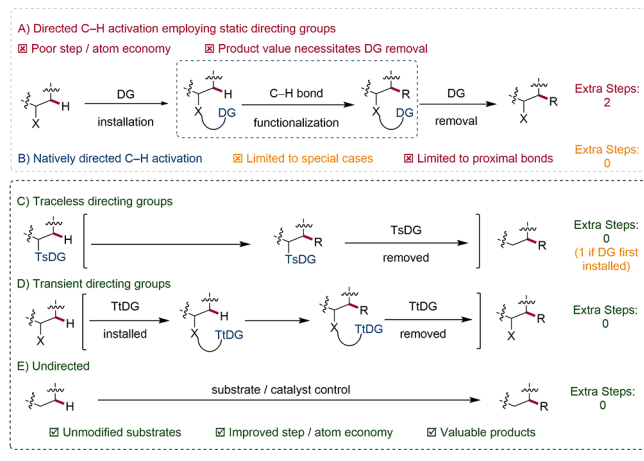


that the addition of weakly coordinating ligands increases the activity of a Pd system used for CDC, enabling improvements in the industrial synthesis of important polymers (Scheme 22B).^{114,115} In Hong's direct arylation, the rigid, planar diimine ligand is thought to allow the reaction to proceed with a TON of up to 290 (Scheme 22C).¹¹⁶

Although exciting developments in undirected C–H activation are forthcoming, it is likely that SDGs will still dominate in the short-to-medium term. In the meantime, more and more groups are exploring the possibilities of traceless and transient DGs. A summary of directing strategies, including a

comparison of their relative step-counts, is given below (Scheme 23).

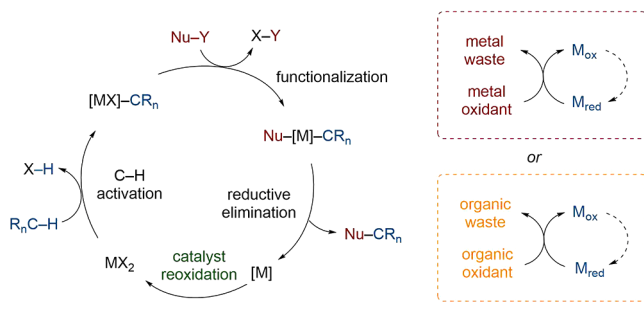
Scheme 23. Greener Alternatives to Static DGs



4. MODERN OXIDATION STRATEGIES

The coupling of C-H bonds and nucleophiles is among the most common of C-H functionalizations. A general such catalytic cycle consists of four steps (Scheme 24): C-H

Scheme 24. General C-H Activation Mechanism Using Stoichiometric Oxidants



activation (1), functionalization of the carbometallic intermediate (2), reductive elimination (3), and finally reoxidation of the metal center (4). Usually, this reoxidation is carried out using (super)stoichiometric oxidants, often outweighing the inherent virtue of catalysis.

Ag(I) and Cu(II) salts are the most commonly used transition metal oxidants. These salts are typically expensive, possess high molecular weights, and may pose safety hazards (Table 1). Their consumption also produces quantitative, potentially toxic metal waste. Organic oxidants, such as BQ, may be less expensive but still contribute significantly to the E factor. There is therefore high interest in avoiding stoichiometric oxidants.

4.1. Internal Oxidants. One strategy involves the use of a pre-installed, internal oxidant that also serves as a DG (Scheme 25).^{117,118} Often these moieties consist of cleavable N-O and N-N bonds, originating from hydroxylamine and hydrazine derivatives produced on ton scale via efficient, established processes. Transformations using these moieties are often milder than their metal oxidant driven alternatives.

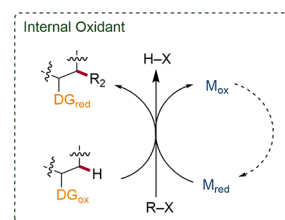
In 2009, the group of Wu revealed that *N*-oxidized quinolines could successfully direct Pd-catalyzed C2 alkenylation with acrylates (Scheme 26A).¹¹⁹ The following year, Hartwig

Table 1. Properties of Common C-H Activation Oxidants

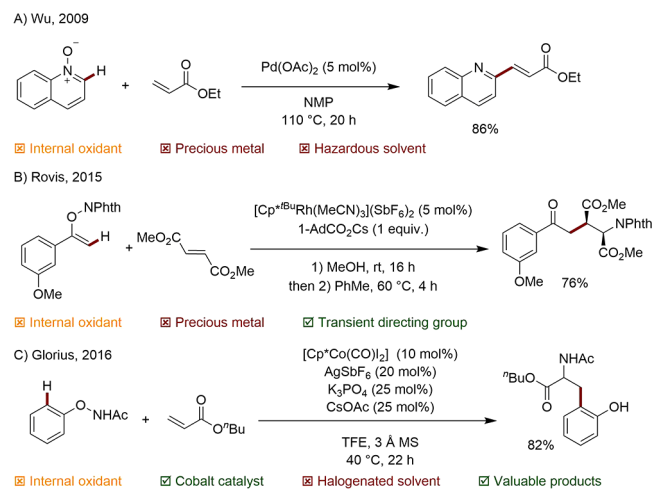
oxidant	M_r	cost/mol (US \$) ^a	major issue
NFSI	315.14	4223	atom economy
PhI(TFA) ₂	430.04	1450	atom economy
Ag ₂ O	231.74	973	precious metal
AgOAc	166.91	883	precious metal
PhI(OAc) ₂	322.10	412	atom economy
Cu(OAc) ₂	181.63	303	metal waste
oxone	307.38	163	waste
K ₂ S ₂ O ₈	270.32	128	waste
^t BuOOH	90.12	51	waste
BQ	108.09	39	waste

^aSource: Sigma-Aldrich, accessed October 2020. Batch size chosen was closest to 100 g; reagent grade or most similar.

Scheme 25. General C-H Activation Mechanism Using a Preoxidized DG



Scheme 26. C-H Functionalizations Using Preoxidized DGs



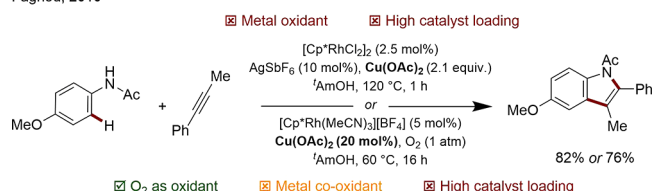
published an efficient, Pd-catalyzed, oxime ester-directed synthesis of indoles.¹²⁰ Later, Rovis was able to apply the concept to the *syn*-carboamination of alkenes using a bulky Cp*-type Rh complex. After undergoing solvolytic ring-opening, the *N*-eneoxy phthalimide starting material is proposed to act as a bidentate directing group as well as offering an oxidizable N-O bond for closure of the catalytic cycle (Scheme 26B).¹²¹ In 2016, the group of Glorius disclosed a synthesis of amino acid esters mediated by a Cp*Co system (Scheme 26C).¹²²

4.2. Molecular Oxygen. The use of molecular oxygen (O₂) is attractive for obvious reasons: O₂ or air is readily available, nontoxic, and inexpensive; water is the only byproduct.¹²³ Unfortunately, this method is normally limited to metal systems with the appropriate redox potential. In 2009, Yu demonstrated that a bulky 2,6-substituted pyridine ligand both promoted *meta*-regioselectivity in a Fujiwara-Moritani reaction and facilitated the reoxidation of Pd(0) to Pd(II) within the catalytic cycle.¹²⁴

Fagnou acknowledged the problematic use of stoichiometric $\text{Cu}(\text{OAc})_2$ in an early Cp^*Rh mediated indole synthesis and demonstrated the reaction could become cocatalytic in Cu using O_2 as the terminal oxidant with a minor modification of the reaction conditions (Scheme 27).¹²⁵

Scheme 27. Indole Syntheses with Stoichiometric and Catalytic Cu Oxidant

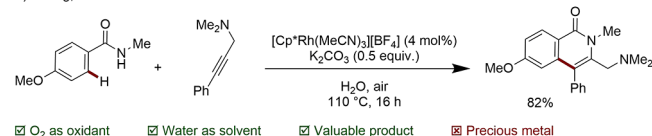
Fagnou, 2010



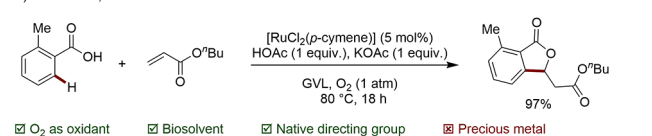
Cheng and co-workers later disclosed a synthesis of isoquinolinones requiring only air as the O_2 source. Furthermore, the products precipitated readily from solution, avoiding resource-intensive purification. The authors applied this method to preparation of the pharmaceutical agent ISQ-1 in 82% yield (Scheme 28A).¹²⁶ Ackermann reported a twofold

Scheme 28. Rh-Catalyzed C–H Alkenylation with Air as the Terminal Oxidant

A) Cheng, 2017



B) Ackermann, 2017

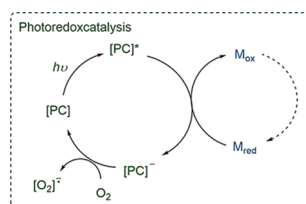


C–H functionalization between benzoic acids and alkenes. C–H Activation was mediated by a Ru biscalboxylate catalyst with O_2 as the terminal oxidant (Scheme 28B).¹²⁷

4.3. Photoredox Catalysis. A further method that has drawn attention is the use of photoredox chemistry. In this case, electrons are transferred to a photoredox catalyst, thus reoxidizing the C–H activating metal center. The photoredox catalyst is then regenerated by a terminal oxidant. Although the use of organic terminal oxidants is preferable to the generation of metal waste, the best examples involve the reduction of O_2 to a superoxide anion and ultimately water (Scheme 29).

Van d'Eycken and co-workers established a procedure for a selective C2-acylation of indoles using a visible-light photoredox

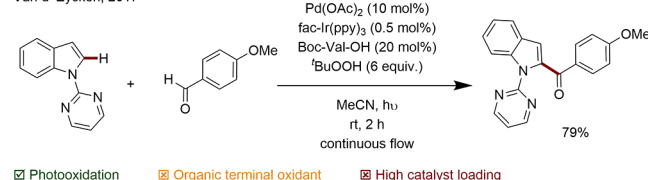
Scheme 29. General C–H Activation Involving Catalyst Photooxidation, with O_2 as Terminal Oxidant



catalyst for the reoxidation of Pd. The reaction procedure was compatible with number of functional groups and was applied to aromatic, primary, and secondary aliphatic aldehydes. The combination of continuous flow and photochemistry allowed a significant decrease in the reaction time and photocatalyst loading (Scheme 30).¹²⁸

Scheme 30. Photoredox Enabled C2-Acylation of Indoles

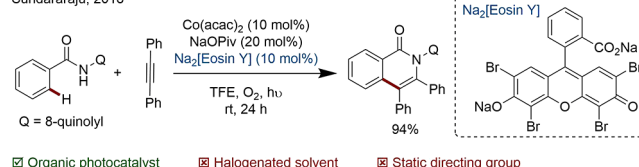
Van d'Eycken, 2017



Sundararaju and Rueping developed a mild protocol for C–H/N–H annulation using a dual catalytic approach and O_2 as the terminal oxidant. $\text{Co}(\text{acac})_2$ mediated the C–H activation, while $\text{Na}_2[\text{Eosin Y}]$ functioned as the electron transfer agent (Scheme 31).¹²⁹

Scheme 31. Sequential C–C and C–N Bond Formation Catalyzed by a Co and a Photoredox Catalyst

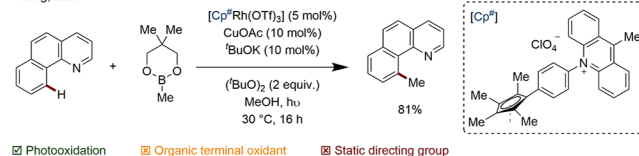
Sundararaju, 2018



In an exciting recent development, Chang and co-workers detailed a bifunctional catalyst containing both a Cp^*Rh center and an acridinium moiety. Internal oxidation of the metal center by the photosensitizing module expedites the reductive elimination step. A cocatalytic Cu salt and an organic terminal oxidant complete the catalytic cycle (Scheme 32).¹³⁰ Developments beyond this proof-of-concept may offer a further alternative to stoichiometric metal oxidants.

Scheme 32. An Integrated Catalyst for C–H Activation and Photooxidation

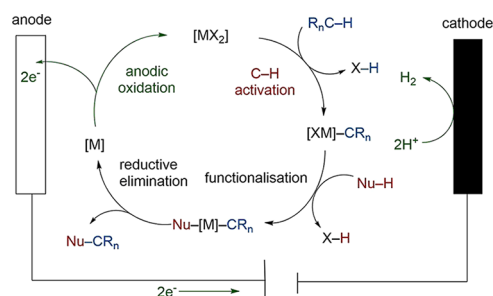
Chang, 2020



4.4. Metallaelectrocatalysis. The upscaling of photochemical reactions is often challenging. Another drawback of photoredox catalysts is the use of mostly precious metals, such as Ir, as photocatalysts, as well as their discrete redox states. To access differing redox potentials, chemical modifications via resource-demanding, multistep synthesis are necessary. Surpassing these shortcomings, the field of metallaelectrocatalysis has emerged.^{36,40,131–133} Redox potentials can be adjusted continuously, for instance, by a potentiostat. This allows broader functional group tolerance and a decreased need for complex

ligand systems. Molecular hydrogen is generated as a potentially useful byproduct (Scheme 33).

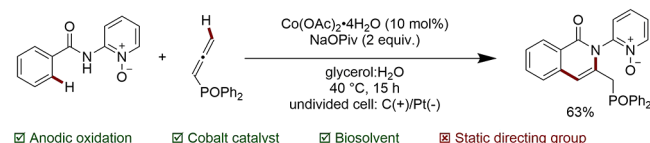
Scheme 33. A Generalized Mechanism of C–H Activation Involving Anodic Oxidation



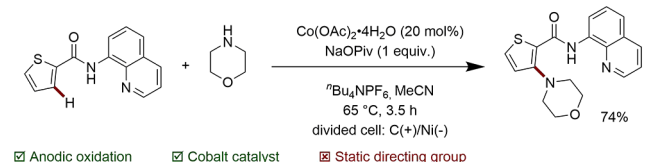
The applicability of Co, Ni, and Cu electrochemistry to C–H functionalization has been demonstrated extensively by Ackermann since 2017.^{90,134–139} In a recent protocol, a challenging C–C/C–N bond formation with a potentially sensitive allene was accomplished under mild conditions in the biosolvent glycerol using simple Co(OAc)₂ salt (Scheme 34A).¹⁴⁰ Furthermore, electricity generated in house

Scheme 34. Cobalta-Electrocatalyzed C–C/C–N Bond Formation

A) Ackermann, 2020



B) Lei, 2018



from wind and solar energy was exploited. Building on Ackermann's earlier work, Lei and co-workers used electrochemistry for the amination of (hetero)arenes including aryls, furans, and thiophenes, up to gram scale (Scheme 34B).^{141,142}

The replacement of metal-based oxidants by greener methods has accelerated in recent years; intensive work in this field has established applicable and sustainable alternatives (Figure 2). While internal and organic oxidants avoid the use of transition metals, these strategies are still responsible for stoichiometric waste. Meanwhile, the use of O₂, photoredox catalysis and electrochemistry offer sustainable alternatives with benign byproducts. These methods have already been applied to a range of substrates and proven compatible with 3d metals and biosolvents.

5. CHOOSING GREENER SOLVENTS

Organic solvents are almost always the largest weight component of reactive chemistry and purification. The environmental impact of solvents has been the topic of extensive industrial interest. Indeed, the CHEM21 consortium of major pharmaceutical companies have released multiple solvent selection guides to aid sustainable process development, which

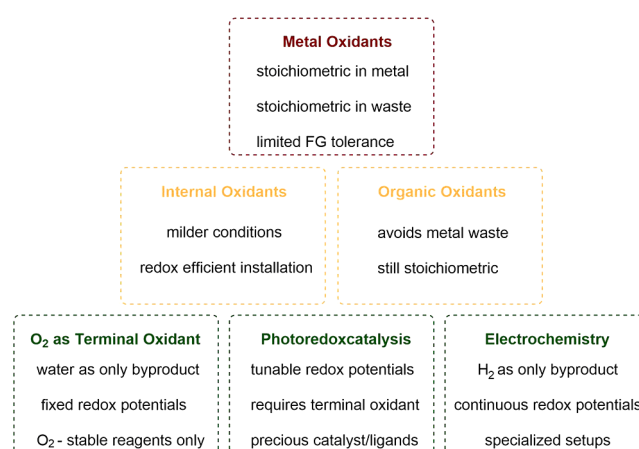


Figure 2. Pyramid of oxidation method sustainability.

quantify solvent attributes such as carbon footprint, reactive hazards, and human health impact.^{22,23,25–28} Choice of solvent (or mixture) is often dictated by the mechanism of the chemistry at hand and by coupling partner solubility or compatibility. In many cases, greener solvents are too quickly overlooked. For example, in C–H activation chemistry involving heterocycle preparation, unsustainable solvents, such as 1,2-DCE, HFIP, and TCE are common (Table 2); many greener alternatives have been shown to be practical under the right conditions.¹⁴³

Table 2. Common Solvents used in C–H Activation, Associated Hazards, and Environmental Burdens^a

solvent	cost/L (US \$) ^b	hazard ^b	environment
HFIP	1170	a, e	f, g
TFA	492	a	g
THF	119	a, b, c	g
DCE	116	a, b, c, d	e, f, g
DMF	109	a, b, c, d	
NMP	104	a, c, d	
1,4-dioxane	92	a, b, c	g
CH ₂ Cl ₂	67	a, b	e, f

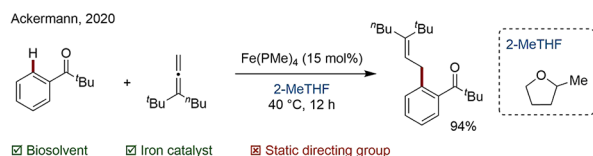
^aa. Toxicity. b. Cancer risk. c. Flammable. d. Fertility risk. e. Severe greenhouse gas. f. Ozone depleter. g. Environmentally persistent. ^bSource: Sigma-Aldrich, accessed October 2020. Batch size chosen was closest to 1 L; solvent grade.

It is appreciated that the environmental impact of solvents is more limited in terms of scale, and receives less attention, within academia than in industry; novel reactions are optimized for yield (or selectivity). Likewise, academic researchers likely do not have ready access to the many emerging biosolvents screened in industry. Nevertheless, the inclusion of sustainable alternatives in deviation tables, even if they do not provide the most optimal results, would provide starting points for applied researchers, including for emerging machine learning-based reaction optimization.^{144,145} Principle component analysis (PCA) is a frequently used method to find compatible alternative solvents based on physicochemical properties.¹⁴⁶ The investigation of the properties of solvent mixtures remains an under-researched area.

5.1. Biosolvents. Biomass-derived solvents, commonly referred to as biosolvents, are increasing in popularity. In comparison to traditional solvents, they typically have lower toxicity and show higher biodegradability. 2-MeTHF is now a

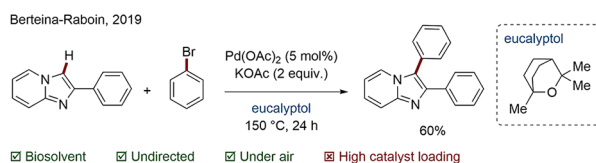
commonly adopted green alternative and has been used as a substitute for THF, 1,4-dioxane, DCE, and others.¹⁴⁷ Its low miscibility in water facilitates purification by organic-water phase separations. Ackermann and co-workers chose 2-MeTHF in their mild C–H activation of allenes using a simple Fe phosphine catalyst (Scheme 35).¹⁴⁸

Scheme 35. Iron-Catalyzed C–H Activation of Allenes in 2-MeTHF



Berteina-Raboin and co-workers published the first C–H activation protocol in which eucalyptol was used as a green solvent (Scheme 36).¹⁴⁹ Eucalyptol is the main constituent of

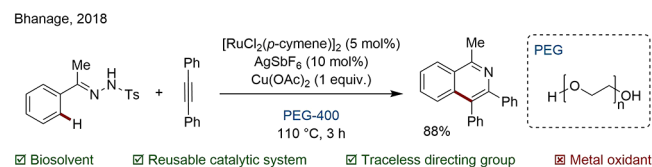
Scheme 36. Direct C–H Arylation in Eucalyptol



eucalyptus essential oil (up to 90%), is immiscible with water, and exhibits low toxicity. On the basis of physical properties, such as its polarity, the authors postulate that eucalyptol may rival 2-MeTHF; it has a comparable cost and shows a lower tendency to form radicals. As a byproduct of the global paper industry, the potential supply of this solvent is estimated to be in the millions of tons; it is also a precursor for the hydrocarbon substitute cymene.¹⁵⁰

Polyethylene glycols (PEGs) are sugar-derived, low volatility, polar liquid polymers with diverse physical properties. Molecular weights ranging from 300 to 10 000 000 g/mol are commercially available. Bhanage and co-workers performed an alkyne annulation via directed C–H/N–H activation using a homogeneous Ru(II)/PEG-400 catalytic system. Remarkably, the catalyst was recovered by extraction during product isolation and reused four times with negligible impact on yield (Scheme 37).¹⁵¹

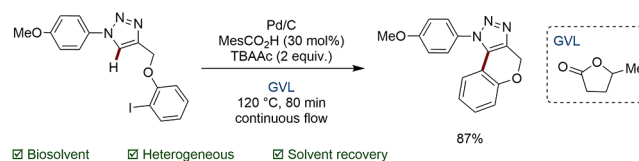
Scheme 37. Ru-Catalyzed Annulation Reaction in PEG-400



γ -Valerolactone (GVL) is another sugar-derived solvent that is often considered as an alternative to polar aprotics like DMF or MeCN. Vaccaro and co-workers accomplished a regioselective C–H functionalization of 1,2,3-triazoles in GVL under continuous flow (Scheme 38).¹⁵² Remarkably, the solvent could be readily recovered by distillation and reused. The product was purified by recrystallization in acetone and water, contributing to a low overall E factor of 23.9. This value was significantly

Scheme 38. Intramolecular C–H Functionalization of 1,2,3-Triazoles in GVL

Vaccaro, 2018



smaller than for previously reported protocols for the synthesis of triazoles. Though the exact figures have to be taken with care, this example underlines the importance of solvent in the mass efficiency of chemical processes: significant improvements can be made by recycling the solvent or by operating under highly concentrated conditions.

Although many are skeptical regarding the cost and supply of biosolvents, with increasing demand the wholesale cost is expected to decrease, especially for large-scale applications (Table 3). We do not discount the role of the more recognized green solvents, which may or may not be obtained from biological sources, such as ethanol and ethyl acetate.

Table 3. Common Biosolvents, Miscibility, Costs, and Sources

solvent	cost/L (US \$) ^a	water miscible	substitutes	source ¹⁵³
GVL	571	yes	polar aprotics	sugars
2-MeTHF	235	no	ethers, chlorinated	sugars
eucalyptol	218	no	various	paper industry
cyrene	191	yes	polar aprotics	cellulose
limonene	144	no	alkanes	citrus waste
ethyl acetate	71	no	esters	sugars or petrochem
ethyl lactate	68	yes	esters	starch
cymene	57	no	alkanes, aryls	paper industry
PEG-400	43	yes	various	sugars
ethanol ^b	40	yes	alcohols	sugars or petrochem

^aSource: Sigma-Aldrich, accessed October 2020. ^bDenatured. Batch size chosen was closest to 1 L; solvent grade.

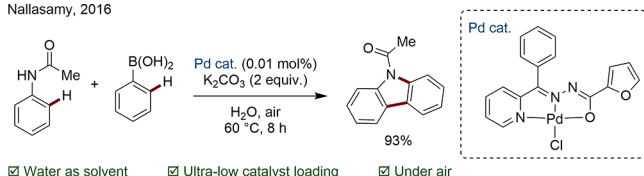
5.2. Aqueous and Solvent-Free Reactions. Provided solvent is not required for heat-transfer purposes, neat chemistry has the potential to offer a sustainability advantage by lowering the E factor, as well as aiding low activity catalytic systems. For example, in 2017 a Mn-catalyzed aryl allylation was accomplished by Glorius and co-workers under solvent-free conditions.¹⁵⁴ Sequential C–H and C–C/C–X bond activation led to the synthesis of diverse, valuable products.

The use of water appears attractive for industrial purposes, since it is inherently safe, poses no health hazard, and is of course highly abundant. An example by Nallasamy is the tandem C–H/N–H activation of acetanilide in water with an active Pd pincer complex (Scheme 39).¹⁵⁵ In another preparation of an Anacetrapib intermediate (recall Scheme 11C), a water-soluble Ru formate based system “MCAT-53” was used to carry out the directed arylation in 73% yield with precipitation of the product from solution. Following an organic wash, the aqueous layer could be reused.¹⁵⁶

Notwithstanding, a significant note of caution must be attached to claims that the use of water is always sustainable.

Scheme 39. Aqueous Tandem C–H/N–H Activation

Nallasamy, 2016



Following isolation of the products, the aqueous waste stream must be safely disposed of. If this cannot be remediated by other means, incineration of the waste is an endergonic process.

C–H Activation is not unique in its hitherto reliance on a narrow range of fossil-fuel derived and chlorinated solvents; as organic chemistry adopts bioderived materials more widely, it is likely that the application of green solvents will become commonplace within this field.

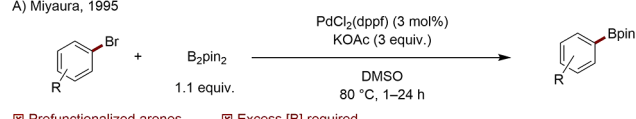
6. CASE STUDY: ARENE C–H BORYLATION

6.1. Origins. In the absence of general and direct systems for many important C–H transformations (e.g., arylations, alkylations, oxidations, halogenations), aryl boron species are highly valued synthetic intermediates. Before the establishment of C–H borylation, such compounds could only be prepared by stoichiometric organometallic chemistry or the Miyaura borylation of aryl halides (Scheme 40A).¹⁵⁷ The group of Smith pioneered the first undirected Ir-catalyzed C–H borylations for installation of the highly versatile bis-(pinacolato)borane (Bpin) handle (Scheme 40B).^{158,159} Although this early work suffered from high metal loading and poor regioselectivity, this was shortly followed a much improved system involving bulkier, more stable bidentate phosphine ligands such as 1,2-bis(diphenylphosphino)ethane (dppe) (Scheme 40C).¹⁶⁰ Simultaneously, the eponymous Ishiyama–Miyaura–Hartwig (IMH) catalyst, consisting of an Ir(I) cyclooctadiene precatalyst and the 4,4′-di-*tert*-butylbipyridine ligand (dtbpy), was shown to be capable of installing the Bpin unit under mild conditions with unrivalled functional group tolerance.¹⁶¹ The somewhat bulky ligand is responsible for the steric control of the reaction, selectively delivering the products from a 1:1 ratio of boron units and starting arenes (Scheme 40D).¹⁶² From an early stage, it was clear the novel system could offer a clear step and atom economy advantage over established methods for aryl boronic ester synthesis, in addition to new product substitution patterns.

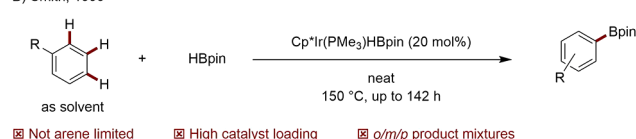
6.2. Development and Applications. Guided by increasing mechanistic understanding,^{163–165} further exploration of the IMH system led to adoption of the ligand 3,4,7,8-tetramethylphenanthroline (tmphen), scope-expansion, and sustainability improvements in the reaction conditions.^{166–170} For example, in 2013 the groups of Krska, Maleczka, and Smith conducted extensive high-throughput screening-optimization from which they elucidated subtle relationships between order-of-addition, precatalyst choice, temperature, and solvent. Using this knowledge, they were able to affect competent borylation systems requiring just 0.25 mol % Ir loadings with simultaneously high boron economy. It was shown that polar solvents, including the biosolvent 2-MeTHF, are amenable to this chemistry (Scheme 40E).¹⁷¹ In 2019, Hartwig and co-workers elucidated that the often superior performance of phenanthroline-based systems over the classic IMH dtbpy catalyst is owing to greater binding stability and hence catalyst lifetime.¹⁷² In a similar vein, Ozerov and co-workers revealed a strikingly active

Scheme 40. Evolution of Precious-Metal-Catalyzed Aryl Borylation

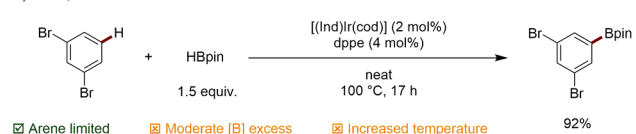
A) Miyaura, 1995



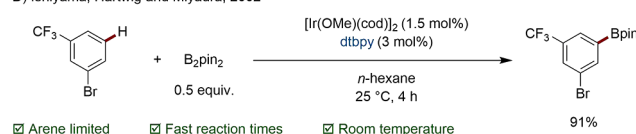
B) Smith, 1999



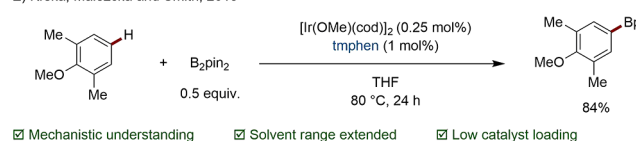
C) Smith, 2002



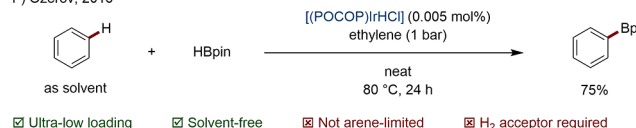
D) Ishiyama, Hartwig and Miyaura, 2002



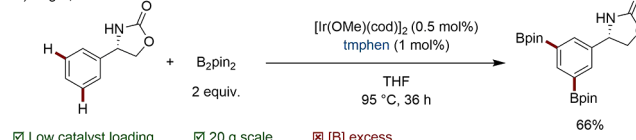
E) Krska, Maleczka and Smith, 2013



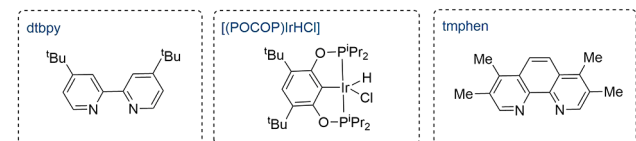
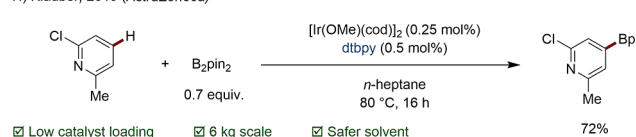
F) Ozerov, 2016



G) Boger, 2020



H) Klauber, 2019 (AstraZeneca)



catalyst based on a POCOP ligand, exhibiting a turnover number (TON) in excess of 20 000 (Scheme 40F).¹⁷³

The compatibility of this chemistry with downstream chemistry in “telescoped” sequences, avoiding potentially wasteful purification, has facilitated its take-up in total syntheses. In 2011, Hartwig harnessed a two-step, one-pot borylation-bromination protocol developed in his laboratory to prepare a key intermediate in his route toward (–)-Taiwaniaquinone H and (–)-Taiwaniaquinol B.^{174,175} In Baran’s total syntheses of Verruculogen and Fumitremorgin A, use of the simple,

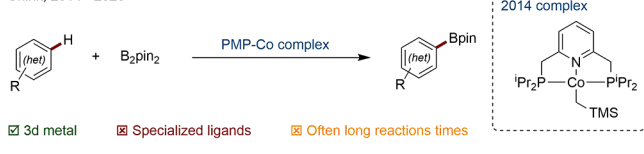
unsubstituted phenanthroline ligand was shown to be optimal for the 10 g borylation of a key indole intermediate.¹⁷⁶ Boger affected a dual 3,5-diborylation on 20 g scale in his preparation of the critically important antibiotic vancomycin (Scheme 40G).¹⁷⁷ There are now multiple process chemistry examples of C–H borylation in the public domain, revealing the industrial uptake of this technology. In Merck's preparation of Dorivirine, a 75 kg scale borylation-oxidation sequence rendered key intermediate 3-bromo-5-iodophenol in 94% yield over two steps (simple bipyridine was used as an adequately performing, low-cost ligand).¹⁷⁸ Pfizer used the tmphen ligand to obtain 19 kg of a borylated nicotine intermediate.¹⁷⁹ AstraZeneca carried out a 6 kg borylation of a key pyridine intermediate using just 0.25% Ir loading to supply their Phase IIA trial of the A_{2A}R agonist AZD4635 (Scheme 40H).^{180,181}

Cumulative advances in sustainability will finally enable the industrial potential of C–H activation to be fulfilled.

6.3. Future Directions. The accumulated knowledge of the past 20 years, in terms of increased catalyst activity and solvent range, suggests there are likely still gains to be found in the effectiveness of this system. This said, one hugely valid criticism remains: the high cost and scarcity of Ir, which may be offset in the cases of highly efficient or heterogeneous, recyclable systems.^{182–187} The development of undirected 3d metal-based systems, which may replicate and complement Ir borylation chemistry, is therefore an exciting area of growth. Ni,^{188–190} Fe,¹⁹¹ and dual-metal¹⁹² systems have been developed, but the most general of the new catalysts seem to be Co based, of which the work of Chirik is best known (Scheme 41).^{193–198} Use of the bis(phosphomethyl)pyridine

Scheme 41. PMP-Co Complex-Mediated Borylation

Chirik, 2014–2020



(PNP) family of ligands was shown to act by providing a suitably electron-rich environment for the Co center to emulate Ir-like behavior. A more user-friendly, air-stable terpyridine-based precatalyst has been disclosed.¹⁹⁹ The discovery of yet more active, faster 3d systems which can be deployed industrially is a highly anticipated development.

7. SUMMARY AND CONCLUSION

In this Outlook, we have sought to highlight active and growing branches of research in C–H activation which exemplify aspects of sustainability. We have showcased the emergence of abundant 3d metal systems, such as Co, Mn, Fe, Ni, and heterogeneous systems as competent and complementary catalysts. We have discussed elegant transformations that do not require coordinating functionality, or can exploit native DGs. We have highlighted exciting, modern alternatives to transition metal-based oxidants including photoredox and electrochemical methods, and reiterated that the selection of green reaction media contributes

substantially toward the mass intensity of a transformation. We hope that researchers will be motivated to explore and understand the sustainability potential of new C–H transformations. With the intention of making environmental considerations from the beginning, we pose ourselves the following questions:

- (1) What is the efficiency of my catalyst? Can I provide an alternative, low-loading optimization with an acceptable yield? Is there a high-abundance metal capable of the elementary steps required by my transformation?
- (2) What is the environmental impact of my solvent choice? Are there commercially available green solvents (or mixtures) available which I may not have considered, that may give similar results? Can I simply increase the reaction concentration?
- (3) Can I minimize or substitute metal-based oxidants with a modern alternative?
- (4) Can I avoid using a DG? Is it genuinely straightforward to remove an SDG; are my products useful if not? Would a novel directed reaction offer a real advantage over an established classical method?
- (5) How robust is my chemistry? Are strictly dried solvent and inert atmosphere really necessary? Can I use air-stable catalysts and additives? Would exploring the sensitivity of my conditions lead to better reproducibility and fewer wasted resources?²⁰⁰
- (6) Can I quantitatively estimate the environmental burden of my transformation, for comparison and targeted improvement?

We envisage that in the future, by combining several green design elements, newly published reactions will offer promising starting points for applied research. Until now, “greenness” has historically taken a back seat to reaction novelty. Nevertheless, we are convinced that cumulative advances in sustainability will finally enable the industrial potential of C–H activation to be fulfilled.

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