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Mild metal-catalyzed C–H activation: examples and concepts

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Organic reactions that involve the direct functionalization of non-activated C–H bonds represent an attractive class of transformations which maximize atom- and step-economy, and simplify chemical synthesis. Due to the high stability of C–H bonds, these processes, however, have most often required harsh reaction conditions, which has drastically limited their use as tools for the synthesis of complex organic molecules. Following the increased understanding of mechanistic aspects of C–H activation gained over recent years, great strides have been taken to design and develop new protocols that proceed efficiently under mild conditions and duly benefit from improved functional group tolerance and selectivity. In this review, we present the current state of the art in this field and detail C–H activation transformations reported since 2011 that proceed either at or below ambient temperature, in the absence of strongly acidic or basic additives or without strong oxidants. Furthermore, by identifying and discussing the major strategies that have led to these improvements, we hope that this review will serve as a useful conceptual overview and inspire the next generation of mild C–H transformations.

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Introduction

At the beginning of this century, the availability of a variety of coupling reactions which use non-activated C–H bonds as reaction sites seemed like an unrealistic dream. However, over the last 15 years, the field of C–H activation has become one of the most rapidly developing areas of homogeneous catalysis,[1]

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reshaping the landscape of both organometallic catalysis and synthetic chemistry.[2] The first years of the C–H activation boom were mainly devoted to the discovery, sometimes quite unpredictably, of new catalytic systems allowing the direct insertion of a metal catalyst into a C–H bond followed by the functionalization of the resulting organometallic intermediates. These early works proved unambiguously that a carefully designed catalytic system is able to engage C–H bonds in organometallic reactions. However, the cleavage of high energy C–H bonds ($\approx$110 kcal mol^{-1} for C(aryl)–H bonds) typically requires harsh reaction conditions resulting in limited substrate scope and low functional group tolerance. As such, C–H activation has not yet found widespread applications in the late stage functionalization of complex molecules, which often contain many functionalities not tolerant of harsh reaction conditions. The driving force of current research is the development of the next generation of C–H transformations, which will help to make these processes truly useful synthetic tools. Alongside improving the efficiency and selectivity of C–H transformations, many groups have focused on developing reactions that proceed under milder conditions. "Mildness", however, is a relative concept that is multi-faceted and can be interpreted in many ways. In 2011, we defined a "truly mild C–H activation reaction" as one that proceeds "at or below ambient temperature, under neutral conditions and in the absence of strong oxidants and reductants."[1e] These reaction conditions can inherently lead to improved functional group tolerance, selectivity and overall applicability of the process. Previously, we reviewed examples of C–H activation reactions published up to 2011 which could be conducted under comparatively mild conditions.[1e] However, over the past five years, interest in this topic has grown rapidly and a large number of very challenging transformations have been disclosed in the literature which occur under surprisingly mild conditions.

Herein we highlight the current state of the art and detail the great advances that have been made in the field of mild C–H activation since 2011. In this regard, we also aim to outline the major concepts that can lead to improvements in the mildness of C–H transformations, and have sorted the processes into several categories accordingly. We hope that a description and discussion of these strategies will serve as a useful guide for the design of C–H transformations and inspire the next generation of mild reactions. In many respects, the progress achieved has resulted from a greater understanding of the mechanistic aspects of C–H activation. As shown in Scheme 1, a typical transformation between a C–H activation substrate (termed the "substrate") and an appropriate reactant (termed the "reaction partner") can be simplistically broken down into four general mechanistic steps: the C–H activation process itself (I), functionalization of the subsequent organometallic species (II), release of the product molecule (III) and finally, if required, regeneration of the active catalyst (IV). For a given reaction, any one of these steps may be "mildness-limiting" and different strategies can be applied to address them. Furthermore, some approaches may enhance certain features of mildness, such as lowering the reaction temperature or removing the requirement for acidic additives, at the expense of other aspects.

In this review, the various concepts that have proved useful for the development of mild C–H transformations are presented under the four headings shown in Scheme 1. In the first section, C–H transformations where modifications to the transition metal catalyst have allowed for mild reaction conditions are discussed. The catalyst is involved throughout every stage of a C–H transformation and optimization of the active catalyst structure can duly enhance any of the four general mechanistic steps shown in Scheme 1. This can be achieved by fine tuning the intrinsic steric and electronic properties of the catalyst by

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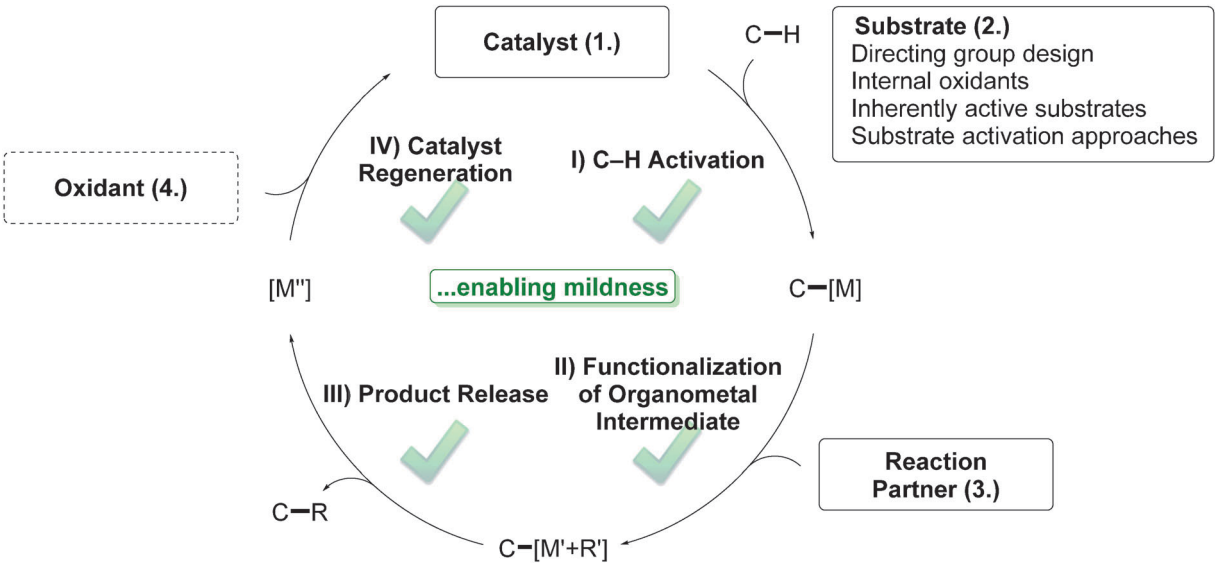


Scheme 1 Generalized mechanistic scheme for C–H activation catalysis and categorization of concepts enabling mildness.

adding ancillary ligands and external additives, or simply by judicious selection of the transition metal itself. Section 2 focuses on the substrate molecule undergoing C–H activation. Installing a strongly-coordinating directing group, for example, can aid the C–H activation step (I) by improving binding to the metal catalyst, while more weakly-coordinating directing groups may enhance the subsequent step in the cycle (II) by facilitating interaction between the generated organometallic species and the reaction partner. Directing groups also act as ligands on the transition metal catalyst and therefore affect each step of the cycle. Furthermore, internal oxidants incorporated into the directing group allow for oxidative transformations to be conducted without a strong external oxidant, fulfilling one of the criteria for mildness as defined above. Other strategies for improving the mildness of C–H transformations have included activating the substrate in ways not involving the directing group. For example, coordination of chromium carbonyl fragments to arenes has been demonstrated to facilitate aryl C–H bond cleavage. Intuitively, mild transformations have been reported utilizing inherently reactive substrates. The selection of activated reaction partners has also been effective for transformations where functionalization of the organometallic intermediate (step II) is "mildness-limiting". Examples of mild C–H transformations for which this strategy has proved useful are highlighted in Section 3 and include room temperature reactions employing Grignard reagents and nitrene precursors. Lastly, in Section 4, oxidative C–H coupling reactions which avoid the use of strong external oxidants are presented. It should be noted, however, that it is often difficult to definitively identify the underlying feature of the process responsible for rendering it mild and many of the examples make use of several of the concepts outlined above. As in our first review on this topic, the discussion is limited to transformations occurring *via* metal-catalyzed inner-sphere C–H bond cleavage directly leading to the formation of C–M intermediates. We do not target an exhaustive presentation of all publications that fulfill at least some of the criteria for mildness but instead highlight seminal examples which best demonstrate the current state of the art or illustrate the concepts under discussion. In this respect, we hope to demonstrate to the scientific community that C–H activation is fast becoming a mature field and can now be considered a truly efficient tool for the synthesis of complex molecules.

1. Tuning of the catalyst's properties

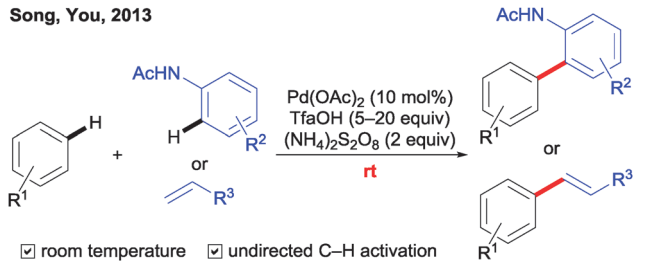
The metal catalyst is involved throughout each stage of a C–H transformation and duly plays a fundamental role in determining its mildness. The identity and oxidation state of the metal largely dictates which C–H activation mechanism operates in any given reaction.[3] High-valent late transition metals such as Pd^{II}, Rh^{III}, Ir^{III} and Ru^{II} typically react *via* electrophilic pathways such as concerted metalation-deprotonation (CMD). Low-valent, electron-rich metals such as Rh^{I} and Ir^{I}, on the other hand, often undergo oxidative addition into C–H bonds. This latter process can greatly benefit from the addition of strongly binding ligands such as phosphines, N-heterocyclic carbenes or bidentate nitrogen-containing molecules which typically increase the electron-density at the metal center and provide a handle for tuning the reactivity. By contrast, C–H transformations catalyzed by high-valent metals generally proceed in the absence of additional donor ligands. This fact can be rationalized by noting that electrophilic C–H activation mechanisms usually require the catalysts to be rather electron-poor in nature. Strong σ-donor ligands can render the metal center overly electron-rich and inhibit C–H bond activation. In addition, directing groups (DGs) typically installed onto the substrate molecules to ensure reactivity and regioselectivity act as ligands on the metal center. The limited number of coordination sites around the metal atom also means that strongly binding ancillary species may prevent

coordination of the reactants, hindering efficient turnover of the catalytic cycle. Consequently, opportunities to finely tune the intrinsic properties of these high-valent catalysts with the intention of improving their reactivity under mild reaction conditions are somewhat limited. Extensive efforts by the scientific community, however, have recently enabled a greater understanding of the mechanistic aspects of C–H activation and have opened the door toward advanced catalytic systems. In the following section, examples of C–H transformations where tuning of the coordination sphere of both low-valent and high-valent metals has allowed for mild reaction conditions are presented.

Pd-based catalytic systems

Among the metals employed as catalysts in direct C–H activation reactions, precious second- and third-row transition metals such as Pd, Rh, Ir and Ru have attracted by far the most attention. Naturally, these metals were the first to be used in pioneering examples of mild, low temperature C–H transformations.[1] One of the first approaches toward this challenging goal involved modifying the electronic properties of the catalyst by rendering it significantly more electrophilic. The use of trifluoroacetic acid (for the sake of clarity, we have adopted the abbreviation TfaOH for trifluoroacetic acid) as an additive in Pd-catalyzed transformations has shown particular promise as a way to generate highly activated $Pd(OTfa)^+$ moieties *in situ*. Although this approach sacrifices one aspect of mildness by employing a strongly acidic additive, it has been shown to enable several impressive room temperature transformations. An overview of this strategy was provided in our previous review, however several recent examples that further illustrate the power of this concept are discussed here.

One of the most important challenges in the field of C–H activation concerns the development of "undirected" processes.[1h] These reactions, which involve the direct functionalization of substrates without the assistance of a directing group, are particularly difficult because the catalyst is not pre-coordinated by the substrate and there is consequently no increased local concentration in close proximity to the metal. Due to these reasons, the dehydrogenative coupling reactions between simple arenes and either anilides (involving two separate C–H activation events) or activated olefins (Fujiwara–Moritani reactions) recently reported by Song and You, which occur smoothly at room temperature, are particularly interesting (Scheme 2).[4] The success of these processes relies on the strongly electrophilic character of the active $Pd(OTfa)_2$ catalyst formed *in situ* from $Pd(OAc)_2$ and trifluoroacetic acid. Kinetic isotope effect (KIE) studies indicate that C–H scission of the simple arene in these transformations probably occurs *via* an electrophilic palladation (S_EAr) pathway. The highly electron-deficient trifluoroacetate-ligated Pd species is well-suited to this kind of mechanism and allows the dehydrogenative C–C couplings to take place at room temperature. It should be noted, however, that the classification of this S_EAr-type process as a C–H activation reaction is debatable according to the definition given in the introduction to this review. In practice, it is often difficult to determine the operating C–H scission mechanism for transformations mediated

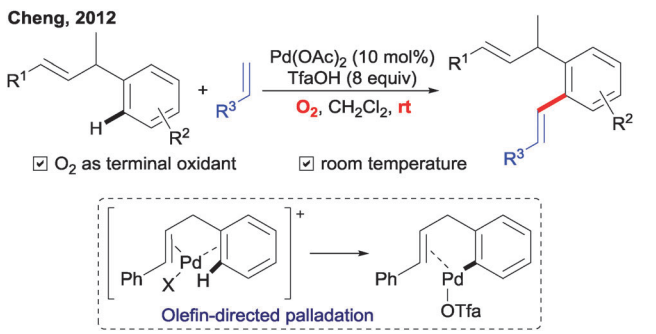


Scheme 2 Undirected mild C–H activation by a strongly electrophilic catalyst.[4]

by highly Lewis-acidic metal species, and different substrate structures and reaction media may promote different pathways.[5] A diverse array of biaryls, arylcoumarins, arylquinolones and styrenes could be prepared with moderate to high regioselectivities according to the intrinsic electronic and steric properties of the benzene derivatives. Although these room temperature reactions utilize an inexpensive Pd source and persulfate oxidant, a large excess of the benzene derivative is required (it is typically used as solvent), limiting their practical utility.

Another interesting Pd-catalyzed mild and challenging C–H functionalization was disclosed in 2012 by Cheng.[6] In this example, an olefin moiety was employed as a π-coordinating group to direct insertion of a metal catalyst into the *ortho*-C–H bond of an aromatic substrate (Scheme 3). The presence of the TfaOH additive, leading to the *in situ* generation of the strongly electrophilic $Pd(OTfa)^+$ species, was crucial to facilitate π-coordination of the C=C bond. Binding of the olefin directs C–H scission at the *ortho*-position and leads to the formation of stabilized chelates. No product formation was observed in the absence of the TfaOH additive or when weaker congeners such as AcOH or PivOH were employed instead. As well as proceeding smoothly at room temperature, this oxidative coupling reaction fulfils another criterion of mildness by employing a relatively benign oxidant: O_2 itself is capable of regenerating the Pd^{II} catalyst after β-hydride elimination and no additional strong oxidant is required.

Following the same strategy involving the generation of highly electrophilic Pd species, Wang used a substoichiometric amount of methanesulfonic acid to promote *ortho*-alkoxylation of acetanilide derivatives.[7] In addition to its role in decreasing the electron-richness of the catalyst, the strong organic acid

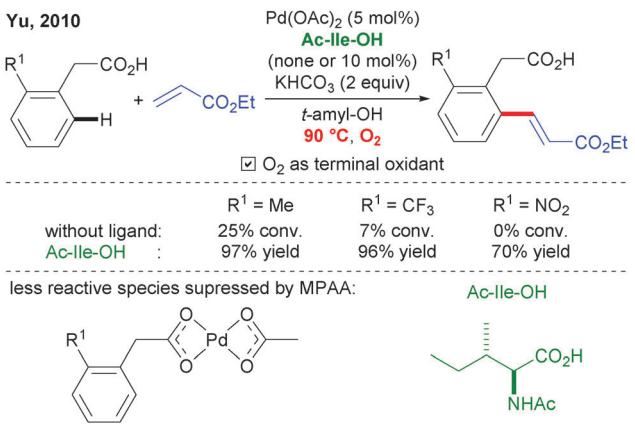


Scheme 3 Olefin-directed C–H activation.[6]

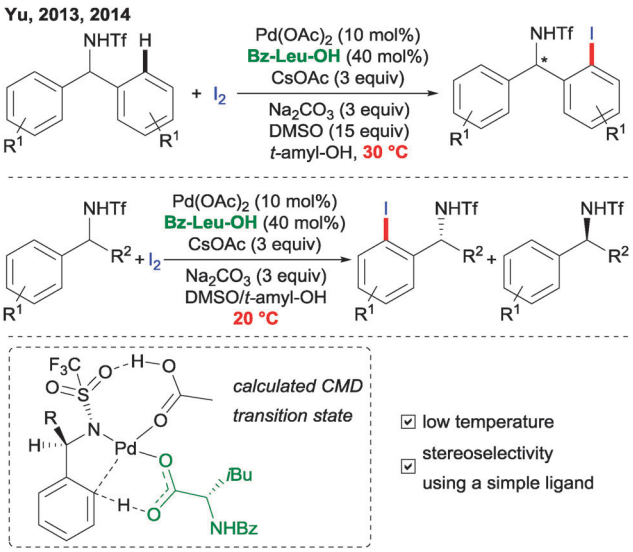
additive also acts as a labile ligand at the Pd center, facilitating coordination of the alcohol coupling partner. This approach allows for the efficient preparation of the C–O coupling products at ambient temperature.

The use of specifically-designed ligands to accelerate Pd-catalyzed C–H activation was initially explored by Yu, who in the middle of the last decade surmised that weakly-donating mono-protected amino acid (MPAA) ligands could drastically impact direct functionalization reactions.[1i,8] To date, MPAA ligands are arguably the most prominent ligands employed in Pd-catalyzed C–H activation reactions, facilitating both enantioselective and very mild transformations of a diverse array of substrates. Mechanistic investigations suggest that the particular potential of these additives may result from their bidentate coordination of the palladium catalyst and the role of the ligand N–H moiety as an intramolecular proton shuttle in the C–H bond cleavage step.[9] Such ligand-improved reactivity is clearly illustrated in the successful C–H transformations of generally unreactive electron-deficient arenes.[10] The authors discovered that the presence of a finely-tuned MPAA ligand not only enhances the turnover number (TON) of the C–H olefination of diversely-substituted phenylacetic acid derivatives, but also leads to the generation of a more active catalytic species (Scheme 4). This accordingly permits the functionalization of electron-deficient substrates which are totally unreactive in similar transformations conducted in the absence of such ligands. A detailed investigation of the reaction kinetics uncovered that the MPAA prevents build-up of mixed acetate–phenylacetate resting states of the palladium catalyst.[10b]

Maybe the most appealing feature of MPAA ligands is their chirality.[11] Recently, MPAAs were employed to access chiral amines *via* two conceptually distinct transformations: desymmetrization and kinetic resolution of racemic substrates.[12] In 2013, Yu and co-workers judiciously used the MPAA *N*-benzoyl-leucine (Bz-Leu-OH) to enhance the iodination reaction of a symmetric diarylmethyl amine.[12a] Given the stereogenic nature of the ligand, an enantioselective outcome was envisaged provided the chirally substituted catalyst species is able to differentiate between two prochiral aromatic moieties (Scheme 5). An extensive optimization study showed that both the *N*-protecting group



Scheme 4 Mono-protected amino acids in mild C–H activation.[10]

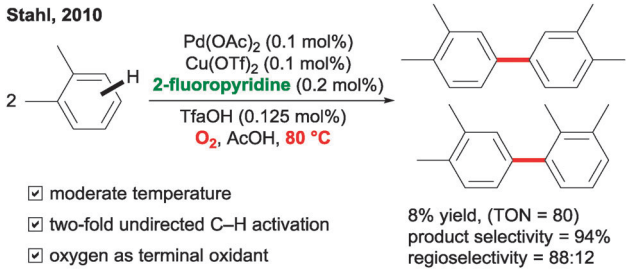


Scheme 5 Pd–MPAA-catalyzed enantioselective C–H activation.[12]

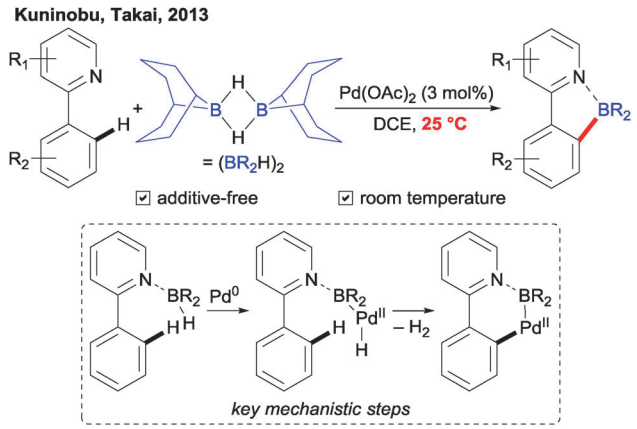
and the hydrocarbon substituent on the ligand have a dramatic impact on the enantioselectivity and efficiency of this transformation. Under the optimized reaction conditions, the targeted chiral amines were delivered in moderate to good yields (51–85%) and with excellent chiral induction. Importantly, the efficiency of this transformation at room temperature maximizes the level of enantioselectivity. Notably, the background racemic reaction catalyzed by a non-ligated catalyst is avoided by the addition of DMSO or DMF, which bind to the uncoordinated Pd^{II} species and inhibit the reaction. In addition to its mildness, the tolerance of this transformation toward air, the use of I_2 as the iodine source, and its efficiency at gram-scale further highlight the overall synthetic utility of this transformation.

Later, the same group explored another synthetic approach toward chiral benzylamines using racemic substrates (Scheme 5). In this case, the Pd(Bz-Leu-OH) complex was able to selectively functionalize one of the enantiomeric substrates in a highly selective kinetic resolution (selectivity up to 244).[12b] Accordingly, the iodinated products were isolated in yields up to 49% and moderate to good ee's (65–93%), and the remaining starting materials were recovered with excellent optical purities (92–99% ee). Furthermore, the recovered optically pure substrates, when resubmitted to the standard reaction conditions but using the MPAA ligand with the opposite configuration, were smoothly converted into the other enantiomers of the iodinated benzylamines. As such, this process allows for the preparation of both enantiomers of the iodinated products in high optical purities at ambient temperature (20 °C). A computational study on the mechanism of this transformation identified a beneficial coordination of acetic acid or DMSO to both the triflate residue on nitrogen and palladium leading to a fixed geometry where interactions between the benzylic substituent and the triflate determine enantioselectivity.[12c]

Another very interesting Pd-catalyzed C–H transformation which benefits from ligand-induced reactivity tuning was reported in 2010 by Izawa and Stahl.[13] The authors sought to



Scheme 6 Homocoupling of *o*-xylene under oxygen.[13]

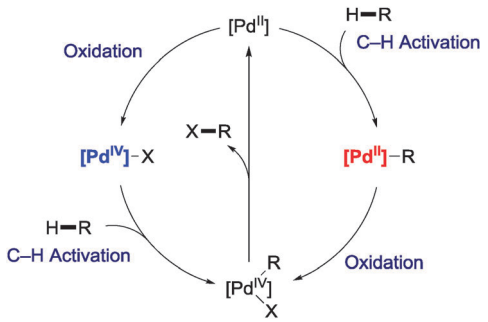


Scheme 7 Mild Pd-catalyzed C–H borylation.[14]

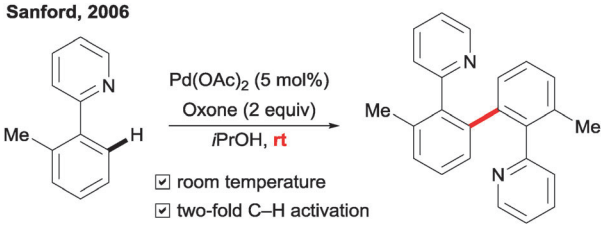
design a catalytic system that would be capable of mediating an industrially relevant, efficient homocoupling of simple *o*-xylene (Scheme 6). The major challenge inherent to this transformation involves controlling the regio- and chemoselectivity to allow the selective formation of the desired biaryl units. Consequently a dual Pd and Cu catalyst system was developed and, hypothesizing that *N*-coordinating ligands may be beneficial for reactivity and selectivity, a range of pyridine additives were tested. Derivatives bearing an electron-withdrawing substituent at the 2-pyridyl position led to improved reactivity and, after a detailed optimization study, 2-fluoropyridine was selected as the optimal ligand. When combined with a low loading of $Pd(OAc)_2$ as the pre-catalyst (0.1 mol%), $Cu(OTf)_2$ (0.1 mol%) and TfaOH as an additive, in acetic acid as the solvent, this ligand led to a radically improved set of conditions for the coupling reaction delivering the desired biaryl product in 94% selectivity compared to the previously reported 40%. Moreover, excellent regioselectivity (88%) and efficiency (TON = 80) were achieved at a reaction temperature substantially lower (80 °C) than the previously reported 140 °C, while oxygen could be used as the terminal oxidant. Although there is still some way to go before this challenging process can be considered truly mild as defined in this review, the substantial improvements achieved in this study demonstrate how judicious use of ligands can greatly improve the mildness of C–H transformations. In this case, the electron-withdrawing character of the fluorine substituent at the 2-position of the pyridine is thought to maintain some degree of electrophilicity of the Pd catalyst upon coordination of the ligand. Pyridine derivatives which are even less basic, however, are unable to modulate the reactivity of the Pd catalyst and there is seemingly a balance that must be found. The coordination sphere of the active Pd catalyst also incorporates both acetate and trifluoroacetate anionic ligands, which are necessary to ensure smooth CMD metalation.[3]

A conceptually very different approach toward mild Pd-catalyzed C–H activation and subsequent C–B bond formation was disclosed by Kuninobu and Takai.[14] This original idea consisted of redefining the role of the directing group, which typically coordinates the metal catalyst, boosting reactivity and regioselectivity. In this particular case, the Lewis basic nitrogen of the pyridine DG was used to form a Lewis base/Lewis acid adduct with the boron atom of the 9-borabicyclo[3.3.1]nonane (9-BBN) reaction partner (Scheme 7). The Pd^0 catalyst subsequently undergoes an oxidative addition into the B–H bond of the borane leading to a Pd^{II} species whose electronic properties are modified by the boryl ligand. Subsequent intramolecular C–H metalation directed to the *ortho*-position leads, after loss of H_2 and C–B bond-forming reductive elimination, to the *ortho*-borylated products at room temperature. Notably, improved yields were obtained when performing this reaction at 25 °C, compared to the initially used 135 °C. In contrast to most other transformations employing high-valent Pd catalysts discussed in this review, which involve electrophilic metalation or CMD mechanisms, the C–H activation step in this process is thought to occur *via* σ-bond metathesis. As such, this transformation showcases the potential of this somewhat underexplored pathway as an approach to achieve mild C–H transformations.

During the development of Pd-catalyzed C–H activation chemistry, it was realized that many transformations occurring in the presence of strong oxidants could in fact proceed *via* Pd^{IV} or Pd^{III} intermediates.[15] The recognition of this possibility sparked the development of methods that deliberately make use of the distinct reactivity of these higher oxidation states with regards to chemoselectivity and facilitated reductive elimination of C–heteroatom bonds. In the vast majority of the C–H activation transformations involving Pd^{IV}, the C–H activation itself most likely occurs at a Pd^{II} species, with oxidation to Pd^{IV} and subsequent product-releasing reductive elimination regenerating Pd^{II} (Scheme 8, right part). In some cases, the distinction between this order of events and an alternative re-oxidation of Pd^0 species after a reductive elimination from Pd^{II} cannot be made clearly when no mechanistic evidence is presented and is probably also dependent on the choice of oxidant. On the other hand, Pd^{IV} intermediates can potentially be involved in the C–H activation step itself (Scheme 8, left part).[16] This scenario has fascinating implications, as different selectivities and reaction conditions should be expected when changing the nature of the catalyst for any given mechanistic step as drastically as changing its oxidation state. To date, very few examples that clearly demonstrate C–H activation by a Pd^{IV} species have been reported. Judging by the current evidence, Pd^{IV} C–H activation catalysis has the potential to proceed at low temperatures with distinct regioselectivity, although the presence of oxidants capable of generating such a high oxidation state at palladium could be a limitation to overall mildness.



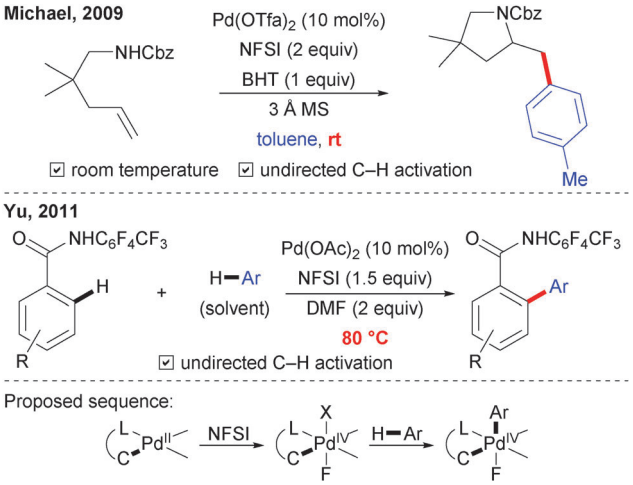
Scheme 8 Alternative pathways in Pd^{II}/Pd^{IV}-catalyzed C–H activation.[16]



Scheme 9 Oxidative arene dimerization involving proposed C–H activation at Pd^{IV}.[17]

In a seminal study, the group of Sanford proposed C–H activation at Pd^{IV} for the first time in 2006. An oxidative coupling process involving two-fold C–H activation of aryl pyridine derivatives proceeded at room temperature using Oxone ($KHSO_5$) as an oxidant (Scheme 9).[17] On the basis of selectivities obtained in experiments using stoichiometric amounts of preformed palladacycles, they proposed a sequence of Pd^{II} and Pd^{IV} mediated C–H activation events. Subsequent studies on the reactivity of isolated aryl Pd^{II} and Pd^{IV} complexes further substantiated the existence of Pd^{IV} mediated C–H activation.[18]

The group of Michael reported an unexpected result during a study on the diamination of olefins. When the reaction was carried out in toluene as solvent in the presence of *N*-fluorobenzenesulfonimide (NFSI), an aminoarylation product was obtained instead of the expected diamination at room temperature (Scheme 10).[19] This product results from an undirected C–H activation of toluene with a very high regioselectivity for the *para*-position. Compared with other undirected C–H activation methods, the low reaction temperature of this process is very uncommon. A number of other arenes could also be employed with high *para*-selectivity, delivering arylated pyrrolidine derivatives in good yields. Based on mechanistic evidence obtained from stoichiometric experiments and KIE studies, the authors suggested that undirected C–H activation of toluene occurs after pre-coordination at a Pd^{IV} intermediate. Yu's group later published a procedure for the *ortho*-arylation of benzamides *via* two-fold C–H activation with a number of simple arenes using $Pd(OAc)_2$ as catalyst and NFSI as oxidant (Scheme 10) at a somewhat higher temperature.[20] Again, very high *para*-selectivity for the non-directed C–H functionalization was observed. This stands in contrast to the relatively low levels of regioselectivity observed in undirected Pd^{II}-catalyzed transformations, and led the authors to propose a



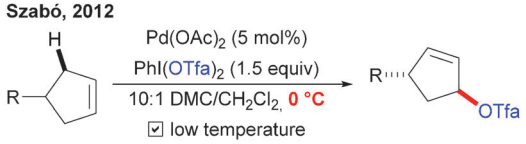
Scheme 10 Highly *para*-selective undirected C–H activation proposed to occur at Pd^{IV} intermediates.[19,20] BHT = 2,6-bis(1,1-dimethylethyl)-4-methylphenol.

mechanistic scenario involving C–H activation at a Pd^{IV} center in analogy to Michael's work. Notably, when $K_2S_2O_8$ was used instead of NFSI, a lower level of *para*-selectivity was observed. It has been noted that NFSI can be considered a by-standing oxidant for promoting chemoselective reductive elimination because the ligated fluoride anions generated upon oxidation do not participate in competing reductive eliminations.[21]

The group of Szabó reported an allylic C–H acyloxylation reaction that proceeds at 0 °C using (bis(trifluoroacetoxy)iodo)benzene (PIFA) as an oxidant and acyloxylating reagent (Scheme 11).[22] The corresponding acetate-substituted analog of the reagent, which is known to be less competent in oxidizing Pd^{II},[18a] failed to give any product while an independently prepared sample of a potential Pd^{II}–allyl intermediate decomposed in the presence of PIFA, with only traces of product being formed. Based on these observations, a Pd^{IV} species was proposed to mediate the actual C–H activation event, which then leads to allylic trifluoroacetate products useful as active substrates in Pd^0-catalyzed allylic functionalization reactions. The exceptionally low reaction temperature may result from the favorable combination of a potent Pd^{IV} catalyst, an intrinsically activated substrate (*vide infra*) and a reactive coupling partner (*vide infra*).

Rh-based catalytic systems

In addition to Pd, Rh is among the most powerful and general catalysts employed in direct C–H functionalization reactions. In particular, Cp^*Rh^{III} (Cp^* = η^5-pentamethylcyclopentadienyl) stands out as a highly potent catalyst for a range of diverse



Scheme 11 Allylic C–H trifluoroacetoxylation *via* proposed allylic C–H activation at Pd^{IV}. DMC = dimethylcarbonate.[22]

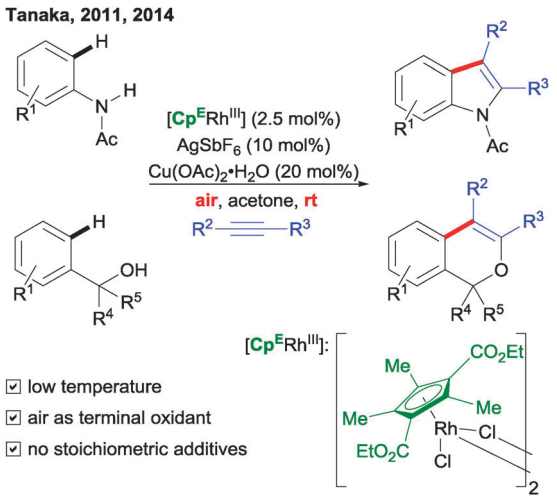
transformations.[1j,23] Although historically rather harsh reaction conditions were required to allow direct activation of nonreactive C–H bonds with this catalyst, several astute strategies such as the use of oxidizing DGs and/or very reactive coupling partners have recently been disclosed to achieve such transformations at room temperature. These discoveries are presented in following sections of this review. Moreover, a few research groups have focused on exploring the electronic and/or steric properties of the Cp* ligand with the goal of developing more reactive or selective Rh catalysts. As for comparable high-valent Pd-based catalytic systems, highly electrophilic Rh^{III} catalysts are desirable to enable a CMD-type C–H activation at ambient temperature. In this context, interesting results were achieved by Tanaka and co-workers, who designed an electron-deficient congener of the Cp* ligand: the diethoxy carbonyl trimethyl cyclopentadienyl (Cp^E).[24] The authors anticipated that the more electrophilic Cp^ERh^{III} species could outcompete the standard Cp^*Rh^{III} catalyst when reacted with electron-rich substrates such as anilides and benzyl alcohols (Scheme 12).[25] Indeed, alkyne annulation of such compounds occurred smoothly at room temperature. Notably, only a small amount of $Cu(OAc)_2{\cdot}H_2O$ (20 mol%) used as a co-oxidant was necessary because air could be employed as an ideal terminal oxidant. The corresponding indoles and isochromenes were delivered in yields generally ranging from 70% to 95% while the same transformations with the standard Cp*Rh catalyst were significantly less efficient. More recently, the same electron-deficient Rh^{III} catalyst was also employed in an oxidative Heck olefination of anilides at room temperature originally reported by Glorius with Cp^*Rh^{III} at 120 °C.[26] As KIE studies revealed that the C–H bond cleavage step is probably turnover-limiting, the finely-tuned electronic properties of the Cp^ERh^{III} catalyst are believed to improve the metalation step for these electron-rich substrates.

Notably, several alternatives to the standard Cp^*Rh^{III}-catalyst have been designed in particular by the groups of Rovis,[27a,b] Satoh and Miura[27c] and Cramer.[27d] In most cases, however, these have been employed to improve selectivity rather than reactivity and aspects of these are presented in following sections of this review.

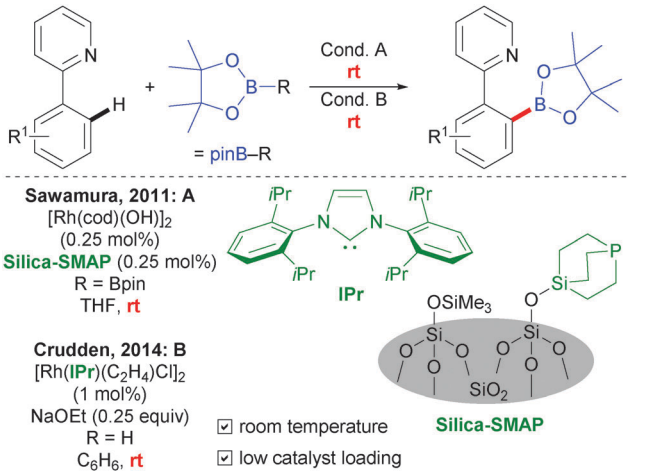
A different approach to catalyst design aimed at generating extremely reactive catalytic species was proposed by Sawamura.[28] The key feature of this work is its use of a Rh^I pre-catalyst. Low-valent metal catalysts such as Rh^I and Ir^I generally react with C–H bonds *via* an oxidative addition pathway and, consequently, increasing their electron richness through the addition of strongly coordinating ligands can be beneficial for reactivity. Following such a hypothesis, the authors discovered that Rh^I precatalysts such as $[Rh(cod)(OH)]_2$ (cod = 1,5-cyclooctadiene), may be very efficiently coordinated by a silica-supported bridgehead mono-phosphine, generating a very efficient heterogeneous catalyst (Scheme 13A). This supported species was capable of mediating the direct borylation of aromatic substrates bearing N-containing DGs. Impressively, the reaction occurred smoothly at room temperature with total consumption of a starting material observed within only one hour. Notably, both the immobilization and constrained geometry of the ligand were essential to ensure good efficiency of the overall transformation. The heterogeneous ligand architecture allows for binding of only one phosphine to the catalyst and hence provides a vacant coordination site necessary to bind the substrate.

More recently, Crudden *et al.* discovered that a much simpler, homogeneous catalytic system based on a Rh^I precatalyst and a strongly-binding and sterically-encumbered N-heterocyclic carbene (NHC) ligand is an appealing alternative to Sawamura's system (Scheme 13B).[29]

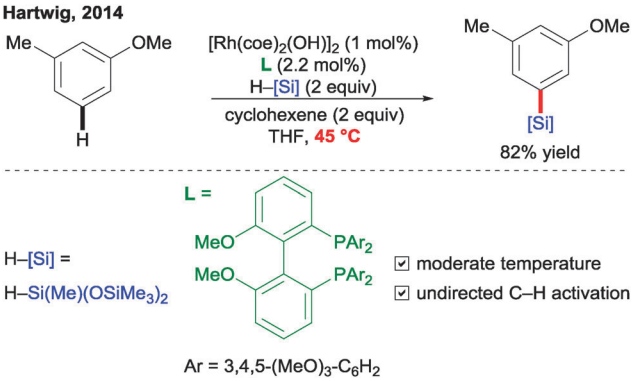
An additional example of Rh^I-catalyzed direct functionalization occurring at relatively low temperature was disclosed by Cheng and Hartwig (Scheme 14).[30] The authors discovered that a catalytic system based on a Rh^I pre-catalyst coordinated by a 2,2′-bisphosphino biaryl ligand, combined with a hydrogen acceptor (olefin) and a silane allows for direct C–Si couplings with simple benzene derivatives. The regioselectivity of this dehydrogenative silylation is controlled by the steric properties of the arene substrate with functionalization occurring predominantly at the less sterically-encumbered position. The presence of the



Scheme 12 Electron-deficient Rh^{III}-catalyst for the functionalization of electron-rich substrates.[24,25]



Scheme 13 Rh^I-catalyzed directed borylation.[28,29]



Scheme 14 Rh^{I}-catalyzed undirected C-silylation.[30] coe = cyclooctene.

strongly-coordinating ligand is essential to achieve a reasonable level of reactivity.

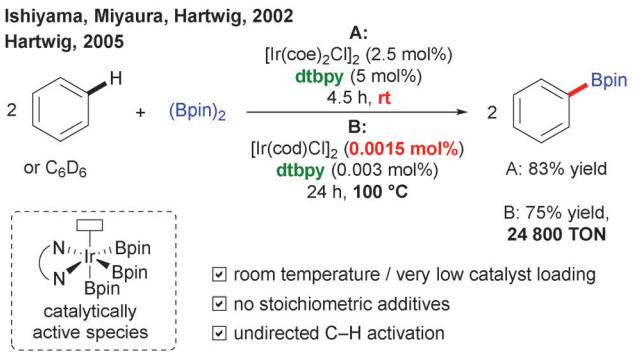
These studies demonstrate that electron-rich Rh^{I}-catalysts are able perform C–H activation at surprisingly moderate temperatures.

Ir-based catalytic systems

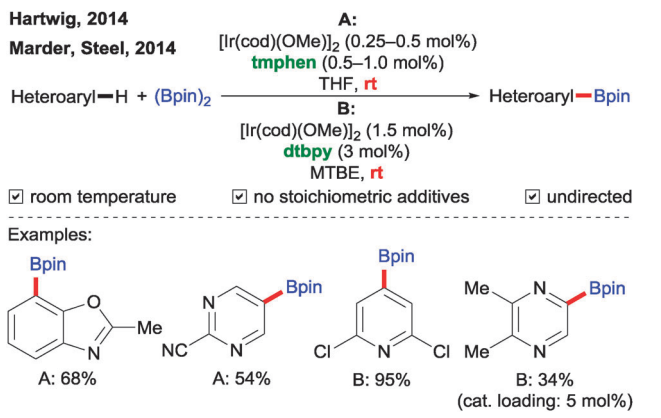
Notwithstanding the importance of several Rh-based catalytic systems that have been employed in mild C–H borylation reactions, historically these processes have been most successfully achieved using Ir catalysts. Already at the beginning of this century, Ishiyama, Miyaura and Hartwig discovered that undirected C–H cleavage/C–B bond formation could occur at temperatures as low as room temperature in the presence of a $[Ir(cod)Cl]_2$/4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) catalyst system (Scheme 15). Exceptionally high TON up to 24 800 for borylation of C_6D_6 at 100 °C with 0.0030 mol% catalyst loading were achieved.[31] Importantly, it is believed that an Ir^{III} species bearing the *N*,*N*-bidentate ligand and three boryl motifs is the active catalyst performing the undirected C–H activation. It seems that the presence of a strongly-coordinating and highly donating ligand is crucial to enhance the electron-richness of the Ir atom bearing three boron moieties. Accordingly, $[Ir(dtbpy)(Bpin)_3]$ appears to be an extremely powerful catalyst, accelerating a rate-limiting C–H bond cleavage not only under mild reaction conditions but also without DG assistance.

Following these seminal works, numerous related catalytic systems aimed at the borylation of various scaffolds have been disclosed. Firstly, significant efforts have been devoted to identifying a catalytic system capable of performing the desired coupling at room temperature and using an equimolar amount of the economically more viable pinacolborane (H-Bpin) reaction partner.[32] In this context, $[Ir(cod)(OMe)]_2$ turned out to be the optimal pre-catalyst, and the critical role of electron-rich bipyridine ligands in favoring the formation of the active C–H activation catalyst with a relatively unhindered coordination sphere was acknowledged. Further design of an optimal ligand led to the selection of 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) as an excellent auxiliary, frequently outcompeting its dtbpy congener. Detailed mechanistic investigations revealed that the improved reactivity of the tmphen ligand probably results from both its increased electron-richness compared to dtbpy and its conformational rigidity, which enforces η^2-coordination to the Ir center.[33] An additional key advantage of this second-generation ligand is that now both $(Bpin)_2$ and H-Bpin species may be used as borylating agents, allowing for improved atom economy and economic viability.

Importantly, such direct transformations are of great synthetic usefulness as they can be employed to prepare functionalized heterocyclic compounds.[34] Indeed, the general protocol for the Ir/tmphen-catalyzed borylation is compatible with various heteroarenes such as azoles, benzoxazoles, benzothiazoles, benzimidazoles, azaindoles and pyridines, among others (Scheme 16). Frequently, these transformations occur readily at room temperature, and in a regioselective manner. In-depth studies by the group of Hartwig rationalized the regioselectivity of these transformations with various substrates. The borylation of benzoxazoles and benzothiazoles was found to be under electronic control and duly occurs at the most acidic position. By contrast, the reactivity of pyridine, quinolone and other azines is strongly influenced by the presence of the basic nitrogen. Functionalization occurs predominantly at the beta or gamma positions with such heterocycles. Finally, if N–H-containing substrates are submitted to the standard reaction conditions, C–H activation occurs at a position distal to the N-atom because rapid N–H borylation creates an unfavorable steric environment adjacent to the nitrogen and directs C–H borylation to the less hindered position. An additional advantage of this strategy



Scheme 15 Pioneering work on Ir-catalyzed borylation.[31]



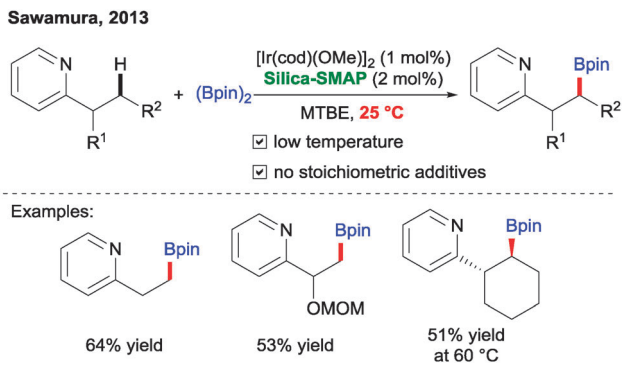
Scheme 16 Direct borylation of heteroarenes.[34,35]

results from the very low catalyst loadings. Good reactivity is maintained using very small amounts of the Ir species, rendering this approach attractive for possible industrial and large-scale applications. Notably, some reactivity enhancement may also be observed when the typically-employed THF solvent is replaced by MTBE (methyl *tert*-butyl ether), as demonstrated in the direct functionalization of pyridines and other azines.[35]

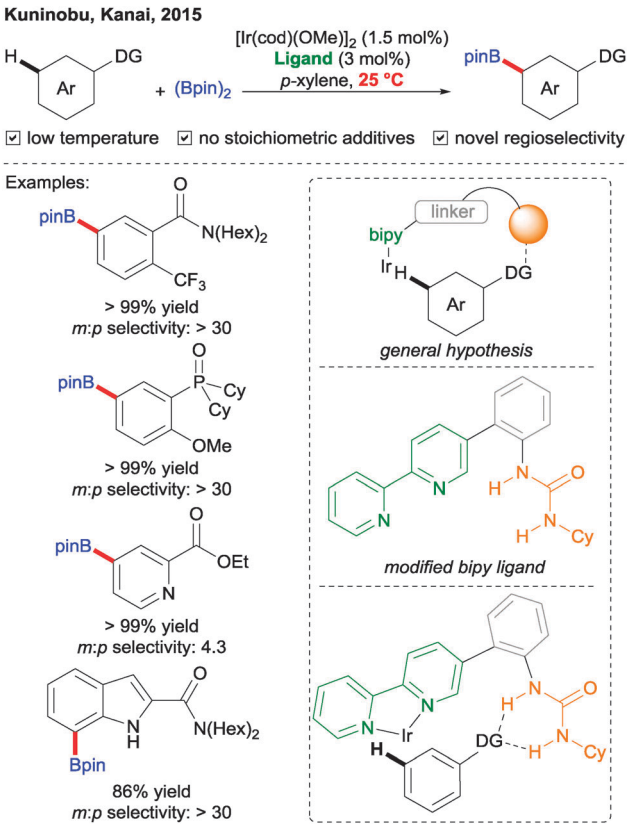
In addition to the direct functionalization of (hetero)arenes, a closely related catalytic system has been shown to also enable borylation of secondary benzylic C–H bonds, cyclopropanes and other aliphatic derivatives.[36] However, as the metalation of C(sp^3)–H bonds is generally much more challenging than C(sp^2)–H bonds, higher reaction temperatures, typically above 80 °C, are required to ensure reasonable catalytic activity.

The low reactivity of aliphatic substrates could be overcome to some extent using Sawamura's heterogeneous catalytic system. This group discovered that a silica-supported phosphine ligand efficiently coordinates the $[Ir(cod)(OMe)]_2$ pre-catalyst to afford a very powerful heterogeneous borylation catalyst (Scheme 17). Several homogeneous phosphine ligands showed significantly lower reactivity even at 60 °C (no reaction at rt), probably due to the lack of a vacant coordination site on the metal atom. Accordingly, the immobilized catalytic system permits mild and selective *ortho*-functionalization of a range of various arenes bearing an ester DG.[37] Furthermore, the scope of this transformation could be extended to other starting materials; in particular to alkylpyridine derivatives.[38] In some cases, the targeted C–H bond cleavage and C–B bond formation were feasible at 25 °C, but, in general, increasing the reaction temperature to 60 °C led to improved outcomes.

Very recently, Kuninobu and Kanai very astutely illustrated that the extremely mild character of these borylation reactions and their compatibility with *N*,*N*-bidentate ligands can facilitate very challenging and original transformations (Scheme 18).[39] They hypothesized that embedding a pendant hydrogen-bond donor moiety on the bipyridine ligand should enable secondary interactions between this ligand and a C–H substrate bearing a hydrogen-bond acceptor DG. Such ligand–substrate coordination could result in otherwise inaccessible regioselectivity in the borylation process. Furthermore, the additive-free nature of the typical borylation reaction was also crucial to maintain supramolecular



Scheme 17 Silica-supported Ir-based heterogeneous catalyst for the direct borylation of C(sp^3)–H bonds.[38]

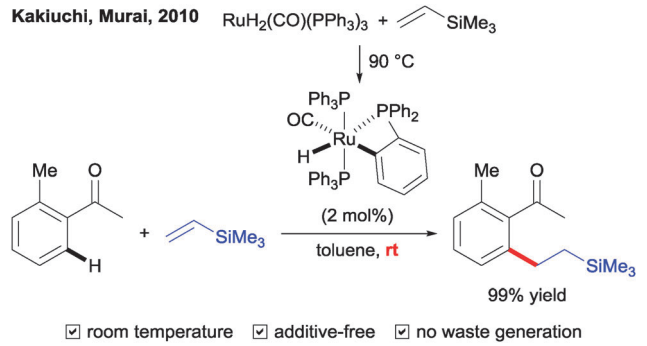


Scheme 18 *meta*-Selective Ir-catalyzed borylation.[39]

ligand–substrate interactions. Following such a hypothesis, several bipyridine ligands with embedded linkers and an additional urea moiety were designed, and an optimal ligand leading to a highly *meta*-selective C–B coupling was discovered. The high regioselectivity of this transformation is maintained with a variety of different DGs such as tertiary esters, amides and phosphorus-containing moieties, while both aromatic and heteroaromatic substrates could be employed. Notably, the coupling is efficient at temperatures as low as 25 °C.

Ru-based catalytic systems

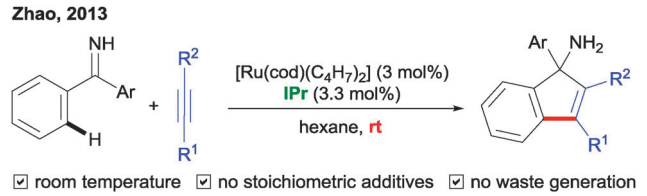
Despite the growing interest of the scientific community in Ru-based C–H activation reactions,[1g,40] transformations catalyzed by this metal occurring under mild conditions are rather rare. One of the most interesting examples was, however, reported in 2010 by Kakiuchi and Murai (Scheme 19).[41] Mechanistic investigations of the catalytic reactivity of a common $RuH_2(CO)(PPh_3)_3$ pre-catalyst in the direct olefination of aromatic ketones revealed that a key step of this transformation involves the generation of the catalytically active species from the pre-catalyst. Indeed, heating $RuH_2(CO)(PPh_3)_3$ in the presence of an olefin coupling partner afforded a new metalacyclic species as a mixture of four geometric isomers. These Ru species are believed to result from C–H activation of a PPh_3 ligand, while the carbonyl ligand remains bound to the Ru center. Intriguingly, while generation of this active catalyst requires high temperature (90 °C), once formed, the metalacycle itself is highly efficient, mediating the



Scheme 19 Early example of Ru-catalyzed C–H cleavage occurring at ambient temperature.[41]

C–H olefination transformation at room temperature. Apparently, conversion of the simple PPh_3 ligand into a bidentate C^P ligand upon heating, although thermodynamically unfavored, drastically modifies the electronic properties of the Ru atom, rendering it more active in the C–H bond cleavage step. The efficiency of this transformation was illustrated by the mild and additive-free coupling of acetophenone derivatives with trimethylvinylsilane. It is important to note that, even at room temperature, the C–H activation step is not rate-determining, and that Ru-species are capable of breaking C–H bonds with remarkable ease.

Another important example of a mild Ru-catalyzed transformation was reported a few years later by Zhao.[42] The improved catalytic reactivity of Ru was achieved not by using a bidentate C^P ligand coordinated to a Ru–hydride species, but rather by employing a strong σ-donating NHC ligand (Scheme 20). It is important to highlight here that the use of such a strong ligand is possible because low valent Ru^0 species are probably the active catalysts in the C–H scission step. As such, an oxidative addition pathway is most likely operating and C–H activation may be aided by strongly donating ligands in a similar fashion to the previously described Rh^I-catalyzed transformations. The authors observed that when benzophenone imine was reacted with an alkyne in the presence of a [Ru(cod)(η^3-methallyl)$_2$] pre-catalyst and IPr, a formal [3+2] carbocyclization occurred at room temperature delivering indenamine products. The remarkable reactivity enhancement observed with the NHC ligand (no reaction was observed without it) was rationalized by its significant electron-richness and the resulting ability to promote insertion of the π-system of the alkyne into the Ru–C bond. The alkyne insertion step is believed to be rate-determining in this system, showcasing the aptitude of the Ru/NHC complex as a catalyst for aromatic C–H bond activation. Furthermore, the redox-neutral nature of this transformation precludes the need for an external oxidant. In addition, the low reaction temperature and the lack of acidic or basic additives and waste generation mean that this process can be considered a truly mild C–H transformation.



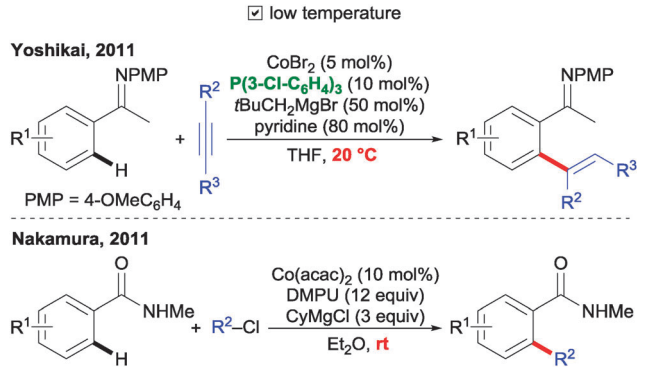
Scheme 20 Ru/NHC-catalyzed [3+2]annulation of ketimines and alkynes.[42]

First-row transition metal catalysts

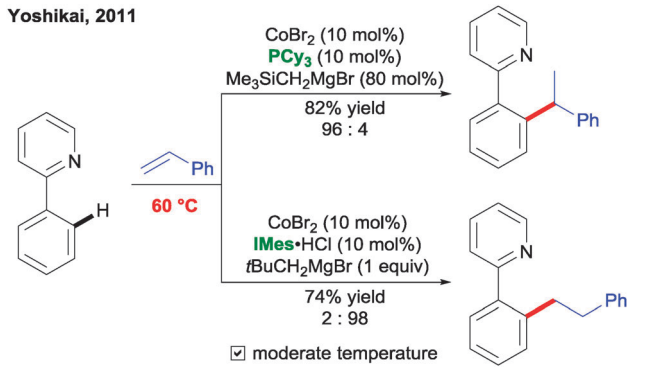
Until the beginning of this century, the field of C–H activation was largely dominated by second-row transition metal catalysts. The use of cost-effective, alternative systems employing other, more abundant metals such as manganese, iron, cobalt and nickel was rather anecdotal and harsh reaction conditions were frequently required to achieve any reactivity. However, over the last few years, major advances toward mild transformations have been achieved.[43]

Co-based catalytic systems

The field of mild C–H activation was strikingly reshaped when the potential of complex catalytic systems based on cobalt complexes was discovered in 2010 by Yoshikai.[44] The Yoshikai group first revealed the unexpected potential of a catalytic system combining a Co^{II} precursor, mono-phosphine ligand, pyridine additive and a Grignard reagent reductant to promote an *ortho*-directed olefination of phenyl pyridine derivatives with alkynes. Subsequently, it was observed that a closely related transformation of aryl imines occurred smoothly at the remarkably low reaction temperature of 20 °C (Scheme 21).[45] A detailed optimization study revealed that all components of this catalytic system are crucial for the success of the overall transformation. Firstly, the electronic properties of the cobalt catalyst need to be finely tuned by adding an ancillary ligand. Triarylphosphine ligands bearing electron-withdrawing substituents were the most promising auxiliaries, but pushing the electron-poor character of these ligands to the extreme, such as when using P(3,5-$(CF_3)_2$–$C_6H_3)_3$ or P($C_6F_5)_3$, led to a total shut down in reactivity. Moreover, no product formation was observed when a trialkyl phosphine (PCy_3) or bidentate phosphines (dppe, dppp, Xantphos) were used. The presence of a sub-stoichiometric amount of a Grignard reagent was essential. Methyl, *tert*-butyl and aryl RMgX species promoted the desired transformation rather poorly and the best results were obtained with 50 mol% of *t*$BuCH_2MgBr$. As the reaction rate dropped significantly when the amount of Grignard reagent was decreased to 40 mol%, it can be reasonably surmised that the role of this additive is not simply limited to the *in situ* reduction of Co^{II} to generate catalytically active low-valent Co^0 species. In addition, the organometallic reagent is thought to react with the cobalt catalyst and form organocobalt(0)-ate species. Finally, the presence of the Lewis basic additive, pyridine, which plays an as yet undefined role, led to a further improvement in efficiency. Under such finely-tuned reaction conditions, the desired direct coupling occurred smoothly with a large range of aryl imines bearing a variety of substituents, including several sensitive functionalities such as amide, cyano and bromo groups. Both symmetric and non-symmetric, as well as aromatic and alkyl-substituted alkyne-coupling partners were tolerated. This pioneering work clearly



Scheme 21 Low-valent Co-catalyzed C–H activation.[45,46]



Scheme 22 Selectivity switch in Co-catalyzed styrene hydroarylation.[49]

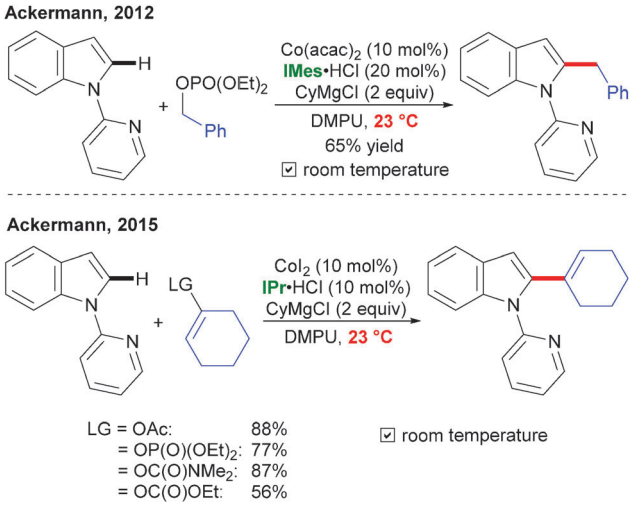
showcases the exceptional potency of low valent Co/PAr_3 species to promote C–H bond cleavage at ambient temperature.

Almost simultaneously but independently, Nakamura and co-workers reported a related Co-based catalytic system for the mild C–H functionalization of benzamides (Scheme 21).[46] In this case, DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) played the role of ancillary ligand facilitating a challenging $C(sp^2)$–$C(sp^3)$ coupling using alkyl chlorides as coupling partners. As with Yoshikai's system, a Grignard reagent (CyMgCl) was required to ensure reactivity, and it was speculated that this reactant plays multiple roles during the catalytic cycle: deprotonating the benzamide nitrogen, removing the hydrogen atom in the C–H cleavage step, aiding reduction of the Co^{II} pre-catalyst and limiting side-reactions involving homocoupling or resulting from β-hydride elimination.

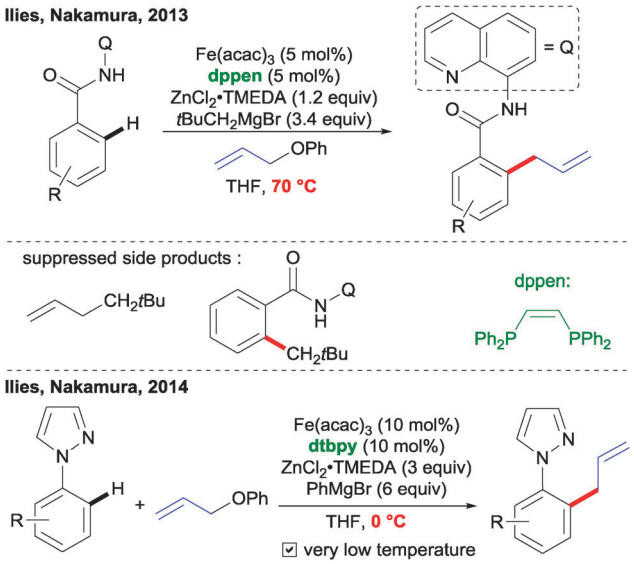
This pioneering work of Yoshikai and Nakamura became a springboard for the discovery of several closely related transformations[43j,47] such as the cobalt-catalyzed alkynylation and alkylation of heterocycles.[48] Moreover, unexpected results were obtained during the development of a hydroarylation of phenylpyridine derivatives with styrenes (Scheme 22).[49] When a Co^{II} precursor was used in combination with Me_3SiCH_2MgCl and PCy_3, branched 1,1-diarylethane derivatives were afforded. However, an almost complete reversal in the regioselectivity of the process toward linear products was observed using an NHC ligand. This interesting switch in selectivity probably results from the increased steric congestion imparted by the NHC ligand, which leads to an increased preference for insertion into the less hindered end of the terminal alkene. When phenylpyridine substrates were employed, a reaction temperature of 60 °C was required, while substrates bearing imine DGs reacted smoothly at lower temperatures (40 °C–rt).[50] In addition, coupling with vinylsilanes and aliphatic olefins at room temperature or 60 °C, respectively, could also be performed when monophosphine ligands were replaced by *N*,*N*-bidentate ancillaries such as phenanthroline or neocuproine, affording the linear products.[51] On the other hand, NHCs were found to be superior ligands to mono-phosphines for the *ortho*-arylation or benzamides with chloroarenes,[52] smoothly delivering the desired products at RT whereas a reaction temperature of 80 °C was required using PEt_3 as ligand. A similar system was also successfully applied in alkylation reactions with alkyl chloride and bromide coupling partners[53] and in a direct ring-opening process with aziridines.[54]

Significant contributions to the field of mild Co-catalyzed C–H activation were also made by the group of Ackermann.[43k,l] In 2012, they discovered that a Co^{II} pre-catalyst in combination with a Grignard reagent and NHC ligand in DMPU smoothly converts phenylpyridine and indole-type substrates into arylated and benzylated derivatives using sulfamate, carbamate and phosphate coupling partners (Scheme 23).[55] Although these transformations generally required a reaction temperature of 60 °C, in some cases reasonable catalytic efficiency was also observed at room temperature. Similarly, a closely related catalytic system was used to perform alkylation reactions using alkyl chlorides as coupling partners. This process was successful even with secondary alkyl derivatives, which are often challenging substrates in this kind of transformation.[56] Finally, the Ackermann group showed very recently that a Co/NHC/RMgCl catalytic system may also be used to perform direct room temperature C–H alkenylation reactions involving C–O bond cleavage of alkenyl acetate, phosphate, carbonate or carbamate coupling partners (Scheme 23).[57] The stereoconvergent nature of this transformation results in the exclusive formation of the *E* diastereomers.

All the examples discussed above clearly demonstrate the versatility of low-valent Co species as catalysts for mild C–H activation. Careful modulation of the electronic properties and coordination environment of cobalt catalysts can be achieved through judicious selection of ligands, which can include mono-phosphines, NHCs or *N*,*N*-bidentate scaffolds. Notably, the fundamental C–H cleavage step appears to be remarkably easy with low valent Co catalysts, irrespective of the ligand. Another interesting feature of this catalytic system, in particular in the case of alkylation reactions, is the potential involvement of radical intermediates and single electron transfer (SET) events in the C–H functionalization mechanism. Indeed, it is believed that SET between the cyclometalated intermediate and an alkyl halide may occur, generating an alkyl radical species with the final product being formed *via* radical coupling (Scheme 24).[43j] In addition, C–H transformations of aromatic substrates bearing OMe, F, CN or Cl groups in the *meta*-position with this metal demonstrate unusual regioselectivity favoring functionalization



Scheme 23 Co-catalyzed benzylation and alkenylation.[55,57]



Scheme 25 Iron-catalyzed C–H allylation.[58,59]

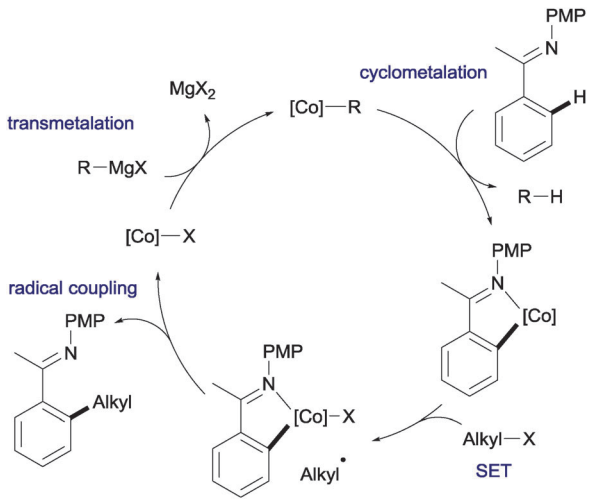
at the more hindered *ortho*-position between these substituents and the DG. Finally, an additional advantage of this mild C–H activation system is its compatibility with cost-efficient yet typically unreactive chlorinated coupling partners.

Although the above-mentioned examples fulfil several of the criteria defining a mild and synthetically useful transformation, the requirement for somewhat reactive Grignard reagent additives could be considered a limitation. Indeed, numerous functional groups are not compatible with these reaction conditions, while the generation of large amounts of by-products as waste is not desirable from an ecological perspective.

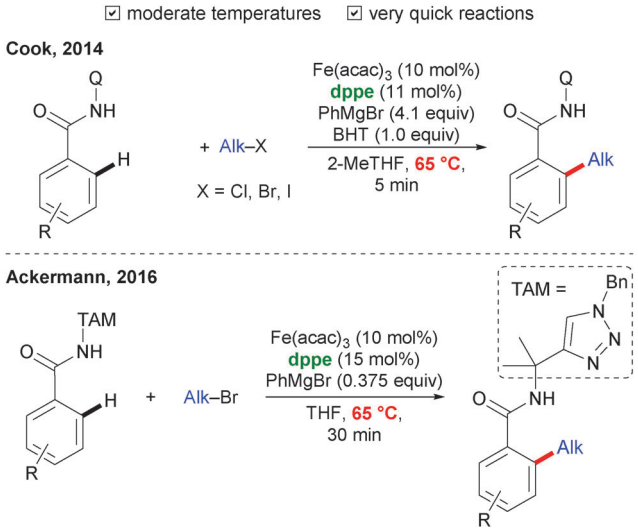
Fe-based catalytic systems

Considering the potential of Co catalysts in mild C–H activation reactions, the scientific community has duly become interested in investigating the reactivity of Fe-based catalysts in these kinds of transformations. In 2013, Ilies and Nakamura reported that, in a similar fashion to Co, low-valent Fe-species also enable rather mild direct functionalization of aryl C–H bonds (Scheme 25).[58] An Fe^{III}-pre-catalyst, in combination with $(tBuCH_2)_2Zn$ generated *in situ* from $tBuCH_2MgBr$ and $ZnCl_2$·TMEDA, and the dppen ligand (*cis*-1,2-bis(diphenylphosphino)ethene) smoothly enabled C–H bond cleavage of an aromatic substrate bearing an *N*-(quinolin-8-yl)benzamide bidentate DG. Notably, when an allyl ether coupling partner was present in the reaction mixture, a clean allylation reaction was observed, and side reactions involving the formation of *ortho*-neopentylated derivatives or C–C coupling products between the neopentyl and allylic moieties were efficiently suppressed. This reaction, which occurred rapidly at 70 °C, was found to be strongly dependent on the choice of organozinc reagent and ligand. When using Me_2Zn or Ph_2Zn, the side-reactions were predominant, while, in the absence of a ligand or in the presence of bypyridine, mono-phosphine or diphosphine additives bearing a flexible backbone, the reactivity was significantly decreased. A further step forward toward mild Fe-catalyzed C–H activation was achieved a few months later when the same group disclosed that replacing the bidentate DG with a mono-coordinating pyrazole DG further increases the reactivity of the catalytic system (Scheme 25).[59] Accordingly, the *ortho*-allylation of 1-arylpyrazoles using the $Fe(acac)_3$ pre-catalyst, $(tBuCH_2)_2Zn$ as a base and reducing agent, and dtbpy as a ligand could be successfully performed at 0 °C. Such a low-temperature C–H bond cleavage is remarkable and clearly demonstrates the potential of low-valent first-row transition metal species as catalysts for C–H transformations. In contrast to the Co-based catalytic systems, which favor functionalization at the more hindered *ortho*-positions of *meta*-substituted arenes, this Fe-based catalyst is more sensitive to steric constraints and mediates allylation at the most accessible *ortho*-position.

In parallel to the reports mentioned above, Cook and co-workers investigated Fe-catalyzed C–H alkylation reactions of aryl substrates bearing widely-employed 8-aminoquinoline DGs (Scheme 26).[60] The catalytic system combining an $Fe(acac)_3$ precursor, dppe as



Scheme 24 Proposed mechanism of the Co-catalyzed alkylation.[43j]



Scheme 26 Low-valent Fe-catalyzed $C(sp^2)$–$C(sp^3)$ couplings.[60,61]

ligand and PhMgBr promoted the desired coupling at 65 °C with remarkable efficiency, delivering the desired products after only a few minutes. Importantly, this catalytic system is also compatible with secondary alkyl precursors, allowing very challenging, hindered $C(sp^2)$–$C(sp^3)$ couplings. A closely related catalytic system applied to $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp^3)$ couplings was disclosed by Ackermann and co-workers in 2014 (Scheme 26). In these processes, a triazolyldimethyl amide (TAM) was designed as a highly efficient bidentate DG (termed a "substrate"-activator).[61]

Notably, despite the obvious potential of these Fe-based catalytic systems, at present they suffer from the same limitations as the Co catalysts described in the section above, resulting from the use of reactive Grignard reagents.

2. Substrate

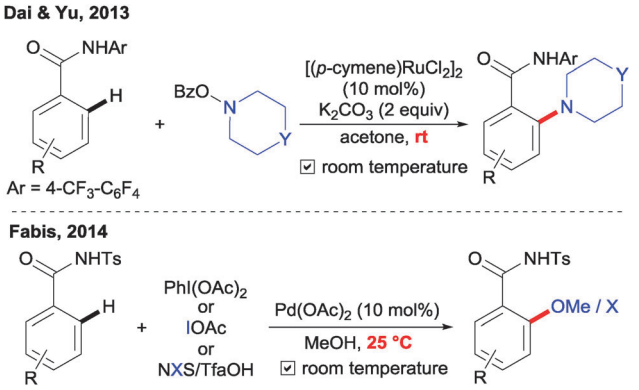
Directing group design

The most widely-applied synthetic strategy to overcome the intrinsic regioselectivity problems encountered in C–H activation involves embedding a coordinating moiety within a substrate.[62] These "directing groups" bind to the metal catalyst and lead to an effective increase in the local concentration of one particular C–H bond at the metal center. Upon coordination, the DG plays the role of a ligand and may significantly influence the electronic properties of the metal catalyst. In particular, the DG can greatly affect the electrophilicity of the metal species and may potentially allow for the stabilization of high oxidation state intermediates. Moreover, the choice of DG has a direct impact on the rate of the C–H cleavage step and greatly influences the stability of the resulting metalacyclic intermediate.

In early works on C–H activation, the majority of catalytic systems employed strongly σ-donating or π-accepting nitrogen-, sulphur- or phosphorus-containing DGs. It was recognized that such strongly coordinating groups favor rapid C–H bond scission and lead to the formation of thermodynamically stable metalacyclic intermediates. As a result, many metalacyclic species could be isolated and fully characterized.[63] However, the high stability of the catalytic intermediates can also be problematic for achieving catalytic turnover and may result in low compatibility with a range of electrophilic and nucleophilic coupling partners. In addition, the presence of such strongly coordinating DGs can be synthetically restrictive due to the limited modifiability of these groups. In contrast, the use of commonly-present functionalities such as carboxylates, ketones, esters or amides, which are weaker coordinating moieties, would greatly increase the synthetic value of C–H activation. Although such weak interactions between the substrate and the metal catalyst could render the C–H cleavage more challenging, the resulting weakly-bound metalacyclic intermediate may be significantly more reactive toward the coupling partners in the other steps of the catalytic cycle. Accordingly, for cases where mechanistic steps subsequent to C–H activation are rate-limiting, milder conditions and a more diverse array of potential transformations could be envisaged. Following this hypothesis, many research groups have focused on designing catalytic systems involving weakly-coordinating DGs.[64]

The amide moiety is one of the most commonly used DGs and is compatible with a variety of transition metal catalysts. Surmising that weaker coordination between this DG and a catalyst may boost the reactivity of a catalytic system, Yu devised a class of secondary *N*-aryl amide DGs bearing electron-withdrawing substituents on the aromatic ring which increase the acidity of the N–H bond. Deprotonation of the amide under weakly basic conditions promotes coordination to the metal in a η^1 manner *via* N, optimizing the geometry of the key intermediates and facilitating the C–H bond cleavage. Accordingly, the electron-deficient amide moiety bearing a 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl substituent was established as the most potent DG and substrates bearing this group have been widely employed in various C–H activation reactions. An illustrative example of a remarkably mild transformation that demonstrates the superior reactivity of this weakly-coordinating auxiliary was reported in 2013.[65] The authors studied a Ru-catalyzed C–H amination reaction and discovered that the desired C–N coupling with *N*-benzoyloxyamines occurred smoothly at room temperature when an arene substrate bearing this electron-deficient amide auxiliary was employed (Scheme 27). Notably, only the weak base potassium carbonate was required for the deprotonation of the amide. Consequently, the scope of this transformation is very broad and the process is even compatible with heterocyclic substrates including pyrazole, thiophene, benzothiophene, furan, benzofuran and indole. Following the same hypothesis, Fabis and co-workers employed *N*-tosylamide as an appealing DG for Pd-catalyzed C–H methoxylation and halogenation reactions of arenes.[66]

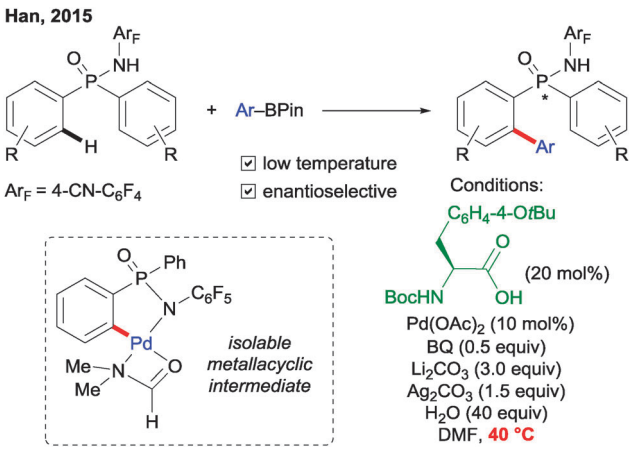
Importantly, in both cases, the formation of metalacyclic intermediates could be monitored at room temperature by ^{1}H NMR. Unfortunately, as no kinetic isotope effect (KIE) studies were conducted for either reaction, it is not possible to comment on the relative rate of the different catalytic steps. It could be reasonably speculated, however, that the weakly coordinating amide DG permits facile C–H bond cleavage and the resulting Ru- or Pd-based metalacyclic intermediates are



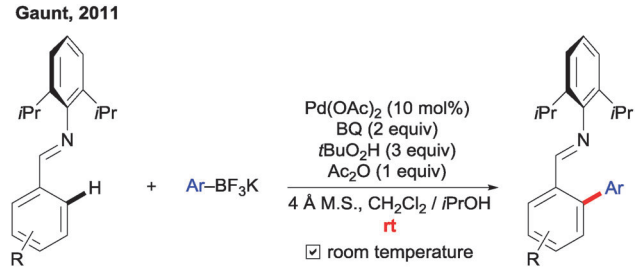
Scheme 27 Weakly coordinating amides as directing groups.[65,66]

subsequently oxidized to afford Ru^{IV} or Pd^{IV} species capable of undergoing fast reductive elimination.

Inspired by the potential of the amide DG bearing an electron deficient aromatic substituent, Han and collaborators hypothesized that the installation of such a coordinating moiety could enable the direct functionalization of arylphosphine derivatives.[67] As expected, the desired direct arylation could be achieved using arylboronic acid derivatives as coupling partners. Remarkably, among five different amide DGs tested, only the electron poor moiety $CONHC_6F_5$ led to conversion of the starting material at 40 °C. As this mild C–H functionalization reaction generated stereogenic phosphinamides, the same group subsequently disclosed a closely related protocol for an enantioselective transformation (Scheme 28).[68] Inspired by Yu's work, an MPAA was selected as a chiral ligand. After an extensive optimization of the reaction conditions, including investigations into the organoboron reaction partner, oxidant, base and solvent, an efficient catalytic system was developed. Notably, in this study, the aromatic substituent of the amide DG was modified, and the $-C_6F_5$ moiety initially used was replaced by another electron-deficient ring, 4-CN–C_6F_4. Interestingly, facile C–H cleavage occurred readily at 40 °C, but the resulting metalacycle was sufficiently stable to be isolated and fully characterized. This species can also be used as the active catalyst.[67]



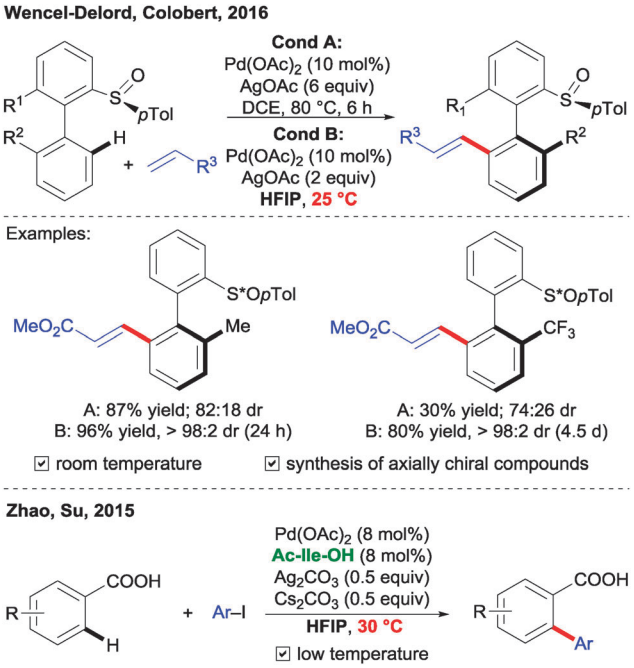
Scheme 28 Enantioselective arylation of phosphonamides.[68]



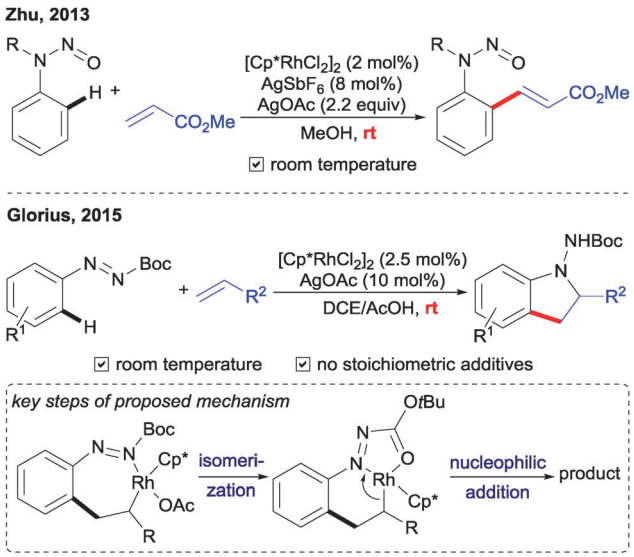
Scheme 29 Imine-directed arylation.[69]

Also exploring the strategy of improving a catalytic system by tuning the properties of DGs, Gaunt and co-workers became interested in the use of imine moieties.[69] They hypothesized that the less electron withdrawing character of this auxiliary, compared to analogous carbonyl groups, would lower the electron deficiency of an aromatic ring and hence enable cyclometalation under mild reaction conditions. Indeed, the cyclopalladation of benzaldimines at room temperature is well described.[63a] However, employing imines in Pd-catalyzed C–H transformations presents an intrinsic difficulty due to the instability of these groups under mildly acidic conditions. The amine derivatives generated by hydrolysis bind strongly to the metal and lead to catalyst poisoning. The authors presumed that imine hydrolysis could be prevented by increasing the steric bulk of the amine component. Accordingly, arylation of a benzaldimine derived from 2,6-diisopropylaniline was achieved at room temperature using aryltrifluoroborates as the reaction partners (Scheme 29). The scope of this transformation is large with regard to both the Ar–BF_3K derivative and the benzaldimines, yielding the desired biaryl compounds in moderate to good yields.

The coordinating properties of the DG may also be influenced by the choice of reactants, additives and solvents used for a targeted C–H activation reaction.[70] Such "*in situ* adjustment" was observed in the case of sulfoxide-directed atropodiastereoselective C–H activation.[71] In this study, biaryl scaffolds bearing a sulfoxide moiety playing a role of both DG and chiral auxiliary were employed as substrates in an oxidative Heck (Fujiwara–Moritani) reaction. Rather surprisingly, a large solvent-effect on both the efficiency and the level of chiral induction of this transformation was observed. While the oxidative Heck reaction performed in 1,2-dichloroethane (DCE) required a rather high reaction temperature of 80 °C to attain a reasonable conversion of the starting material and was only rather moderately diastereoselective, using the highly polar, polyfluorinated alcohol HFIP (1,1,1,3,3,3-hexafluoroisopropanol) as solvent led to an exceptional increase in both reactivity and atroposelectivity (Scheme 30). Since mechanistic studies revealed the formation of a strong hydrogen bond between the sulfoxide DG and HFIP solvent, it can be presumed that such DG/solvent interactions amend the electronic properties of the DG, rendering it less coordinating (weaker DG), while simultaneously modifying the chiral environment around the catalyst. Thus, the sulfoxide-directed Fujiwara–Moritani reaction conducted in HFIP permitted the synthesis of versatile atropisomeric scaffolds in generally excellent yield and very high optical purity. Notably, a related direct acetoxylation and



Scheme 30 HFIP-assisted C–H activation at low temperatures.[71,73]



Scheme 31 N–N-containing directing groups in Rh-catalyzed C–H activation.[75,76]

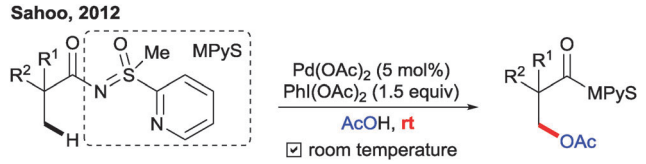
iodination, when performed in HFIP, delivered the corresponding diastereoselective C–O and C–I coupling products at room temperature.[72] KIE studies conducted for both C–C and C–O couplings suggested that, in the first case, the metalation step is rate-determining, whereas under acetoxylation conditions, C–H cleavage is reversible, and the reductive elimination is believed to be the kinetically limiting step. Such divergent outcomes clearly show that sulfoxide directed C–H activation is relatively fast at room temperature in HFIP and the rate of the overall transformation is dependent on the kinetics of each step in the cycle (reductive elimination to afford C–C bonds is arguably much easier than C–O bond formation).

A related mild arylation of benzoic acids with a ligand-supported Pd catalyst was reported by Zhao and Su.[73] In analogy to the sulfoxide-directed reaction, this direct functionalization of electron-deficient aromatics was efficiently conducted in HFIP while no reaction occurred in other solvents such as 2,2,2-trifluoroethanol (TFE), water, acetic acid, dimethylformamide or benzene (Scheme 30). Although the key role of HFIP in this reaction was not clearly elucidated, the same type of "H-bond substrate activation" by interaction of HFIP with the DG could be expected.[74]

Another example of how design of DGs can lead to the development of mild C–H transformations involves the use of N–N moieties in Rh^{III}-catalyzed reactions. A seminal *N*-nitroso-directed olefination of arenes was disclosed by Zhu (Scheme 31).[75] The particular potential of the nitroso-DG can be attributed to the variety of coordination modes, such as η^1-*O*-binding, η^1-*N*-binding and bridged μ-η^1:η^1-*N*,*O*-binding, by which this group may interact with metal centers. Accordingly, the reactivity of the cyclometalated intermediates can be regulated through adjustments in the coordination mode of the DG. This *N*-nitroso directing group imparts sufficient stabilization to the metalacyclic intermediate formed upon C–H activation to render it isolable. The nature of the substituent on the C–H substrate drastically affects the outcome of the C–H cleavage event as irreversible *ortho*-rhodation was observed for electron-poor substrates and reversible *ortho*-rhodation was observed for electron-rich substrates. This discrepancy could suggest that, although the rate-determining step is different in each case, the cyclometalation remains sufficiently efficient to be performed under moderate temperatures even with more challenging, electron-deficient substrates.

Very recently, Glorius and co-workers used a diazenecarboxylate DG to perform a C–H activation/nucleophilic addition sequence yielding 1-aminoindolines (Scheme 31).[76a] This polarized, unsaturated DG not only enabled cyclometalation at room temperature, but also underwent subsequent cyclization *via* nucleophilic addition of a C(sp^2)–Rh species onto the N=N moiety. In this particular case, the C–H scission remains the slowest step of the catalytic cycle, while the rhodacycle is relatively stable (isolable in 80% yield). Notably, the presence of a coordinating substituent, such as a *tert*-butyloxycarbonyl (Boc) group, on the DG is crucial to prevent problematic β-hydride elimination and this moiety might stabilize the olefin insertion product by chelation. A computational study furthermore suggests that this chelation also facilitates the isomerization to a 6-membered rhodacycle.[76b]

Finally, another trend in C–H activation involves the design and use of bidentate DGs.[77] In general, such bidentate auxiliaries have an increased affinity for coordination of a metal catalyst and hence favor the C–H cleavage step. The resulting well-defined metalacyclic intermediates are also highly stable.[78] Accordingly, this approach is appealing for the mild functionalization of especially unreactive C–H bonds. In particular, several C–H transformations of aliphatic C(sp^3)–H bonds have been reported although generally rather high reaction temperatures are still necessary to ensure reasonable catalytic efficiency.[79]



Scheme 32 A bidentate directing group as a handle for mild Pd-catalyzed aliphatic C–H activation.[80]

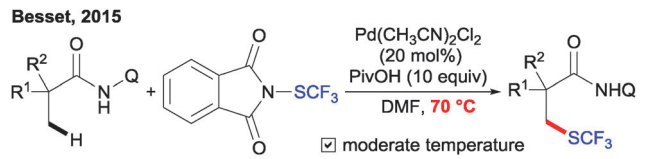
A clear illustration of such a phenomenon was reported in 2012 by Sahoo.[80] This group discovered the particular potential of the *S*-methyl-*S*-2-pyridyl-sulfoximine (MPyS) bicoordinating DG[81] to enhance direct functionalization of unactivated primary β-C(sp^3)–H bonds (Scheme 32). The challenging cyclometalation of an aliphatic C–H bond was triggered by facile coordination of palladium by the two coordinating moieties of MPyS (the pyridyl and sulfoximine nitrogens). Notably, the choice of this DG resulted in an efficient targeted C(sp^3)-acetoxylation at ambient temperature whereas other *N*,*N* and *N*,*S*-bidentate DGs failed to afford the oxidized product. The exceptional ability of this bidentate DG to facilitate C–H scission is illustrated by the fact that C–H activation is reversible in this system. The facile cleavage and easy recovery of the MPyS further highlights the synthetic value of this protocol. Following this work, Sahoo developed a related catalytic system for MPyS-directed acetoxylation of C(sp^2)–H bonds which could be followed by an intramolecular cyclization to afford benzofuranones.[82]

The bidentate 8-aminoquinoline moiety was also employed to facilitate direct Pd-catalyzed trifluoromethylthiolation of C(sp^3)–H bonds under relatively mild reaction conditions (Scheme 33).[83]

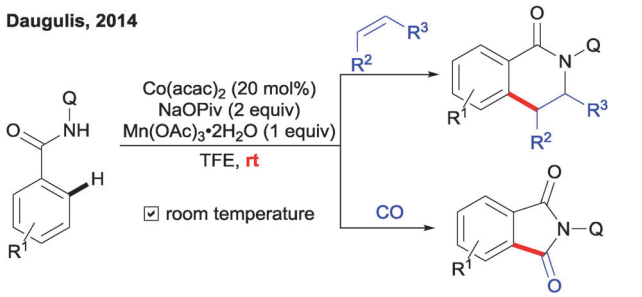
Recently, Daugulis discovered that a bidentate DG may also be a useful handle to promote cobalt-catalyzed C–H activation of aromatic substrates under very mild conditions.[84] When reacted in the presence of a Co^{II} precatalyst, $Mn(OAc)_3{\cdot}2H_2O$ as a co-oxidant and a base, the 8-aminoquinoline-substituted benzamide underwent mild *ortho*-metalation and subsequent coupling with alkenes or carbon monoxide to yield heterocyclic compounds (Scheme 34).[85] These transformations are believed to proceed *via* a Co^{III} intermediate formed by oxidation of $Co(OAc)_2$ in the presence of the aminoquinoline amide ligand. An advantage of this high-valent catalytic system is its excellent functional group tolerance with even iodo-, nitro-, heteroaryl- and cyano-groups being tolerated.

Internal oxidants

The development of directing groups that serve as internal oxidants has revolutionized oxidative C–C bond forming C–H activation, especially under Rh^{III} catalysis. In this context, an



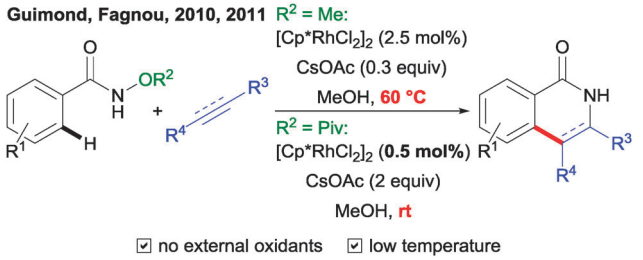
Scheme 33 C(sp^3)–H trifluoromethylthiolation with a bidentate DG.[83]



Scheme 34 Co-catalyzed functionalization of aromatic substrates bearing bidentate directing groups.[85]

internal oxidant is considered a moiety in the C–H activation substrate that is both a DG and an oxidant for the catalyst species either after or before a reductive step in the catalytic cycle. In practice, these moieties contain cleavable N–N or N–O bonds. Generally, milder conditions can be employed compared to similar reactions using external oxidants and no extra metal waste is formed. The decreased reaction temperatures can be a consequence of the intramolecular nature of the re-oxidation step. The low-valent metal species is formed in the vicinity of the internal oxidant and re-oxidation can occur immediately in an inner-sphere sense. In some cases, the order of events can also be reversed when the internal oxidant triggers an oxidatively induced reductive elimination. This specificity of the oxidation mechanism is beneficial for the tolerance of the reaction toward oxidatively-sensitive functional groups. Additionally, some oxidizing DGs aid the C–H activation step in their role as directing groups, as exemplified by the use of hydroxamates in redox-neutral transformations. As the nature of the directing group changes during the course of the oxidation, complete control for mono-functionalization is generally inherent to this concept. Over-reaction can otherwise be a limitation with certain directing groups that bind strongly to the catalyst. In many methods involving this approach, the initial metalacycle functionalization is followed up by a cyclization event, forming interesting heterocyclic products which incorporate part of the former directing group. On the downside, extra steps may be required to install a suitable oxidizing directing group, potentially involving oxidation steps and thus merely shifting the use of an oxidant to another part of the synthesis. Additionally, in most cases a stoichiometric by-product is formed by the cleavage of the N–N or N–O bond. The topic of internal oxidants as directing groups has been reviewed recently[86] and we will therefore limit the discussion of this enabling technology to a selection of examples that demonstrate exceptional mildness.

The concept of oxidizing directing groups was introduced to the field of C–H activation by the group of Neuville and Zhu in 2008[87a] and shortly thereafter by the groups of Cui and Wu[87b] and Hartwig[87c] in reactions demonstrating two fundamentally different uses of internal oxidants. In the first example, a Pd^0-catalyzed annulation of acyl oximes with arynes, the oxidation of Pd^0 by addition into the N–O bond initiates the reaction.[87a] Hartwig's Pd^0-catalyzed internal arene amination with oxime esters is related to this mode of action.[87c] On the other hand,

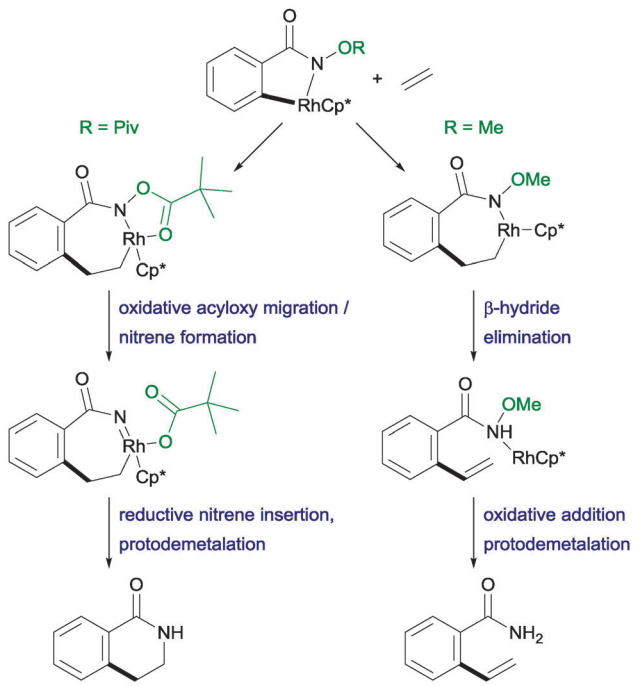


Scheme 35 Seminal studies employing hydroxamate directing groups in Rh^{III}-catalyzed C–H activation.[88,89b]

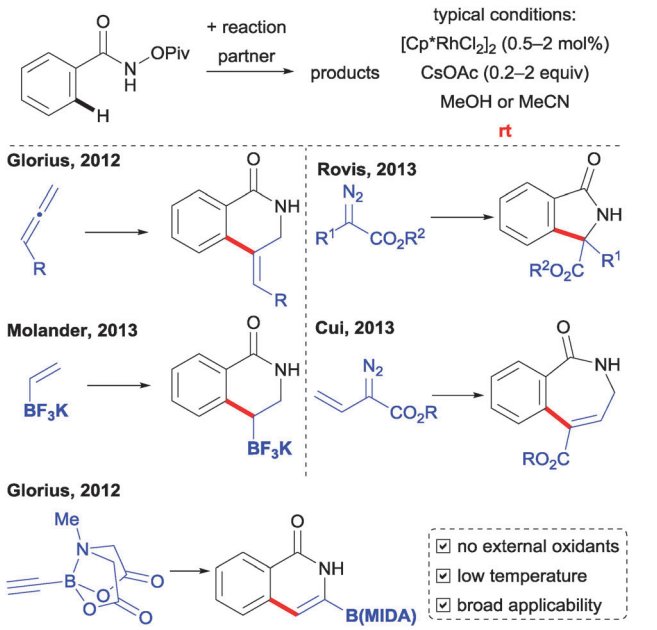
the second example was a Pd^{II}-catalyzed alkenylation of quinoline-*N*-oxides with acrylates where the re-oxidation of Pd^{0} after reductive elimination closes the catalytic cycle.[87b] While enabling oxidative transformations without stoichiometric external oxidants, the targeted transformations still required very high reaction temperatures. A real breakthrough toward milder C–H activation was disclosed by the group of Guimond and Fagnou who found that benzhydroxamates are particularly appealing substrates for Rh^{III} catalysis (Scheme 35).[88] Following their initial report on an isoquinolone synthesis from *O*-methyl benzhydroxamates and alkynes at 60 °C, it was shown that the use of *O*-pivaloyl benzhydroxamates as substrates enabled alkyne and alkene insertion and subsequent cyclization to the corresponding (dihydro)-isoquinolones at temperatures as low as room temperature.[89] The alkene insertion, however does not yield dihydroisoquinolones from *O*-methyl benzhydroxamates, demonstrating how striking differences in reactivity can arise from apparently small changes in the directing group substitution. Later, computational studies were able to rationalize this reactivity (Scheme 36).[90] First of all, the ability of the pivalate to stabilize catalytic intermediates through chelation with the carbonyl group is thought to be responsible for the increased reactivity of the *O*-pivaloyl benzhydroxamates. Furthermore, this chelation prevents β-hydride elimination after the alkene insertion step. The lack of such stabilization leads to the formation of olefinated products with *O*-methyl benzhydroxamate substrates (Scheme 36, right side). Intriguingly, the authors identified an oxidative acyloxy migration to a nitrene intermediate formally featuring Rh^{V} as the favored pathway with *O*-pivaloyl benzhydroxamates (Scheme 36, left side). Subsequent reductive nitrene insertion into the Rh–C bond and protodemetalation then afford the cyclized product.[90] On the other hand, no nitrene intermediate is involved in the computed mechanism for the cyclization with alkynes. Instead, a sequence of C–N reductive elimination and N–O oxidative addition succeeds the alkyne insertion.[91] In contrast to the reactivity of *O*-methyl benzhydroxamates under Rh^{III} catalysis, cyclization reactions can be performed with alkynes and alkenes under Ru^{II} catalysis at low temperatures using these substrates, furnishing related (dihydro)isoquinolone products.[92]

Subsequent work has showcased the versatility of the *O*-pivaloyl hydroxamic acid directing group in Rh^{III} catalysis for the mild synthesis of a number of heterocyclic motives (Scheme 37). This diversity is exemplified by the synthesis of isoquinolone derivatives with synthetically valuable moieties such as *exo*-double bonds[93] and borates[94] with predictable selectivities, as well as by the development of isoindolone and benzoazepinone syntheses using diazo compounds as carbene precursors.[95]

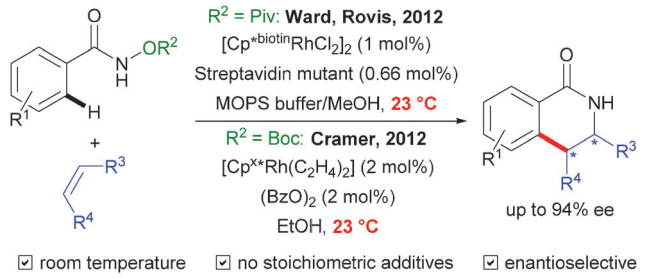
Notably, the mildness of the transformations involving oxidizing directing groups has encouraged the development of enantioselective Rh^{III}-catalyzed C–H transformations. Based on the dihydroisoquinolone synthesis from *O*-pivaloyl benzhydroxamic



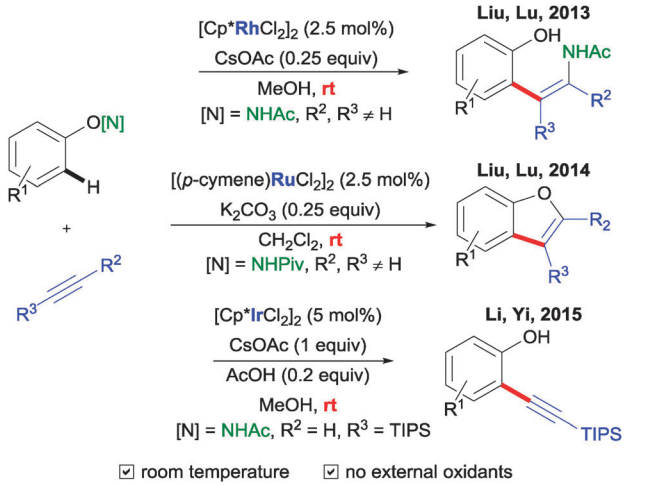
Scheme 36 Computed mechanism of the Cp*Rh^{III}-catalyzed reaction of benzhydroxamates with alkenes.[90]



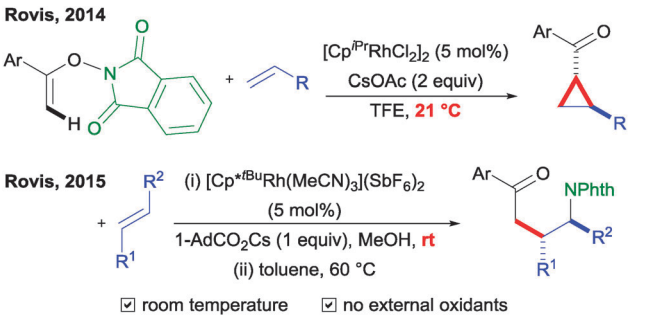
Scheme 37 Examples of Cp*Rh^{III}-catalyzed transformations of *O*-pivaloyl benzhydroxamates at room temperature.[93–95]



Scheme 38 Enantioselective Rh^{III}-catalyzed C–H functionalization.[96]



Scheme 39 Versatile reactivity of phenoxyamides.[97]



Scheme 40 Divergent reactivity of enoxyphthalimides with alkenes under Rh^{III} catalysis.[98]

acids originally presented by Glorius[89a] and Guimond,[89b] the groups of Cramer, and Ward and Rovis independently presented two concepts for the synthesis of enantioenriched dihydroisoquinolones from benzhydroxamates and olefins (Scheme 38).[96] Ward and Rovis developed an artificial metalloenzyme containing the $CpRh^{III}$ fragment bound through a biotin tag on the cyclopentadienyl ligand to a streptavidin mutant.[96a] The compatibility with enzyme catalysis demonstrates the mildness of the transformation achieved using the oxidizing directing group. Cramer's group focused on the development of chiral cyclopentadienyl derivatives surmising that selectivity could be achieved using a shielding element and symmetrical positional locks on the ligand.[96b] Using this design, they achieved the enantioselective annulation of olefins and *O-tert*-butoxycarbonyloxy-benzhydroxamates in ee's up to 94%. Further development led to a second generation of ligands bearing an annulated binaphthyl motif on the cyclopentadienyl, which have been used in an enantioselective carbene insertion reaction delivering isoindolones at room temperature.[27d,96c]

The diverse reactivity of phenoxy- and enoxyamides with different catalyst systems under mild conditions further illustrates the potential of oxidizing directing groups in combination with strategic planning and finely tuned reaction conditions. The group of Liu and Lu achieved an intramolecular functional group transfer under Rh catalysis. After alkyne insertion, the acetamide group is transferred from oxygen to carbon *via* O–N bond cleavage to afford enamides as products in what is effectively a carboamination of the alkyne. This process thus avoids the generation of a stoichiometric by-product during the course of the oxidation (Scheme 39).[97a] Under slightly different reaction conditions, the authors instead obtained cyclized benzofuran products, which are also produced in a ruthenium-catalyzed variant of this reaction.[97b] Notably, under iridium catalysis, terminal alkynes could be used as reaction partners, yielding alkynylated phenol products (Scheme 39).[97c]

The Rovis group encountered an intriguing result in the reaction between *N*-enoxyphthalimides and alkenes under rhodium catalysis. Instead of generating β-olefinated ketones, they obtained cyclopropanes in a formal [2+1] annulation where the C–H activation substrate serves as one-carbon component (Scheme 40). Through variation of the cyclopentadienyl ligand on rhodium, they achieved the diastereoselective synthesis of *trans*-disubstituted cyclopropenes.[98a] Further tuning the cyclopentadienyl ligand substitution and reaction conditions, however, resulted in a high selectivity for *trans*-carboamination products from the same starting materials, again incorporating the former oxidizing directing group completely into the product.[98b]

Intrinsically active substrates

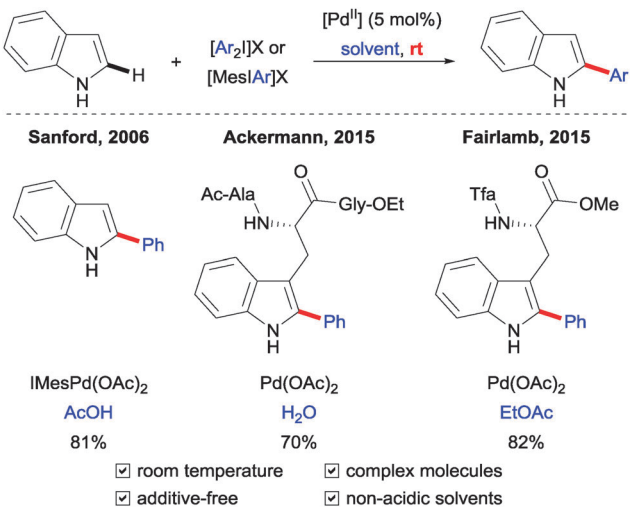
Mild reaction conditions can be a consequence of the intrinsically high reactivity of a substrate either toward C–H activation or in the subsequent functionalization of the organometallic intermediate generated upon C–H activation. In this regard, deprotonative C–H activation is facilitated in substrates containing acidic C–H bonds. On the other hand, metalation at electron-rich positions can lead to strong C–metal bonds, thus driving a C–H metalation equilibrium. Furthermore, electron-rich substrates can afford highly nucleophilic organometallic intermediates, which readily undergo functionalization with electrophilic reaction partners. In this section, selected examples of mild C–H transformations which employ active substrates are presented although it should be noted that many related reactions have been reported and the selection is not exhaustive.

Heterocycles are a highly diverse class of compounds that have received considerable interest as substrates for direct C–H functionalization due to the ubiquity of heterocycles in bioactive compounds. Among the successfully employed compounds, there are both examples of electron-poor heterocycles containing acidic C–H bonds such as (benz)oxazoles ($pK_a < 30$ at C2), and

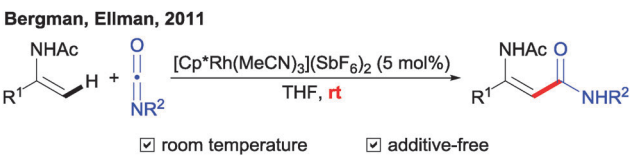
examples of electron-rich, nucleophilic compounds such as indoles. A multitude of methods involving a variety of different C–H activation pathways including deprotonation by an external base, radical mechanisms and electrophilic addition have been developed for a variety of metal catalysts employing intrinsically activated compounds.[99] Determining the operative mechanism of any given transformation can sometimes be difficult, and it may depend on the precise reaction conditions.

The palladium-catalyzed arylation of indoles with diaryliodonium salts can proceed under very mild conditions. In contrast to electron rich phosphine–Pd^0 catalysts that had previously been employed in $Pd^{0/II}$ cycles for the arylation of indoles, the use of more electrophilic Pd^{II} catalysts resulted in increased reactivity and very mild conditions. The proposed mechanism involves an initial electrophilic palladation at the most nucleophilic C3-position of indole, followed by a 1,2-migration of the palladium to the 2-position, which leads to a more stable C–Pd bond. After the original report of this method by the group of Sanford, more recent work by the groups of Ackermann and Fairlamb was focused on using highly-functionalized tryptophan derivatives and oligopeptides for the late-stage functionalization of biologically relevant compounds (Scheme 41).[100] They found that solvents such as water and ethyl acetate can replace the acetic acid reaction medium that was originally employed, thus achieving very mild reaction conditions. Overall, this process is additive-free, uses a benign solvent and proceeds smoothly at room temperature.

The group of Bergman and Ellman disclosed a Rh^{III}-catalyzed, acetamide-directed C–H activation process followed by isocyanate insertion (Scheme 42).[101] The reaction proceeds under additive-free



Scheme 41 Mild Pd-catalyzed indole C–H arylation.[100]

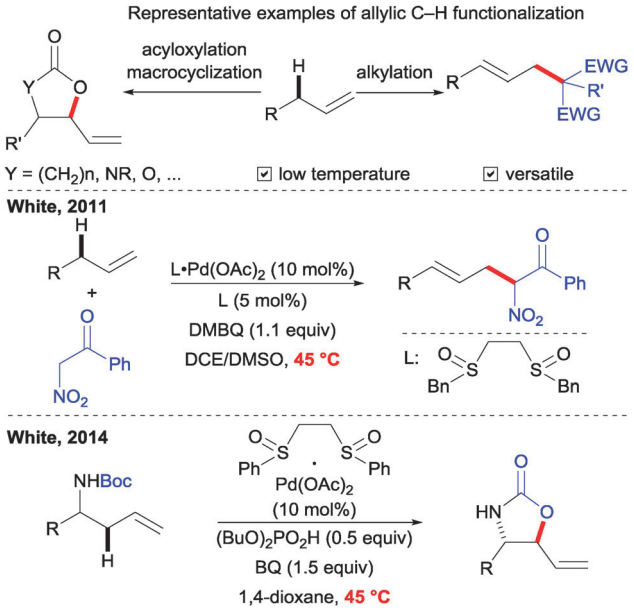


Scheme 42 Mild Rh^{III}-catalyzed enamide C–H activation.[101]

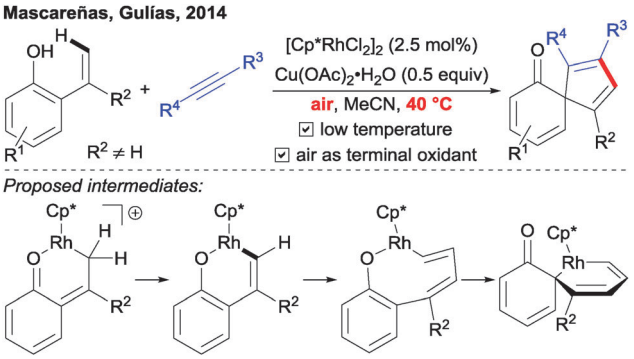
conditions at room temperature using enamide substrates. By contrast, conducting the same reaction with aromatic acetanilide substrates required a higher reaction temperature of 75 °C, demonstrating the increased reactivity of the enamides. Under the reaction conditions, deuterium scrambling was observed at the arene C–H bond of acetanilide, but not for the enamide C–H bond of cyclohexenyl acetamide. Thus, while arene C–H activation is reversible under these conditions, the enamide C–H activation appears to be irreversible. This is most likely due to acceleration of the subsequent nucleophilic addition step to the isonitrile as a result of the increased nucleophilicity of the enamide relative to the arene.

Allylic C–H functionalization has been developed into a mature and versatile field in its own right, often using a catalyst system consisting of Pd^{II} precursors, (bis-)sulfoxide ligands and benzoquinone as a redox-promoter and/or oxidant.[102] Generally, these reactions can be performed at 45 °C or less and proceed with high selectivity for the branched over the linear functionalization products. Remarkably, applications in the late stage syntheses of complex molecules have proven the applicability of this mild methodology.[103] Although a highly optimized catalyst system is employed with finely-tuned ligand properties, the overall "mildness-determining feature" of this class of transformations is the increased reactivity of allylic C–H bonds. The allyl anion is stabilized by conjugation, thus facilitating deprotonation of the substrate. Additionally, the stabilizing η^3-binding mode of Pd in the resulting organometallic intermediate is a further driving force for the C–H cleavage. In a computational study, the C–H activation step itself was found to proceed *via* intramolecular CMD with acetate, in analogy to Pd-catalyzed C–H activations of other substrate classes.[104] We wish to demonstrate the mildness and versatility of the allylic C–H functionalization with two recent examples. Firstly, the allylic alkylation of various alkenes with α-nitroketones was achieved at 45 °C under neutral conditions by taking advantage of a finely-tuned ligand system.[105] A bis-(sulfoxide) ligand promotes the allylic C–H abstraction step, DMSO promotes the consequent functionalization and 2,6-dimethylbenzoquinone (DMBQ) promotes the re-oxidation of the palladium (Scheme 43). White's group dubbed this mechanism involving the proposed switching between specialized weakly coordinating ligands at each intermediate "Serial Ligand Catalysis". Also, an intramolecular cyclization of *N*-Boc protected homoallylic amines was achieved by the addition of a phosphoric acid that assists in the allylic C–H cleavage and activates the resulting allyl–Pd intermediate for attack by the weakly nucleophilic carbamate oxygen. In this process, oxazolidinones were obtained with novel regioselectivities.[106]

The group of Mascareñas and Gulías observed an intriguing result during their studies into Rh^{III}-catalyzed annulation reactions of *ortho*-vinyl phenols with alkynes. When they used geminally disubstituted olefins as substrates, a dearomatizing (3+2) annulation occurred, furnishing spirocyclic products (Scheme 44).[107] In deuteration studies in the absence of the alkyne reaction partner, both terminal hydrogens of the olefin underwent H/D-scrambling. However, in the presence of the



Scheme 43 Selective allylic C–H functionalization.[105,106]

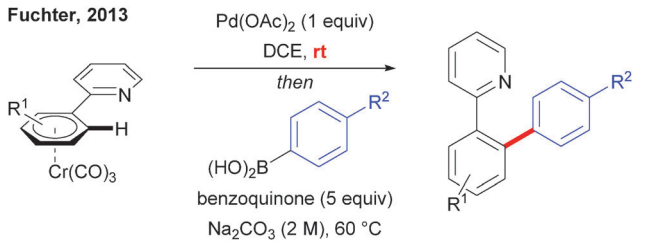


Scheme 44 Rh-catalyzed dearomatizing annulation of *ortho*-vinyl phenol with alkynes.[107]

reaction partner, no deuteration was observed, indicating that C–H cleavage is irreversible under the reaction conditions. The authors proposed a mechanism involving formation of an *ortho*-quinone methide prior to C–H abstraction. Thus, in this special substrate class, the Rh-catalyst can activate C–H bonds by generating a cationic intermediate with highly acidic allylic protons, rather than through an agostic interaction as in CMD-type mechanisms. Due to steric repulsion, the 8-membered metalacycle obtained after alkyne insertion was proposed to isomerize to a more stable spirometalacycle.

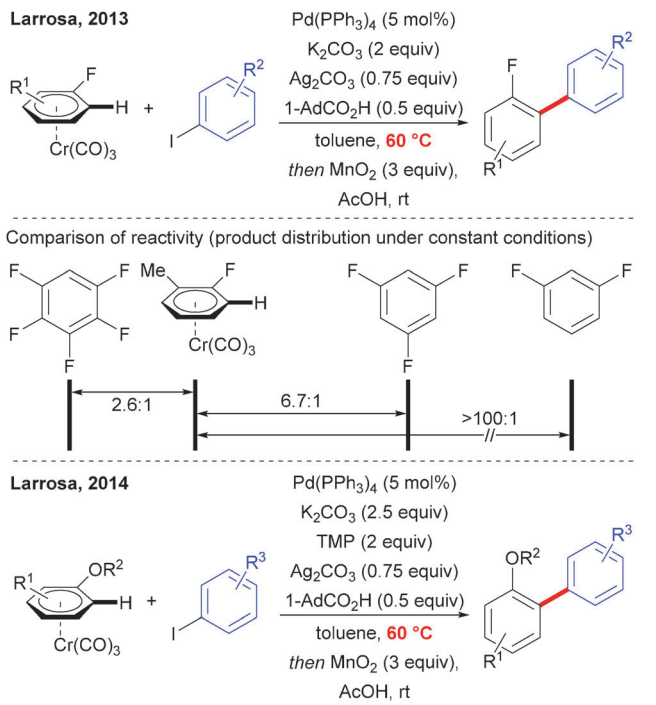
Substrate activation

A very appealing yet rarely applied strategy for achieving mildness in C–H activation is the reversible, temporary activation of one of the reaction partners toward the desired reaction. Despite the potential power of this concept, very few reports successfully employing an *in situ* substrate activation strategy have appeared to date. In 2013, two groups independently reported the C–H arylation of η^6-arene $Cr^0(CO)_3$ complexes with palladium. For several years, the coordination of arenes



Scheme 45 Direct arylation of η^6-arene $Cr^0(CO)_3$ complexes *via* stoichiometric palladation.[109]

to Cr^0 fragments has been known to activate the arene toward nucleophilic aromatic substitution and to increase the acidity of the aryl C–H bonds.[108] Moreover, the stoichiometric C–H cyclometalation of arene Cr^0 complexes with a directing group such as pyridine on the arene had been demonstrated with a number of metals previously, although the conditions employed in these studies were not intrinsically milder than those using non-coordinated arenes. Fuchter and co-workers reasoned that the increased C–H bond acidity should correlate with an increased reactivity toward C–H activation with Pd^{II} and demonstrated a stoichiometric two-step protocol for a room temperature cyclometalation and subsequent arylation with aryl boronic acids (Scheme 45).[109] The group of Larrosa developed a related method for the catalytic direct arylation of arene Cr^0 complexes using a Pd^0 pre-catalyst and aryl iodides as coupling partners (Scheme 46).[110] They did not employ a chelating directing group on the coordinated arene substrates, and instead took advantage of the *ortho* directing effect of a fluorine substituent on palladation. In competition experiments with fluorobenzenes, it was shown that the chromium complexes display increased reactivity toward C–H activation by at



Scheme 46 Substrate activation by Cr^0 complexation in catalytic direct arylation.[110,111] TMP = 2,2,6,6-tetramethylpiperidine.

least two orders of magnitude *versus* the non-complexed arenes. A distortion/interaction analysis based on DFT calculations suggests that the increased reactivity is due to more facile bending of the C–H bond to be activated in the chromium complexes compared to the free arenes. Contrary to the initial hypothesis, the electronic changes to the arene ring upon complexation to chromium are actually detrimental to the C–H activation step. In a subsequent study, the same group extended the Cr^0-complexation strategy to the selective *ortho*-arylation of Cr^0-coordinated alkoxyarenes.[111] Under these conditions, the direct arylation of free anisole is both four orders of magnitude less efficient and less regioselective than the analogous process with the Cr^0 complexed substrate.[112] While the complexation enables the C–H activation of arenes to be carried out at lower temperatures, the conditions of the complexation and the oxidative cleavage of the chromium fragment can be a limitation to functional group tolerance.

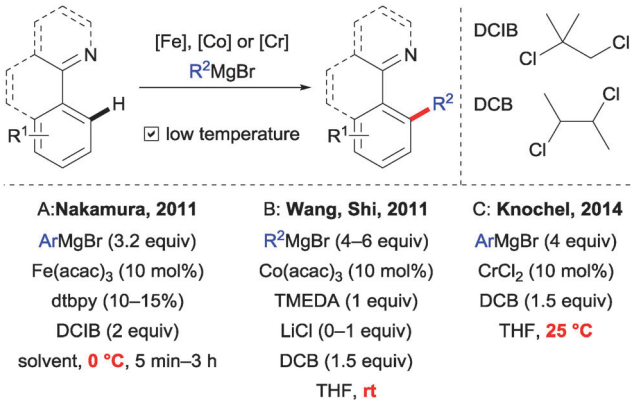
3. Reaction partner

Very mild transformations can result from the combination of an efficient catalyst system and very active reaction partners. With many of the established catalyst systems, C–H activation itself can occur readily at room temperature under certain circumstances as indicated by numerous deuteration studies in the literature. Despite this, most C–H activation methods possess significant kinetic isotope effects, indicating participation of C–H bond breaking in the rate determining step. Reasons for this apparent contradiction include the reversibility of deprotonation-type C–H activation favoring the starting material side of the equilibrium, or that interactions between a reaction partner and the catalyst can inhibit C–H activation, for example by outcompeting substrate binding. These factors are controlled by the specific catalyst structure, additives and reaction partners. When C–H activation is facile, other aspects of a transformation might necessitate higher reaction temperatures or otherwise less mild reaction conditions. Thus, if the reaction partners are highly active in combination with the catalyst system, mild transformations can be achieved. This can either be due to a ready functionalization of the organometallic intermediate or through modification of the catalyst itself by the reaction partner. These latter cases make use of the catalyst activation strategy described earlier with the reaction partner playing a dual role as both reactant and activator.

This chapter on reactive reaction partners encompasses many transformations that do not easily fall into any of the other categories and for which the mildness of the transformation cannot be otherwise explained. In many methods described in other parts of this review, highly active reaction partners are also employed, but, in our opinion, another aspect of the reaction represents the concept of achieving mildness more accurately. The included examples are meant to represent the concepts and we do not seek a comprehensive collection.

Organometallic reagents

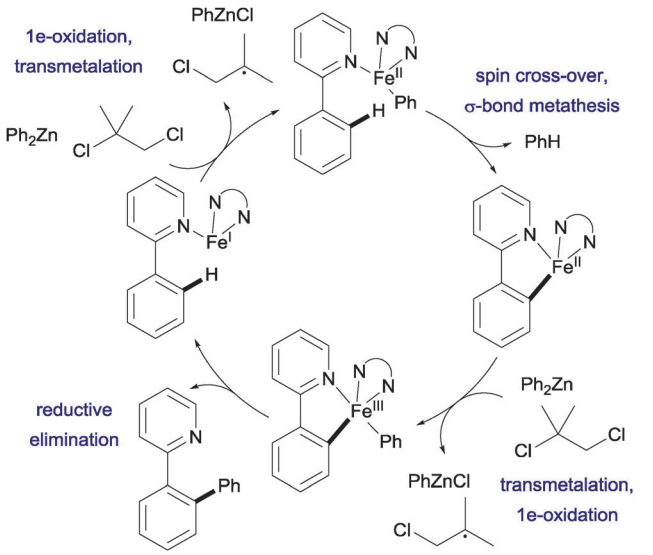
Organo-main group metal compounds are highly reactive reagents in general. In the context of transition metal-catalyzed



Scheme 47 Iron-, cobalt- and chromium-catalyzed directed C–H arylation/alkylation with Grignard reagents.[113,115,117]

C–H functionalization, these compounds find use as catalyst modifiers (*vide supra*) and, especially, as reaction partners for direct coupling processes between the C–H and the C–metal constituents. Several catalyst systems, mostly based on first-row transition metals, have been reported that enable such couplings at or below room temperature. On the other hand, the use of (super)-stoichiometric amounts of reactive organometallic reagents can be a limitation in terms of functional group tolerance and overall practical applicability.

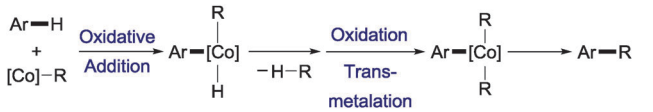
The group of Nakamura presented a series of methods for direct C–H arylation with aryl Grignard or arylzinc reagents under iron catalysis, which proceed at 0 °C in very short reaction times (Scheme 47A).[113] The catalyst system consists of a Fe^{III} pre-catalyst such as $Fe(acac)_3$, the bipyridine ligand dtbpy and dichloroisobutane as an oxidant. Depending on the precise conditions, the Grignard reagents either act themselves as coupling partners or can be first transformed into arylzinc reagents *in situ*. Moreover, the organomagnesium derivatives themselves can be generated *in situ* from the corresponding aryl bromides and elemental magnesium. The latter conditions avoid the presence of stoichiometric amounts of the organometallic reagent, improving the mildness and substrate scope of the transformation.[113f] N-heterocycles, imines and amides have been used as directing groups to activate aryl and vinyl C–H bonds. Mechanistic investigations suggested that the C–H activation event occurs with aryliron species formed upon transmetalation from the aryl Grignard reagent.[113e] The C–C bond-forming reductive elimination from the metalacyclic diaryliron species was found to require the presence of the external oxidant in a stoichiometric experiment. A recent detailed computational study on the arylation with zinc compounds uncovered a unique two-state reactivity of the iron catalyst (Scheme 48).[114] In one likely scenario, the high-spin Fe^{II} reactant complex undergoes C–H cleavage after a spin transition to the low-spin singlet state, returning to the high-spin state after cyclometalation. The actual metalation proceeds *via* σ-bond metathesis, where the proton is transferred to a phenyl ligand on iron simultaneously to the formation of the Fe–C bond. Subsequent to a transmetalation, a one-electron oxidation to Fe^{III} triggers the C–C reductive elimination.



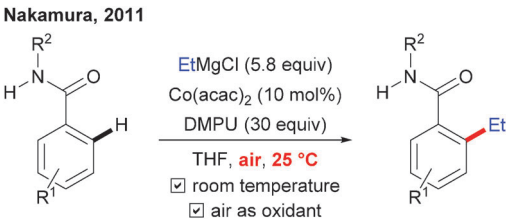
Scheme 48 Proposed mechanism of the Fe-catalyzed C–H arylation.[114]

Direct C–H arylation and even alkylation using Grignard reagents at low temperatures has also been achieved with related catalyst systems based on cobalt and chromium. Wang and Shi presented a method using a catalyst system consisting of $Co(acac)_3$ as pre-catalyst, TMEDA as ligand and 2,3-dichlorobutane (DCB) as oxidant for the arylation and alkylation of benzoquinolines and phenylpyridines at room temperature (Scheme 47B).[115] From mechanistic studies, the involvement of radical pathways was ruled out and a C–H activation pathway involving oxidative addition onto Co^{I}–aryl species was proposed, followed by a sequence of reductive elimination of a hydrocarbon, oxidation, transmetalation and reductive elimination of the product (Scheme 49). In light of the similarity of this reaction to the iron-catalyzed variant, the analogous σ-bond metathesis mechanism is plausible, too. It is interesting to note the differences between iron and cobalt in these related transformations, though. Kinetic isotope effects of 3.1 and 3.4 from intra- and intermolecular competition experiments measured for the iron-catalyzed process suggest a participation of C–H cleavage in the rate determining step.[113g] On the other hand, a KIE of 1.04 was observed in a parallel experiment using cobalt catalysis, suggesting C–H cleavage is not rate limiting.[115]

Subsequently, the group of Nakamura published an alternative procedure for the alkylation of benzamides with alkyl Grignard reagents (Scheme 50).[116] The catalyst system employed in this room temperature transformation consisted of $Co(acac)_2$ and DMPU, while air was used as the sole oxidant. Furthermore, in a report by Knochel and co-workers, $CrCl_2$ was found to catalyze the direct arylation of arenes with N-heterocycle- or imine-based directing



Scheme 49 Proposed mechanism of the cobalt-catalyzed direct coupling.[115]



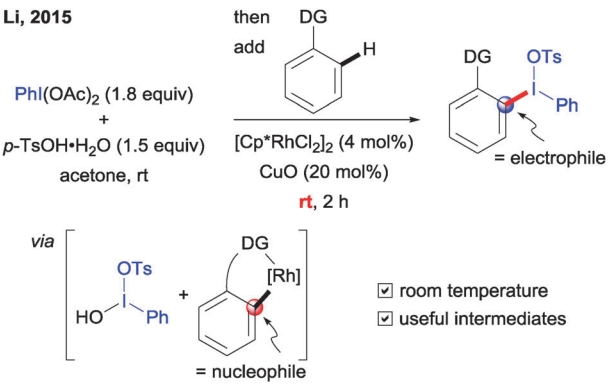
Scheme 50 Cobalt-catalyzed alkylation.[116]

groups at room temperature without additional ligands using DCB as oxidant (Scheme 47C).[117]

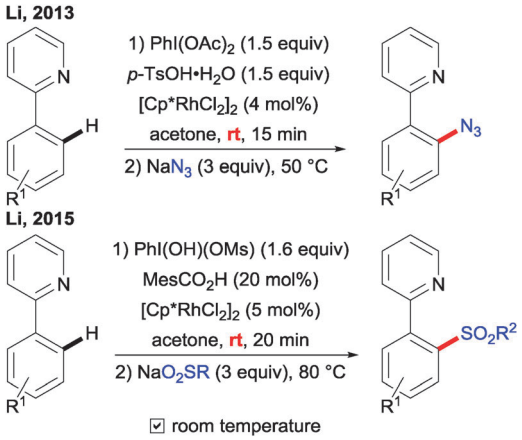
Hypervalent iodine reagents

The use of high-valent iodine compounds is firmly established in organic synthesis due to their high and versatile reactivity. In C–H activation, I^{III} compounds have also proven to be highly active coupling partners enabling mild transformations. The high-valent iodine acts as a strongly electron withdrawing substituent, resulting in electrophilic organic residues that can react readily with organometallic nucleophiles generated upon C–H activation. The Rh^{III}-catalyzed coupling of arenes with high-valent iodine fragments can occur readily at room temperature in very short reaction times, generating diaryliodonium species from $PhI(OAc)_2$ (PIDA) or PhI(OH)(OTs) (Koser's reagent) *via* C–H activation (Scheme 51).[118] This transformation represents an umpolung of the substrate, as the nucleophilic organometallic intermediate is turned into an electrophile in the diaryliodonium product. A number of *in situ* transformations of the generated diaryliodonium species with nucleophiles such as azides, nitrites, halides and sulfonates have been developed (Scheme 52).[119] At first, the intermediacy of diaryliodonium species was not considered in these transformations and mechanisms involving Rh^{V} intermediates were proposed. However, the isolation of diaryliodonium products under similar reaction conditions[119b] and the propensity of these isolated products to react with the same nucleophiles without any catalyst highly suggests this order of events.

In contrast to the C–H hyperiodination process discussed above, the majority of C–H functionalization reactions involving I^{III} reagents proceed through interaction of the metalated

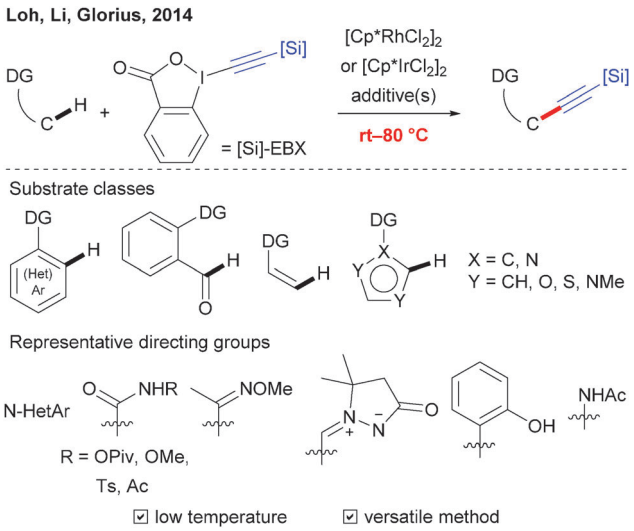


Scheme 51 Mild rhodium-catalyzed hyperiodination.[118]

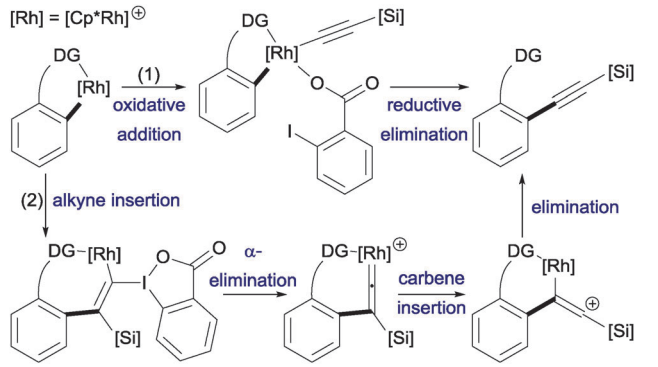


Scheme 52 C–H azidation and sulfonylation *via* Rh-catalyzed hyper-iodination.[119]

substrate with one of the residues on I^{III} rather than with the iodine itself. The C–H alkynylation reaction with alkynyl-substituted iodine(III) reagents (EBX derivatives) is a very general transformation proceeding under exceptionally mild conditions using a range of different catalytic systems. The Cp^*Rh^{III} and Cp^*Ir^{III}-catalyzed directed alkynylation of (hetero)arenes and olefins with TIPS-EBX was independently reported by the groups of Loh, Li and Glorius in 2014 (Scheme 53).[120] This method is compatible with a remarkably wide range of directing groups, demonstrates a broad substrate scope and can be carried out at temperatures between room temperature and 80 °C depending on the substrates.[23d,e] Several mechanisms have been proposed in the literature. Despite the considerable interest in this mild and versatile transformation, evidence regarding the mechanism is still rather scarce. One proposed scenario involves oxidative addition of the hypervalent iodine reagent into the metalacycle formed upon C–H activation followed by a product-releasing reductive elimination from a Rh^V intermediate (Scheme 54(1)). Another proposal invokes an alkyne insertion into the Rh–C



Scheme 53 Mild directed C–H alkynylation.[23d,e,120]



Scheme 54 Proposed mechanisms for the Rh-catalyzed alkynylation.[120]

bond of the metalacycle (Scheme 54(2)). α-Elimination of *o*-iodobenzoate could result in the formation of a Rh–vinylidene intermediate which should rearrange by 1,2-migration or *via* stepwise carbene insertion and elimination to afford the product.

Amination

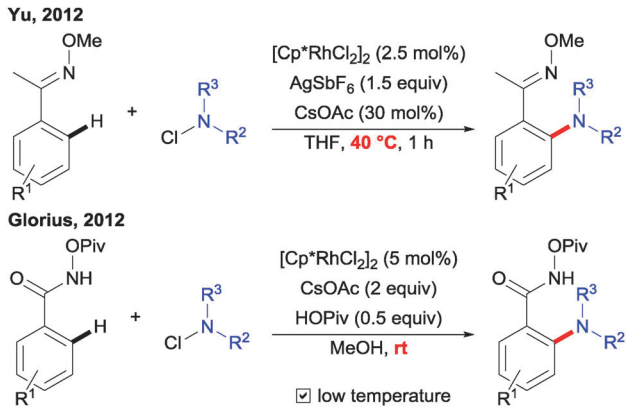
Reliable methods for C–N coupling are of significant importance due to the synthetic utility of amine derivatives and their ubiquitous presence in bioactive compounds. While C–N bond-forming reductive elimination is generally recognized as a challenging step, mild transformations are required for the late stage introduction of nitrogen into complex molecules. In this context, many procedures have been developed for C–H amination or amidation using stoichiometric or *in situ*-generated electrophilic amine reagents or nitrene precursors as highly reactive nitrogen transfer reagents.[121] The reactive nature of these reagents can lead to mild reaction conditions with a wide range of substrates under Ir^{III}, Rh^{III}, Co^{III}, or Ru^{II} catalysis. When preformed amination reagents are employed, no additional oxidant is required, as the overall transformations are redox neutral. On the other hand, the pre-activation steps required to generate the reagents prior to C–H amination can reduce the attractiveness of the overall synthesis.

Electrophilic amination reagents

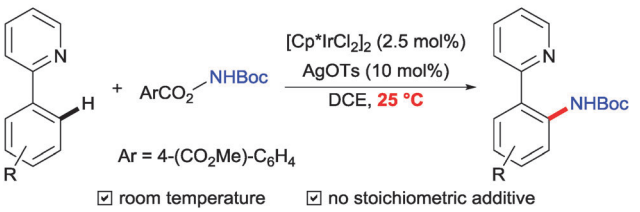
Mild C–N coupling reactions using electrophilic amine reagents were reported simultaneously by the groups of Yu and Glorius[122] using *N*-chloroamines under Cp^*Rh^{III} catalysis (Scheme 55) and later using *N*-aroyloxyamines under ruthenium- and iridium catalysis (Scheme 56).[65,123] The transformation proceeds at temperatures between room temperature and 40 °C and requires no external oxidant. The metalacycle formed upon C–H activation likely reacts as a nucleophile with the electrophilic amine derivatives in a formal nucleophilic substitution at nitrogen, though alternative mechanisms involving oxidative addition of the N–heteroatom bond to the catalyst cannot be completely ruled out.

Nitrene precursors as nitrogen transfer reagents

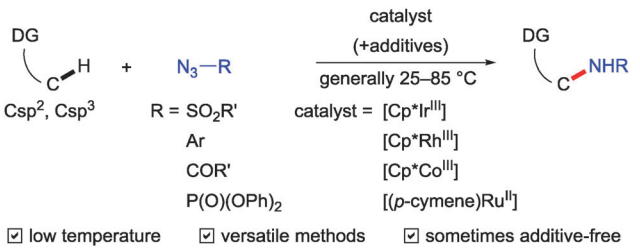
Directed C–H amidation and amination reactions with organic azides as transfer reagents have attracted significant interest



Scheme 55 Rh-catalyzed amination with *N*-chloroamines.[122]



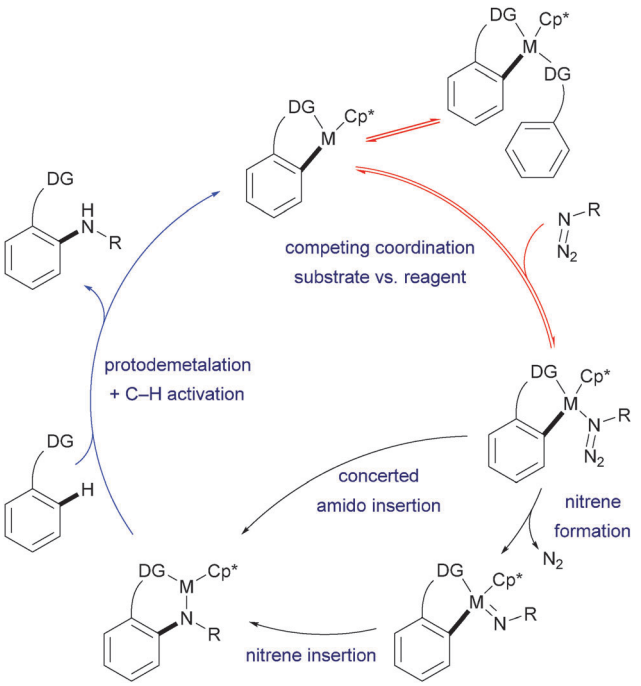
Scheme 56 Mild Ir-catalyzed amination with an electrophilic reagent.[123]



Scheme 57 Directed C–H amidation and amination with organic azides.[121]

due to their broad applicability using a range of catalyst systems, azide derivatives and directing groups (Scheme 57).[121b,c] This development was sparked by the reports of additive-free Cp*Rh^{III} catalyzed sulfonamidation and amination by the group of Chang in 2012 using tosyl azide and aryl azides, respectively.[124] Even milder conditions could be employed in a related amidation reaction using Cp*Ir^{III} catalysts. In this system, the C–N coupling reaction with acyl azides could be carried out at 25 °C without any stoichiometric additives (Scheme 58).[125] Detailed investigations revealed a mechanism proceeding *via* C–H activation, nitrene

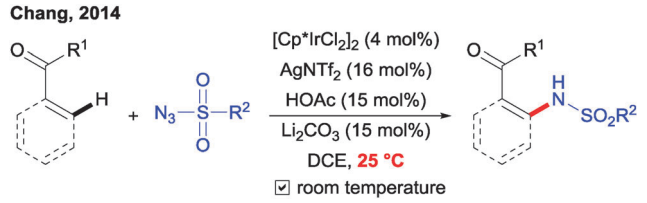
Scheme 58 Mild iridium-catalyzed C–H amidation.[125]



Scheme 59 Proposed mechanism for the directed amidation with organic azides.[126]

formation at the metalacycle and subsequent nitrene insertion into the C–metal bond (Scheme 59).[126] Alternatively, a concerted amido insertion pathway might be relevant under specific conditions. The protodemetalation step, which results in the release of the product molecule, occurs upon C–H activation of another equivalent of the substrate. This process can be rate-limiting depending on the reaction partners, demonstrating the facile nature of the reaction between azides and metalacycles. The thermodynamic gain from the release of dinitrogen in the reaction probably contributes to the mildness of this transformation. Intramolecular hydrogen bonding between the newly-formed N–H moiety and the directing group is proposed to prevent product inhibition as well as difunctionalization. A number of groups extended the amidation strategy to a broader range of transformations including a C(sp^3)–H amidation reaction, ruthenium- and cobalt-catalyzed protocols and a phosphoramidation process.[121] In many of these more challenging reactions, some aspects of mildness had to be compromised to attain reactivity, such as through increasing the reaction temperature or employing acidic or basic additives that influence various parts of the catalytic cycle.

For example, the use of a combination of both basic and acidic additives was optimal for achieving mild Ir-catalyzed C–N coupling reactions using weak directing groups.[127] The initial hypothesis presumed that the binding efficiency of weakly coordinating substrates toward a metal center could be improved in the presence of both base and acid additives. Although basic species are recognized to assist CMD C–H activation, they also coordinate strongly to the metal catalyst and can consequently outcompete substrate binding when weakly coordinating directing groups are employed. Acidic additives, on the other hand, promote dissociation of such



Scheme 60 Amidation of ketone derivatives.[127]

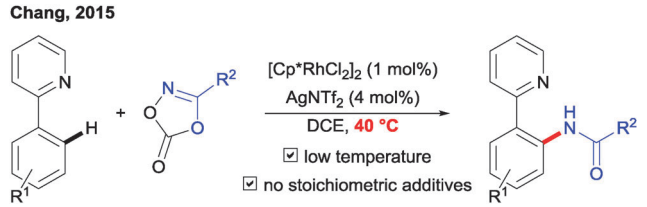
anionic ligands. After optimization, a well-orchestrated catalytic system combining Cp^*Ir^{III} and catalytic amounts of acetic acid and lithium carbonate allowed for a room temperature ketone-directed C–H amidation reaction (Scheme 60).

In search of an even milder and more general system for directed C–H amidation, the group of Chang studied the behavior of nitrene precursors in stoichiometric reactions with preformed rhodacycles. These studies revealed that product formation is inhibited by an excess of the substrate, phenylpyridine, due to preferential binding of the substrate to the rhodium over the benzoyl azide reaction partner (red in Scheme 59). Consequently, they found that aryl dioxazolones, which can also act as nitrene precursors upon extrusion of CO_2, can better compete for coordination to the rhodacycle. While this reagent is a more complex amide source, it can be synthesized easily, and its stability allows safe handling and indefinite storage. Using this insight, an additive-free rhodium-catalyzed amidation of aryl pyridine derivatives at 40 °C was developed with dioxazolones as new amidation reagents (Scheme 61).[128]

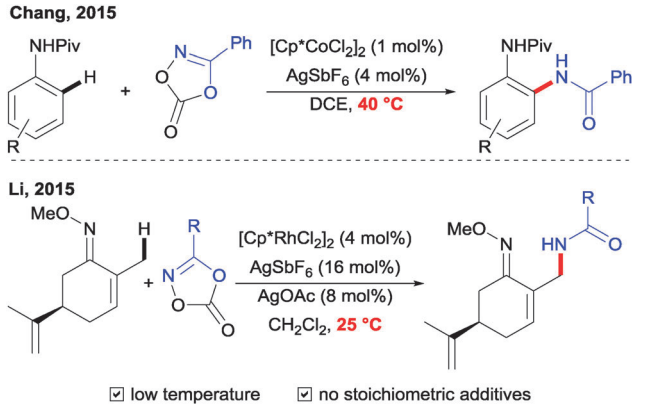
The general utility of dioxazolones as amidating agents was further demonstrated by the development of two room temperature amidation reactions: a cobalt-catalyzed process reported by Chang and co-workers (Scheme 62)[129a] and a rhodium-catalyzed directed C(sp^3)–H functionalization (Scheme 62).[129b] Both of these methods demonstrate the complementarity of the different catalyst metals for different aspects of C–H amidation. Under the conditions for the Co^{III}-catalyzed amidation of anilides, no product was observed with the corresponding Rh^{III} catalyst and lower yields were obtained with Ir^{III}. On the other hand, the rhodium-catalyzed C(sp^3)–H amidation proceeds with the same substrates at lower temperatures than the previously-described amidation with tosyl azides under iridium-catalysis.

Amines and oxidants

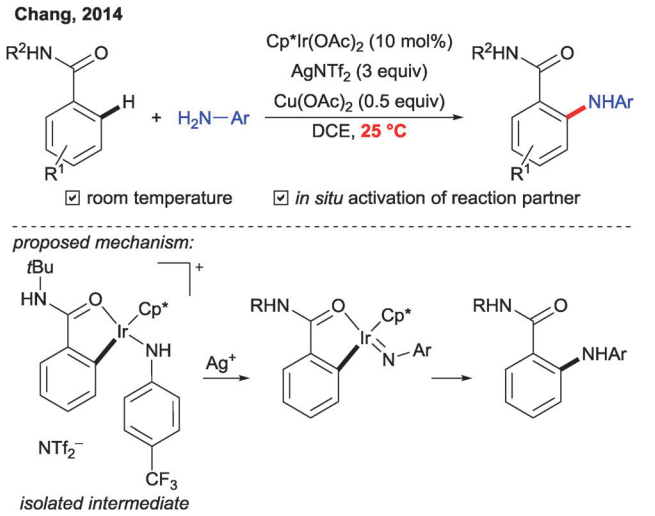
As an alternative to using pre-activated nitrogen coupling partners in C–H amination reactions, the combination of primary amines or amides with oxidants can be employed to generate the active N-transfer reagent *in situ*.



Scheme 61 Mild C–H amidation using dioxazolones.[128]



Scheme 62 Dioxazolones in mild cobalt-catalyzed amidation and C(sp^3)–H amidation.[129]



Scheme 63 Iridium-catalyzed C–H amination with anilines.[130]

The group of Chang found that Cp^*Ir^{III} catalyzes the directed amination of benzamides with anilines at room temperature (Scheme 63), and with primary alkyl amines at a slightly elevated temperature, in the presence of a silver salt oxidant.[130] In contrast to previously-reported palladium- and rhodium-catalyzed amidation methods using external oxidants, they observed no product formation upon using persulfate, [F^+], iodonium salts or any oxidants other than Ag^I either in a stoichiometric reaction with the cyclometalated amido complex or in catalytic reactions. Based on the reactivity of isolated intermediates of the amination reaction, the authors proposed that a nitrene species is generated at the iridacycle *via* stepwise oxidation (Scheme 63). Insertion of the nitrene into the Ir–C bond and protodemetalation then afford the product.

Unsaturated reaction partners

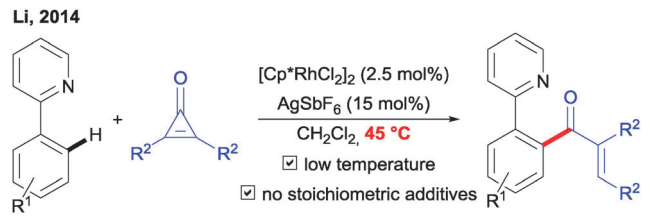
The sequence of C–H activation *via* a deprotonation-type mechanism such as CMD, followed by insertion of an unsaturated

moiety into the C–metal bond and protodemetalation can in principle proceed under additive-free conditions without the generation of side products, if the protons generated from C–H activation engage in the protodemetalation step. Accordingly, a number of reactions using unsaturated coupling partners have been presented that follow this reasoning. In some cases, especially reactive coupling partners enable mild reactions that may be additive-free or run at room temperature.

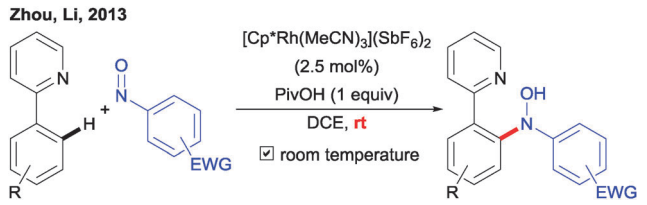
The reaction of polar unsaturated moieties with organometallic species can be represented as a formal insertion into the C–metal bond or as a nucleophilic addition of the organometallic species onto the electrophilic part of the unsaturated system. The use of organo-transition metal nucleophiles generated upon C–H activation can result in more chemoselective and milder transformations than the use of more classical organo-main group metal nucleophiles. This has been demonstrated by the groups of Bergman and Ellman, and Shi in Cp^*Rh^{III}-catalyzed additions of C–H metalated substrates to imines, aldehydes and isocyanates (*vide supra*) under additive-free conditions. Generally, these reactions proceed at slightly elevated temperatures. In addition, the hydroarylation of carbonyl derivatives achieved using these methods can be followed by various cyclization events to afford valuable heterocyclic products. This type of reaction has been already presented in recent reviews and is not discussed in detail here.[23a,131]

Cyclopropenones are highly strained molecules which exhibit an increased reactivity toward rhodacycles compared to ketones. This was demonstrated by the successful development of a low temperature method combining nucleophilic addition to a cyclopropenone, ring-opening and subsequent protodemetalation to generate chalcone derivatives (Scheme 64).[132] Notably, the strained cyclopropenone structure is responsible for the increased reactivity, as regular ketones are not known electrophiles in reactions with rhodacycles. In fact, the potential tertiary alcohol products of such ketone hydroarylation reactions undergo the reverse process affording the ketones and arenes *via* C–C bond cleavage.

Nitroso compounds have proven to be very reactive reaction partners for C–H nucleophilic addition reactions under mild conditions. A room temperature, Rh^{III}-catalyzed hydroarylation of nitrosobenzene was presented with phenyl pyridine derivatives by Zhou and Li in 2013 (Scheme 65).[133] A range of *N*,*N*-diarylhydroxylamines were obtained in this transformation, although electron-withdrawing substituents on the nitrosobenzene reaction partner were required, presumably due to their effect in increasing the electrophilicity of the nitrogen atom. Furthermore, copper-catalyzed oxidation of *N*-hydroxycarbamates can generate similarly



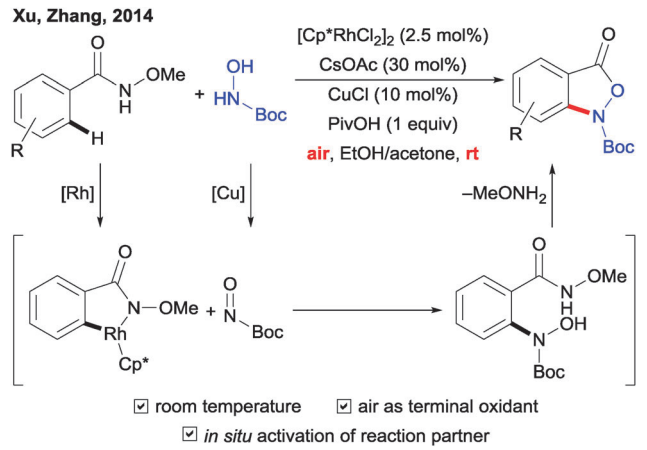
Scheme 64 Chalcone synthesis using cyclopropenones.[132]



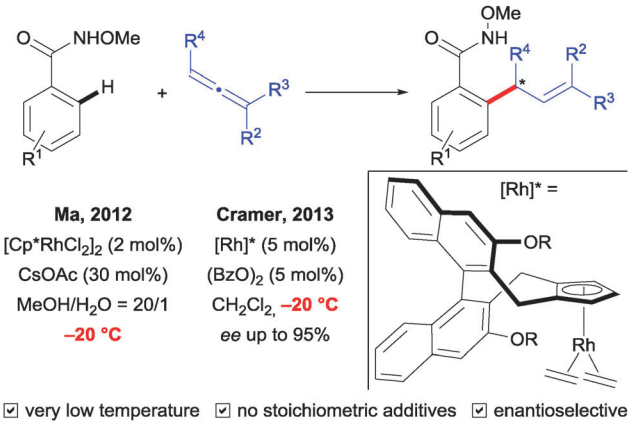
Scheme 65 Mild hydroarylation of nitrosobenzene.[133]

reactive nitrosocarbonyl compounds *in situ*. This process was utilized in a dual Rh/Cu catalytic system for the C–H amination of *N*-methoxybenzamides leading to benzo[*c*]isoxazolones at room temperature.[134] Nitrosoformate derivatives, generated *in situ via* the copper-catalyzed cycle, participate as the electrophile in the hydroarylation process with rhodacycles formed upon *ortho*-C–H bond activation of the *N*-methoxybenzamide. This is followed by a nucleophilic substitution at the directing group, resulting in the formation of an N–O containing heterocycle (Scheme 66).

Olefins are classical coupling partners in C–H activation. Nevertheless, some carbon-based unsaturated moieties possess a higher reactivity toward organometallic intermediates, resulting in overall milder transformations. For example, allenes have been shown simultaneously by the groups of Glorius and Ma to undergo carboamination (*vide supra*) and hydroarylation reactions under exceptionally mild conditions under Cp^*Rh^{III} catalysis, demonstrating an increased reactivity compared to regular olefins.[93,135] The hydroarylation with *O*-methyl benzhydroxamates occurs readily at room temperature and even at −20 °C in what might be a low temperature record in C–H activation. The reaction proceeds with di- and trisubstituted allenes in a highly selective manner, resulting exclusively in the insertion of the lesser substituted double bond and formation of linear allylation products (Scheme 67). Also, axial chirality of the allene can be transferred to central chirality in the allyl product without loss of ee. KIE measurements suggest that C–H bond cleavage is rate determining, signifying the high reactivity of allenes toward rhodacycles. Cramer's group took advantage of the mildness and selectivity of this transformation in an enantioselective allylation



Scheme 66 Dual copper- and rhodium-catalyzed condensation.[134]

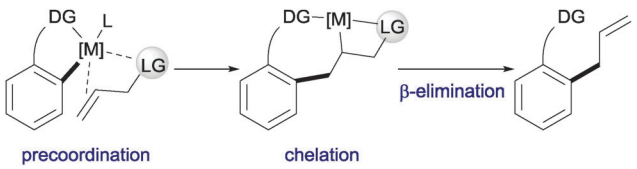


Scheme 67 Mild Rh-catalyzed allylation with allenes.[135,136]

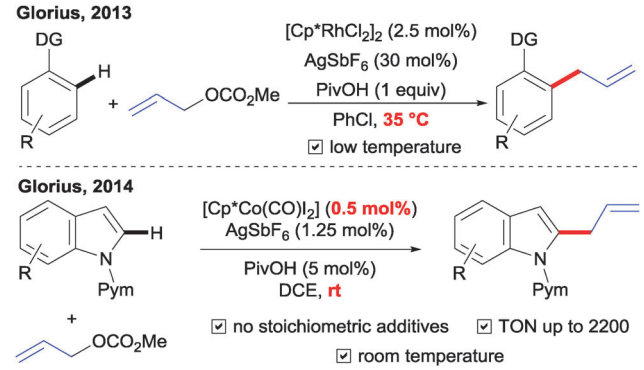
reaction of benzamides using a Rh^{III} complex bearing a chiral Cp derivative as ligand. This process could be conducted smoothly at −20 °C, affording the corresponding allylated arenes with ee's of up to 95% (Scheme 67).[136] In addition, an intramolecular hydroarylation process was developed using olefins tethered to the C–H activation substrate. Using another Cp derivative as a chiral ligand on Rh, high enantioselectivities were achieved at room temperature, demonstrating that the intramolecular alkene insertion is a more efficient process than the corresponding intermolecular variant.[137] Ma's group devised a transformation combining allene carborhodation and subsequent cyclization with a tethered olefin to prepare polycyclic products featuring eight-membered lactams.[138]

Assisted insertion

Direct C–H allylation using allyl transfer reagents carrying a leaving group has been shown to proceed under very mild conditions in a number of rhodium-, ruthenium-, and cobalt-catalyzed, formal S_N-type transformations. While these generally electron-rich olefins would not normally be expected to undergo facile insertion into a C–metal bond, the unifying feature of these reaction partners is the presence of additional donor moieties. Accordingly, insertion of the olefin is facilitated by an initial pre-coordination of the coupling partner to the metal species in a similar fashion to a directing group. Moreover, the resulting organometallic species generated upon insertion is stabilized by chelation (Scheme 68). The allyl moiety is subsequently formed upon β-elimination of the leaving group. The chelation furthermore largely prevents β-H-elimination by forming a rigid coordination environment where all hydrogen atoms are in an almost *trans* arrangement to the metal. If β-H-elimination



Scheme 68 Proposed general mechanistic steps of the coordination-assisted allylation.

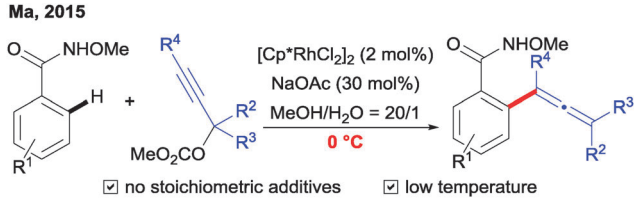


Scheme 69 Mild C–H allylation using allyl carbonates.[139,140]

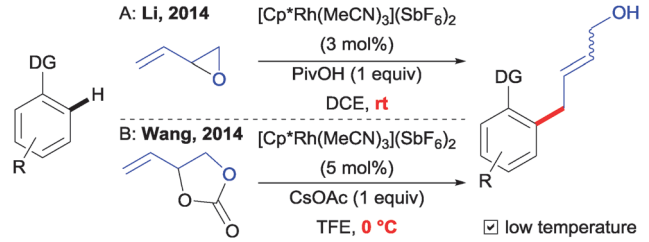
occurs to some extent, the resulting metal hydride species can catalyze isomerization of the allyl products to conjugated styrene derivatives, in what is usually an undesired side-reaction.

Allyl carbonates have been used by the group of Glorius in the directed allylation reaction of various arenes with Cp^*Rh^{III} at 35 °C[139] and in an allylation of *N*-pyrimidyl (Pym) indoles using Cp^*Co^{III} at room temperature.[140] This latter process is successful at remarkably low catalyst loadings with turnover numbers of up to 2200 (Scheme 69). Similarly, allyl acetates were employed as reaction partners in a rare example of a Ru^{II}-catalyzed room temperature C–H functionalization process occurring without additives.[141] The group of Ma employed a similar approach to develop a very mild allenylation reaction of *N*-methoxybenzamides at 0 °C using propargyl carbonates as transfer reagents under Cp^*Rh^{III} catalysis (Scheme 70).[142] The authors proposed that the coordination of rhodium to the carbonate is essential in ensuring regioselective alkyne insertion.

Complementary methods to introduce functionalized allyl moieties have been developed using cyclic reagents capable of undergoing ring opening either due to the presence of an intramolecular leaving group or in order to release ring strain. Thus, vinyloxirane was used as a reaction partner in the synthesis of allylic alcohols at room temperature with Cp^*Rh^{III}.[143] Arenes and heteroarenes bearing a range of directing groups could be employed to generate the corresponding products as *E*/*Z* mixtures with selectivities between 1.5 : 1 and 6.1 : 1 (Scheme 71A). Similar products could also be obtained from vinyl 1,3-dioxolan-2-one using the same catalyst at 0 °C (Scheme 71B).[144] When no further substitution is present on the transfer reagent, the *E*-isomer is formed with >20 : 1 selectivity relative to the *Z* isomer. Geminally di-acceptor substituted vinyl cyclopropanes have been employed in directed allylation reactions at 30 °C using Cp^*Rh^{III}.[145]



Scheme 70 Coordination-assisted allenylation.[142]



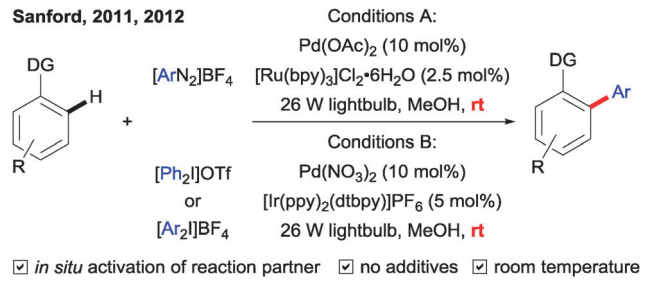
Scheme 71 Synthesis of allylic alcohols by C–H allylation.[143,144]

In this case, product-releasing β-C elimination occurs after assisted olefin insertion into the rhodacycle.

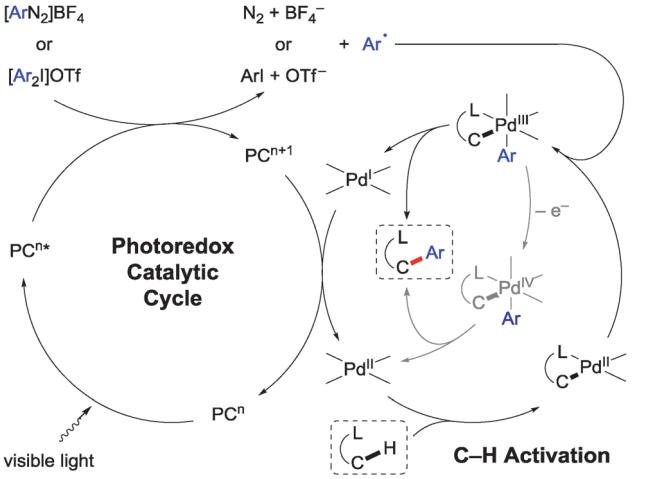
Radicals

The intrinsically high reactivity of radicals makes them interesting reaction partners in catalysis in general. In the context of directed C–H activation, unconventional selectivities may be observed using radicals as coupling partners. Due to the high reactivity of radicals, functionalization of the metalated species generated upon C–H activation is not kinetically relevant and other steps in the process determine the overall mildness. Indeed, besides the C–H activation step itself, radical generation and catalyst oxidation can be "mildness-limiting". Thus, the controlled release of suitable radical species under mild conditions can enable overall mild C–H transformations.

One such approach involves the generation of aryl radicals from diaryliodonium or aryldiazonium salts. These compounds decompose thermally or upon reaction with radical initiators at elevated temperatures and C–H arylation reactions under palladium catalysis have accordingly been described at 100 °C. The group of Sanford devised a dual catalytic process where a photocatalyst is employed to both generate aryl radicals *in situ* and oxidize palladium during the subsequent arylation of an appropriate substrate. The authors proposed that the visible light-promoted radical generation should occur under milder conditions than the thermal or ionic pathways employed in previous methods. Combining Pd-catalyzed C–H activation with photocatalysis for the first time, the directed C–H arylation of various arene derivatives with aryldiazonium salts was achieved at room temperature using $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as a photocatalyst and $Pd(OAc)_2$ as a C–H activation catalyst under irradiation with light from by a 26 W compact fluorescent lamp (CFL, Scheme 72A).[146] N-Heterocycles, amides and oximes were used as directing groups and generally no further additives,



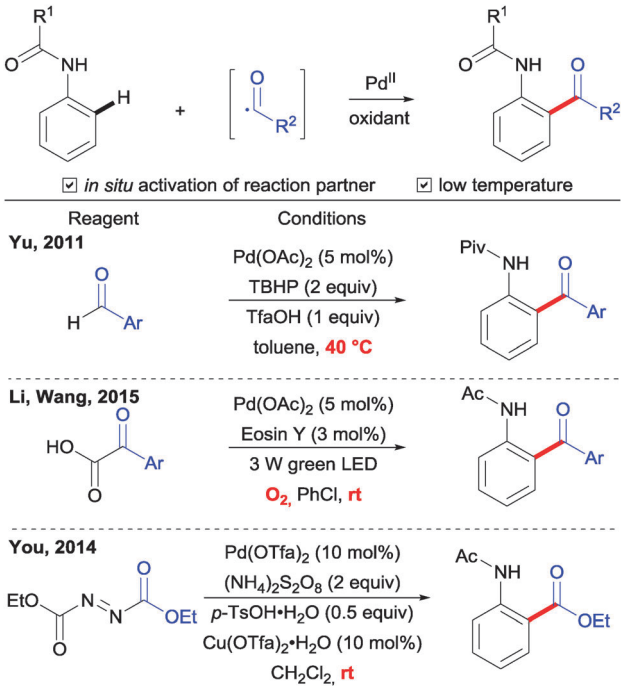
Scheme 72 Mild arylation *via* dual C–H activation and photocatalysis.[146,147]



Scheme 73 Proposed mechanisms of the dual palladium- and photocatalytic C–H arylation.[146,148]

such as oxidants or bases, were required. Furthermore, a room temperature arylation process with easier-to-handle diaryliodonium salts was also developed using an Ir-based photocatalyst and $Pd(NO_3)_2$ (Scheme 72B).[147] The two protocols show complementary reactivity with some DGs, such as benzamides and oximes, but generally perform similarly with most demonstrated substrates. Experimental evidence suggests a radical mechanism in both methods. The authors proposed that a Pd^{III} species is generated upon radical addition to the metalacycle and that single electron oxidation to Pd^{IV} with concomitant regeneration the ground state photocatalyst precedes reductive elimination of the product (Scheme 73, grey pathway). A computational study by the group of Malacria later suggested a different order of events (Scheme 73, black pathway), where reductive elimination of the product occurs directly from the Pd^{III} intermediate generated upon radical addition and that subsequent oxidation of the resulting Pd^{I} species regenerates both the photo- and the C–H activation catalysts.[148]

Palladium-catalyzed C–H carbonylation and carboxylation reactions have also been proposed to involve the generation of acyl radicals under oxidative conditions. While many such transformations require high reaction temperatures or strongly oxidizing conditions, the choice of suitable precursors and oxidants can result in much milder methods. Thus, the *ortho*-acylation of anilides at 40 °C was reported using *tert*-butyl hydroperoxide as oxidant and (hetero)aryl- or alkyl aldehydes as acylating reagents (Scheme 74).[149] Later, α-ketocarboxylic acids were similarly used as precursors for acyl radicals in Pd^{II}-catalyzed directed acylation at room temperature.[150] In this reaction, an organic photocatalyst (Eosin Y) was employed to facilitate visible light-promoted oxidative decarboxylation of the ketoacids in another example of dual photoredox/C–H activation catalysis. *ortho*-Carboxylation of anilides at room temperature was realized by the oxidative decomposition of diethyl azodicarboxylate (DEAD), generating ethoxyacyl radicals.[151] Ammonium peroxodisulfate and a catalytic amount of a Cu^{II} salt were found to be the optimal oxidants for this process.

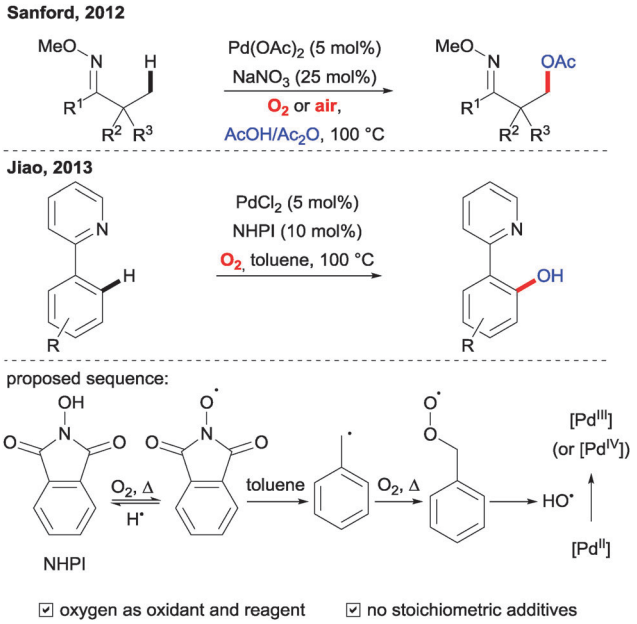


Scheme 74 Mild Pd-catalyzed C–H functionalization employing acyl radicals.[149–151]

In each of these transformations, experimental evidence was presented to support the involvement of radical species as the coupling partner for the C–H palladated species.

4. Oxidant

C–H activation reactions may be redox-neutral and hence not require the presence of an external oxidant to achieve catalytic turnover. However, in numerous transformations such as dehydrogenative coupling, reoxidation of the catalyst is necessary. The well-known Wacker process is an early example of redox co-catalysis, where a catalyst is re-oxidized to its active form after a reductive step in the mechanism by a redox catalyst. The redox catalyst in turn is then re-oxidized by a stoichiometric oxidant, preferably dioxygen from air. The feasibility of such a process is poorly rationalized in many cases and depends on the specific reaction conditions and redox potentials of the species involved, which in turn are affected by any additives and reactants present. For this reason, a number of redox catalysts have been investigated in the literature and sometimes air or oxygen can even be used as oxidant without an additional mediator. In most cases, however, oxidative C–H transformations still rely on the presence of (super)stoichiometric amounts of oxidants, which can be problematic in terms of functional group tolerance, waste generation and cost. In addition to numerous examples presented throughout the review where we commented on the use of air or oxygen as oxidant, we wish to demonstrate some recent examples employing redox co-catalysis or directly using air as the oxidant. For a more detailed discussion on this matter, the reader is referred to other recent reviews.[152]

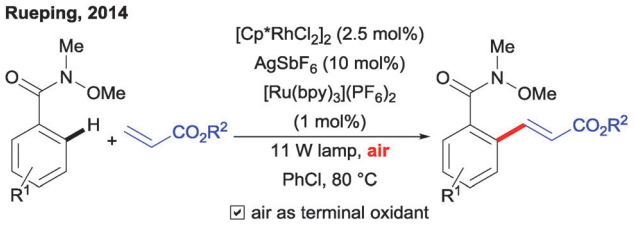


Scheme 75 Redox co-catalysts in Pd-catalyzed C–H activation.[153,155]

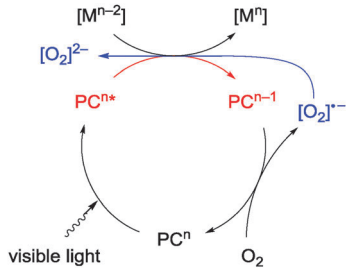
The group of Sanford presented a method for the acyloxylation of C(sp^3)–H bonds using air as terminal oxidant which employed nitrate salts as redox co-catalysts (Scheme 75).[153] In using this system, stoichiometric amounts of the iodine(III) reagent $PhI(OAc)_2$, which is commonly used as the oxidant in such transformations, could be avoided. They proposed that a secondary NO_2/NO cycle mediates the oxidation of Pd^{II} to Pd^{IV} in the C–H activation cycle. Together with recent results from the Stahl group who employed fuming nitric acid as redox mediators in a benzene acetoxylation,[154] these results can also have interesting implications considering the common presence of nitrate impurities in commercial $Pd(OAc)_2$. Another approach to redox co-catalysis was taken by Jiao's group with *N*-hydroxyphthalimide (NHPI), which can initiate a sequence of steps resulting in the generation of hydroxyl radicals from oxygen (Scheme 75).[155] These hydroxyl radicals, in turn, then oxidize the C–H activation catalyst to a high-valent hydroxo species which then undergoes reductive elimination forming hydroxylated products. In this transformation, the redox-co-catalyst enables the use of oxygen as both a terminal oxidant and reactant.

The group of Rueping demonstrated that photoredox catalysis can be employed to replace stoichiometric oxidant additives by air in C–H activation catalysis.[156] Ru and Ir based photocatalysts were employed to effect oxidation of the metal after a reductive step in Rh^{III}- and Ru^{II}-catalyzed oxidative olefinations as well as in the Pd^{II}-catalyzed indole synthesis originally reported by Glorius (Scheme 76).[157] As proposed by the authors, re-oxidation can either proceed directly with the excited photocatalyst (Scheme 77, red) or *via* superoxide anions generated upon single electron reduction of dioxygen by the reduced photocatalyst (Scheme 77, blue).[156]

A strategy for facilitating directed Pd-catalyzed C–H activation reactions conducted in the presence of heterocycles that relies on the relatively inefficient oxidation of Pd^0 by air was

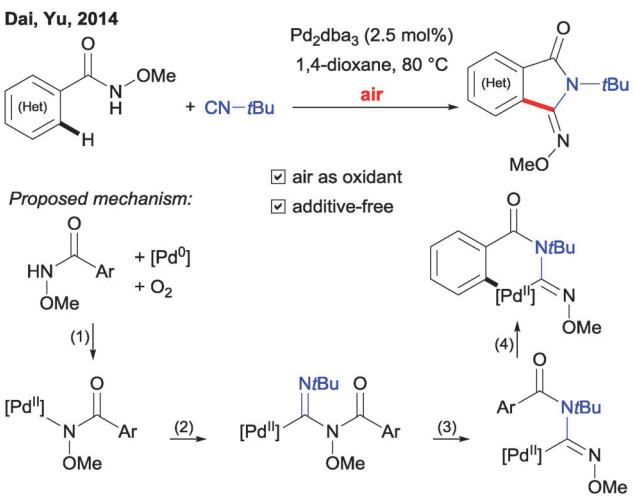


Scheme 76 Rh^{III}-catalyzed oxidative olefination using photoredox catalysis to replace stoichiometric amounts of oxidant with air.[156]

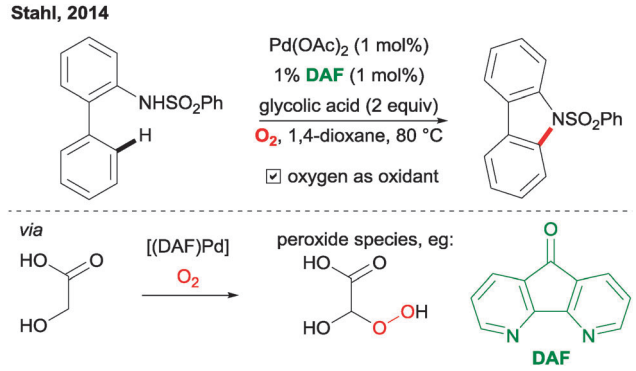


Scheme 77 Generalized scheme of the proposed metal reoxidation mechanisms under photoredox catalysis.[156]

demonstrated by the group of Dai and Yu.[158] They argued that while heterocycles bind strongly to Pd^{II}, thus inhibiting transformations in their presence, a lower affinity for Pd^{0} would allow exchange between the heterocycles and the *O*-methyl hydroxamate directing group present in their substrates. Furthermore, the hydroxamate should become an anionic ligand on deprotonation, thereby aiding the oxidation and binding strongly to Pd. Thus, by keeping the catalyst resting state in the lower oxidation state, catalyst saturation would be prevented because the oxidation to Pd^{II} should only occur once the metal is bound by the directing group. This concept was demonstrated in an annulation reaction with *tert*-butyl isonitrile affording iminoisoindolones (Scheme 78) which was proposed to proceed *via* oxidation to Pd^{II} and coordination to the directing group (1), isonitrile insertion (2), acyl migration (3), C–H activation (4) and, finally, reductive



Scheme 78 Pd-catalyzed iminoisoindolinone synthesis under air.[158]

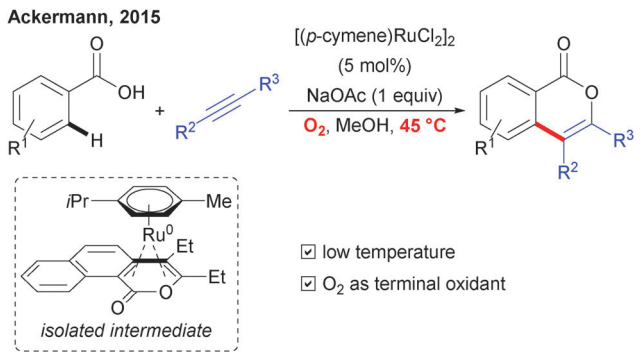


Scheme 79 Intramolecular C–H amination with oxygen as oxidant.[160]

elimination. A very recent computational study confirmed this order of events and highlighted the crucial role of the *O*-methyl hydroxamate for the success of this transformation as it can be easily oxidized.[159]

For several years, the group of Stahl has been working on technologies for the use of air and oxygen as terminal oxidants in C–H functionalization and oxidation catalysis, especially with palladium and copper.[152a] Building on insight gained from detailed mechanistic studies, they introduced 4,5-diazafluorenone (DAF) and related non-innocent redox active compounds as potent ligands facilitating oxidation of palladium. Among other transformations, they investigated an intramolecular Pd-catalyzed C–H amination of 2-aminobiphenyl derivatives affording carbazoles using oxygen in 1,4-dioxane (Scheme 79).[160] Noticing decomposition of the solvent under the reaction conditions, they observed that glycolic acid had an accelerating effect on the desired transformation. Glycolic acid can be formed by autoxidation of 1,4-dioxane and can itself be oxidized to peroxide species under the reaction conditions, thus aiding the catalyst re-oxidation.

In some cases, oxidative C–H functionalization can also be carried out under air or oxygen without a redox co-catalyst system or special ligand. Often, the success of this process is difficult to predict and results from a judicious combination of the reaction conditions and reagents or products. One such example is an annulation reaction forming isocoumarins from benzoic acids and alkynes under Ru^{II}-catalysis reported by the group of Ackermann (Scheme 80).[161] This reaction proceeds



Scheme 80 Ru-catalyzed oxidative annulation reaction employing oxygen.[161]

at low temperatures using oxygen (or even air) as oxidant. Stoichiometric transformations with isolated ruthenacycles led to the observation and isolation of Ru^0–isocoumarin complexes, giving an opportunity to separately study the re-oxidation step. No reaction occurred in the presence of oxygen, $Cu(OAc)_2 \cdot H_2O$ or NaOAc alone, and further studies revealed that acetic acid is required for re-oxidation to occur.

Conclusion

As is evident from the many impressive examples discussed in the previous sections, the field of C–H activation has come a long way over the last few decades. Whereas harsh reaction conditions were once considered obligatory to achieve reasonable reactivity, nowadays efficient C–H transformations can often be conducted at or below ambient temperature, in the absence of acidic or basic additives and/or without strong external oxidants. In this review, we have sought to provide an update of this field by collecting together examples of mild C–H activation reactions disclosed since 2011. By categorizing the examples according to the conceptual strategies they have employed, we have also tried to demonstrate how greater insight into the mechanistic aspects of C–H activation has led to an improved understanding of how modifications to the substrate, reaction partners and catalyst can affect reactivity at each stage of the catalytic cycle.

For example, installing internal oxidants onto the substrate directing groups avoids the need for additional external oxidizing agents, while several room temperature reactions have been conducted employing olefinic reaction partners which bear carbonyl moieties capable of pre-coordinating the metal center. Furthermore, significant recent advances have been made using ancillary ligands to modulate catalyst reactivity. In Pd catalysis, MPAA ligands pioneered by the Yu group may assist C–H bond cleavage by acting as intramolecular proton shuttles, while σ-donating ligands can enhance oxidative addition-type C–H activation by increasing the electron richness of low-valent metal centers. The recent studies employing less well-established first-row transition metals such iron and cobalt as catalysts for C–H transformations have also opened up new promising avenues for investigation.

We hope that by providing an overview of the current state of the art and outlining the conceptual similarities between them, this review will act as a useful guide to the community and inspire future developments toward truly mild C–H transformations.

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Notes and references

1 For selected general reviews on C–H activation see: (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (*b*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292; (*c*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345; (*d*) D. Zhao, J. You and C. Hu, *Chem. – Eur. J.*, 2011, **17**, 5466–5492; (*e*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761; (*f*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814–825; (*g*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918; (*h*) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 10236–10254; (*i*) K. M. Engle and J.-Q. Yu, *J. Org. Chem.*, 2013, **78**, 8927–8955; (*j*) N. Kuhl, N. Schröder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443–1460; (*k*) F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Chem. Commun.*, 2015, **51**, 7986–7995; (*l*) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev.*, 2015, **115**, 12138–12204; (*m*) *C–H Bond Activation and Catalytic Functionalization I*, ed. P. H. Dixneuf and H. Doucet, Springer International Publishing, Cham, 2016, vol. 55; (*n*) *C–H Bond Activation and Catalytic Functionalization II*, ed. P. H. Dixneuf and H. Doucet, Springer International Publishing, Cham, 2016, vol. 56; (*o*) B. Zhao, Z. Shi and Y. Yuan, *Chem. Rec.*, 2016, DOI: 10.1002/tcr.201500241.

2 For selected reviews concerning the application of the C–H activation see: (*a*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885–1898; (*b*) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362–3374; (*c*) D. Y.-K. Chen and S. W. Youn, *Chem. – Eur. J.*, 2012, **18**, 9452–9474; (*d*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960–9009; (*e*) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369–375; (*f*) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2015, **54**, 66–81; (*g*) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.

3 For selected publications on mechanisms of C–H activation, see: (*a*) D. L. Davies, S. M. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754–13755; (*b*) S. I. Gorelsky, D. Lapointe and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 10848–10849; (*c*) D. Balcells, E. Clot and O. Eisenstein, *Chem. Rev.*, 2010, **110**, 749–823; (*d*) D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1118–1126; (*e*) S. I. Gorelsky, *Coord. Chem. Rev.*, 2013, **257**, 153–164; (*f*) K. T. C. Carr, S. A. Macgregor and C. L. McMullin, *Top. Organomet. Chem.*, 2016, **55**, 53–76; (*g*) W. D. Jones, *Top. Organomet. Chem.*, 2016, **56**, 67–89.

4 (*a*) F. Yang, F. Song, W. Li, J. Lan and J. You, *RSC Adv.*, 2013, **3**, 9649–9652; (*b*) Z. She, Y. Shi, Y. Huang, Y. Cheng, F. Song and J. You, *Chem. Commun.*, 2014, **50**, 13914–13916.

5 D. Munz, M. Webster-Gardiner, R. Fu, T. Strassner, W. A. Goddard III and T. B. Gunnoe, *ACS Catal.*, 2015, **5**, 769–775.

6 P. Gandeepan and C.-H. Cheng, *J. Am. Chem. Soc.*, 2012, **134**, 5738–5741.

7 T.-S. Jiang and G.-W. Wang, *J. Org. Chem.*, 2012, **77**, 9504–9509.

8 For selected early examples see: (*a*) B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**,

4882–4886; (*b*) D. H. Wang, K. M. Engle, B.-F. Shi and J.-Q. Yu, *Science*, 2010, **327**, 315–319; (*c*) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 460–461; (*d*) Y. Lu, D.-H. Wang, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 5916–5921.

9 D. G. Musaev, A. Kaledin, B.-F. Shi and J.-Q. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 1690–1698.

10 (*a*) K. M. Engle, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 14137–14151; (*b*) R. D. Baxter, D. Sale, K. M. Engle, J.-Q. Yu and D. G. Blackmond, *J. Am. Chem. Soc.*, 2012, **134**, 4600–4606.

11 For selected reviews on asymmetric C–H activation see: (*a*) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272; (*b*) N. Cramer, *Chimia*, 2012, **66**, 869–872; (*c*) J. Wencel-Delord and F. Colobert, *Chem. – Eur. J.*, 2013, **19**, 14010–14017; (*d*) C. Zheng and S.-L. You, *RSC Adv.*, 2014, **4**, 6173–6214; (*e*) J. Wencel-Delord and F. Colobert, *Synlett*, 2015, **26**, 2644–2658.

12 (*a*) L. Chu, X.-C. Wang, C. E. Moore, A. L. Rheingold and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 16344–16347; (*b*) L. Chu, K.-J. Xiao and J.-Q. Yu, *Science*, 2014, **346**, 451–455; For mechanistic studies, see: (*c*) M.-J. Zhou, T.-L. Yang and L. Dang, *J. Org. Chem.*, 2016, **81**, 1006–1020.

13 (*a*) Y. Izawa and S. S. Stahl, *Adv. Synth. Catal.*, 2010, **352**, 3223–3229; (*b*) D. Wang, Y. Izawa and S. S. Stahl, *J. Am. Chem. Soc.*, 2014, **136**, 9914–9917.

14 Y. Kuninobu, T. Iwanaga, T. Omura and K. Takai, *Angew. Chem., Int. Ed.*, 2013, **52**, 4431–4434.

15 Recent reviews on Pd^{IV} chemistry: (*a*) K. Muñiz, *Angew. Chem., Int. Ed.*, 2009, **48**, 9412–9423; (*b*) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712–733; (*c*) P. Sehnal, R. J. K. Taylor and I. J. S. Fairlamb, *Chem. Rev.*, 2010, **110**, 824–889; (*d*) A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177–185. Pd^{III} in catalysis: (*e*) D. C. Powers and T. Ritter, *Top. Organomet. Chem.*, 2011, **35**, 129–156; (*f*) D. C. Powers and T. Ritter, *Acc. Chem. Res.*, 2012, **45**, 840–850.

16 J. J. Topczewski and M. S. Sanford, *Chem. Sci.*, 2015, **6**, 70–76.

17 K. L. Hull, E. L. Lanni and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 14047–14049.

18 (*a*) J. M. Racowski, N. D. Ball and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18022–18025; (*b*) A. Maleckis, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2013, **135**, 6618–6625.

19 (*a*) C. F. Rosewall, P. A. Sibbald, D. V. Liskin and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 9488–9489; (*b*) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 15945–15951.

20 X. Wang, D. Leow and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 13864–13867.

21 K. M. Engle, T.-S. Mei, X. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1478–1491.

22 R. Alam, L. T. Pilarski, E. Pershagen and K. J. Szabó, *J. Am. Chem. Soc.*, 2012, **134**, 8778–8781.

23 For selected reviews see: (*a*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624–655; (*b*) T. Satoh and M. Miura, *Chem. – Eur. J.*, 2010, **16**, 11212–11222; (*c*) F. W. Patureau, J. Wencel-Delord and F. Glorius, *Aldrichimica Acta*, 2012, **45**, 31–41; (*d*) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007–1020; (*e*) J. Wencel-Delord, F. W. Patureau and F. Glorius, *Top. Organomet. Chem.*, 2016, **55**, 1–28.

24 Y. Shibata and K. Tanaka, *Angew. Chem., Int. Ed.*, 2011, **50**, 10917–10921.

25 (*a*) Y. Hoshino, Y. Shibata and K. Tanaka, *Adv. Synth. Catal.*, 2014, **356**, 1577–1585; (*b*) M. Fukui, Y. Hoshino, T. Satoh, M. Miura and K. Tanaka, *Adv. Synth. Catal.*, 2014, **356**, 1638–1644.

26 (*a*) Y. Takahama, Y. Shibata and K. Tanaka, *Chem. – Eur. J.*, 2015, **21**, 9053–9056; (*b*) F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9982–9983.

27 (*a*) T. K. Hyster and T. Rovis, *Chem. Sci.*, 2011, **2**, 1606–1610; (*b*) T. K. Hyster and T. Rovis, *Chem. Commun.*, 2011, **47**, 11846–11848; (*c*) N. Umeda, K. Hirano, T. Satoh, N. Shibata, H. Sato and M. Miura, *J. Org. Chem.*, 2011, **76**, 13–24; (*d*) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308–1318.

28 S. Kawamorita, T. Miyazaki, H. Ohmiya, T. Iwai and M. Sawamura, *J. Am. Chem. Soc.*, 2011, **133**, 19310–19313.

29 E. C. Keske, B. D. Moore, O. V. Zenkina, R. Wang, G. Schatte and C. M. Crudden, *Chem. Commun.*, 2014, **50**, 9883–9886.

30 (*a*) C. Cheng and J. F. Hartwig, *Science*, 2014, **343**, 853–857; (*b*) C. Cheng and J. F. Hartwig, *Chem. Rev.*, 2015, **115**, 8946–8975.

31 (*a*) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 390–391; (*b*) T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 14263–14278.

32 T. Ishiyama, Y. Nobuta, J. F. Hartwig and N. Miyaura, *Chem. Commun.*, 2003, 2924–2925.

33 S. M. Preshlock, B. Ghaffari, P. E. Maligres, S. W. Krska, R. E. Maleczka Jr. and M. R. Smith III, *J. Am. Chem. Soc.*, 2013, **135**, 7572–7582.

34 M. A. Larsen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 4287–4299.

35 S. A. Sadler, H. Tajuddin, I. A. I. Mkhalid, A. S. Batsanov, D. Albesa-Jove, M. Sing Cheung, A. C. Maxwell, L. Shukla, B. Roberts, D. C. Blakemore, Z. Lin, T. B. Marder and P. G. Steel, *Org. Biomol. Chem.*, 2014, **12**, 7318–7327.

36 (*a*) S. Hwan Cho and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 8157–8160; (*b*) C. W. Liskey and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 3375–3378; (*c*) C. W. Liskey and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 12422–12425.

37 S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka and M. Sawamura, *J. Am. Chem. Soc.*, 2009, **131**, 5058–5059.

38 S. Kawamorita, R. Murakami, T. Iwai and M. Sawamura, *J. Am. Chem. Soc.*, 2013, **135**, 2947–2950.

39 Y. Kuninobu, H. Ida, M. Nishi and M. Kanai, *Nat. Chem.*, 2015, **7**, 712–717.

40 (*a*) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295; (*b*) C. Bruneau and P. H. Dixneuf, *Top. Organomet. Chem.*, 2016, **55**, 137–188; (*c*) S. Dana, M. R. Yadav and A. K. Sahoo, *Top. Organomet. Chem.*, 2016, **55**, 189–216.

41 F. Kakiuchi, T. Kochi, E. Mizushima and S. Murai, *J. Am. Chem. Soc.*, 2010, **132**, 17741–17750.

42 J. Zhang, A. Ugrinov and P. Zhao, *Angew. Chem., Int. Ed.*, 2013, **52**, 6681–6684.

43 Selected reviews: (*a*) A. A. Kulkarni and O. Daugulis, *Synthesis*, 2009, **24**, 4087–4109; (*b*) J. J. Mousseau and A. B. Charette, *Acc. Chem. Res.*, 2013, **46**, 412–424; (*c*) T. K. Hyster, *Catal. Lett.*, 2015, **145**, 458–467; (*d*) Y. Liang, Y.-F. Liang and N. Jiao, *Org. Chem. Front.*, 2015, **2**, 403–415; (*e*) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, **48**, 886–896. Manganese: (*f*) C. Wang, *Synlett*, 2013, **24**, 1606–1613. Iron: (*g*) E. Nakamura and N. Yoshikai, *J. Org. Chem.*, 2010, **75**, 6061–6067; (*h*) I. Bauer and H.-J. Knölker, *Chem. Rev.*, 2015, **115**, 3170–3387; (*i*) L. Ilies and E. Nakamura, *Top. Organomet. Chem.*, 2016, **56**, 1–18. Cobalt: (*j*) K. Gao and N. Yoshikai, *Acc. Chem. Res.*, 2014, **47**, 1208–1219; (*k*) L. Ackermann, *J. Org. Chem.*, 2014, **79**, 8948–8954; (*l*) N. Yoshikai, *ChemCatChem*, 2015, **7**, 732–734; (*m*) M. Moselage, J. Li and L. Ackermann, *ACS Catal.*, 2016, **6**, 498–525. Nickel: (*n*) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299–309; (*o*) X.-H. Cai and B. Xie, *ARKIVOC*, 2015, 184–211; (*p*) N. Chatani, *Top. Organomet. Chem.*, 2016, **56**, 19–46. Copper: (*q*) M. Zhang, *Appl. Organomet. Chem.*, 2010, **24**, 269–284; (*r*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062–11087; (*s*) R. T. Gephart III and T. H. Warren, *Organometallics*, 2012, **31**, 7728–7752; (*t*) K. Hirano and M. Miura, *Chem. Lett.*, 2015, **44**, 868–873; (*u*) K. Hirano and M. Miura, *Top. Organomet. Chem.*, 2016, **56**, 47–65.

44 K. Gao, P.-S. Lee, T. Fujita and N. Yoshikai, *J. Am. Chem. Soc.*, 2010, **132**, 12249–12251.

45 P.-S. Lee, T. Fujita and N. Yoshikai, *J. Am. Chem. Soc.*, 2011, **133**, 17283–17295.

46 (*a*) Q. Chen, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 428–429; (*b*) Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, *Org. Lett.*, 2011, **13**, 3232–3234.

47 K. Gao, T. Yamakawa and N. Yoshikai, *Synthesis*, 2014, **46**, 2024–2039.

48 (*a*) Z. Ding and N. Yoshikai, *Org. Lett.*, 2010, **12**, 4180–4183; (*b*) Z. Ding and N. Yoshikai, *Synthesis*, 2011, 2561–2566; (*c*) Z. Ding and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2012, **51**, 4698–4701.

49 K. Gao and N. Yoshikai, *J. Am. Chem. Soc.*, 2011, **133**, 400–402.

50 (*a*) P.-S. Lee and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 1240–1244; (*b*) J. Dong, P.-S. Lee and N. Yoshikai, *Chem. Lett.*, 2013, **42**, 1140–1142.

51 K. Gao and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2011, **50**, 6888–6892.

52 K. Gao, P.-S. Lee, C. Long and N. Yoshikai, *Org. Lett.*, 2012, **14**, 4234–4237.

53 K. Gao and N. Yoshikai, *J. Am. Chem. Soc.*, 2013, **135**, 9279–9282.

54 K. Gao, R. Paira and N. Yoshikai, *Adv. Synth. Catal.*, 2014, **356**, 1486–1490.

55 W. Song and L. Ackermann, *Angew. Chem., Int. Ed.*, 2012, **51**, 8251–8254.

56 B. Punji, W. Song, G. A. Shevchenko and L. Ackermann, *Chem. – Eur. J.*, 2013, **19**, 10605–10610.

57 M. Moselage, N. Sauermann, S. C. Richter and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 6352–6355.

58 S. Asako, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2013, **135**, 17755–17757.

59 S. Asako, J. Norinder, L. Ilies, N. Yoshikai and E. Nakamura, *Adv. Synth. Catal.*, 2014, **356**, 1481–1485.

60 (*a*) E. R. Fruchey, B. M. Monks and S. P. Cook, *J. Am. Chem. Soc.*, 2014, **136**, 13130–13133; (*b*) B. M. Monks, E. R. Fruchey and S. P. Cook, *Angew. Chem., Int. Ed.*, 2014, **53**, 11065–11069.

61 (*a*) Q. Gu, H. H. Al Mamari, K. Graczyk, E. Diers and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 3868–3871; (*b*) G. Cera, T. Haven and L. Ackermann, *Angew. Chem., Int. Ed.*, 2016, **55**, 1484–1488.

62 (*a*) C. Wang and Y. Huang, *Synlett*, 2012, **24**, 145–149; (*b*) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.*, 2014, **1**, 843–895; (*c*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107–1295.

63 Selected reviews: (*a*) J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527–2572; (*b*) M. Albrecht, in *C–H bond Activation: From Palladacycles: Synthesis, Characterisation and Applications*, ed. J. Dupont and M. Pfeffer, 2008, pp. 13–34; (*c*) M. Albrecht, *Chem. Rev.*, 2010, **110**, 576–623; (*d*) Y. F. Han and G.-X. Jin, *Chem. Soc. Rev.*, 2014, **43**, 2799–2823.

64 (*a*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (*b*) S. De Sarkar, W. Liu, S. I. Kozhushkov and L. Ackermann, *Adv. Synth. Catal.*, 2014, **356**, 1461–1479.

65 M. Shang, S.-H. Zeng, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *Org. Lett.*, 2013, **15**, 5286–5289.

66 F. Péron, C. Fossey, J. Sopkova-de Oliveira Santos, T. Cailly and F. Fabis, *Chem. – Eur. J.*, 2014, **20**, 7507–7513.

67 J. Guan, G.-J. Wu and F.-S. Han, *Chem. – Eur. J.*, 2014, **20**, 3301–3305.

68 Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao and F.-S. Han, *J. Am. Chem. Soc.*, 2015, **137**, 632–635.

69 M. J. Tredwell, M. Gulias, N. Gaunt Bremeyer, C. C. C. Johansson, B. S. L. Collins and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 1076–1079.

70 J. Wencel-Delord and F. Colobert, *Org. Chem. Front.*, 2016, **3**, 394–400.

71 (*a*) Q. Dherbassy, G. Schwertz, M. Chessé, C. K. Hazra, J. Wencel-Delord and F. Colobert, *Chem. – Eur. J.*, 2016, **22**, 1735–1743; for pioneering work see: (*b*) T. Wesch, F. R. Leroux and F. Colobert, *Adv. Synth. Catal.*, 2013, **355**, 2139–2144.

72 C. K. Hazra, Q. Dherbassy, J. Wencel-Delord and F. Colobert, *Angew. Chem., Int. Ed.*, 2014, **53**, 13871–13875.

73 C. Zhu, Y. Zhang, J. Kan, H. Zhao and W. Su, *Org. Lett.*, 2015, **17**, 3418–3421.

74 For a related example of direct functionalization of benzoic acid occuring preferentially in HFIP see: (*a*) G. Cheng, T.-J. Li and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 10950–10953. For a related example of mild dehydrogenative cross-coupling of arenes bearing carbonyl DGs occuring in HFIP see: (*b*) C. Zhang and Y. Rao, *Org. Lett.*, 2015, **17**, 4456–4459.
75 B. Liu, Y. Fang, Y. Gao, C. Sun, C. Xu and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 468–473.
76 (*a*) D. Zhao, S. Vásquez-Céspedes and F. Glorius, *Angew. Chem., Int. Ed.*, 2015, **54**, 1657–1661; (*b*) M. J. Ajitha and K. Huang, *Organometallics*, 2016, **35**, 450–455.
77 (*a*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726–11743; (*b*) L. C. M. Castro and N. Chatani, *Chem. Lett.*, 2015, **44**, 410–421.
78 H. Tang, X.-R. Huang, J. Yao and H. Chen, *J. Org. Chem.*, 2015, **80**, 4672–4682.
79 For selected reviews on C(sp^3)–H activation see: (*a*) C. Li, *Acc. Chem. Res.*, 2009, **42**, 335–344; (*b*) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74–100; (*c*) G. Qiu and J. Wu, *Org. Chem. Front.*, 2015, **2**, 169–178; (*d*) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064; (*e*) R. K. Rit, M. R. Yadav, K. Ghosh and A. K. Sahoo, *Tetrahedron*, 2015, **71**, 4450–4459; (*f*) W. Zhang, N.-X. Wang and Y. Xing, *Synlett*, 2015, **26**, 2088–2098.
80 R. K. Rit, M. R. Yadav and A. K. Sahoo, *Org. Lett.*, 2012, **14**, 3724–3727.
81 O. G. Mancheño and C. Bolm, *Chem. – Eur. J.*, 2007, **13**, 6674–6681.
82 R. K. Rit, M. R. Yadav and A. K. Sahoo, *Org. Lett.*, 2014, **16**, 968–971.
83 H.-Y. Xiong, T. Besset, D. Cahard and X. Pannecoucke, *J. Org. Chem.*, 2015, **80**, 4204–4212.
84 L. Grigorjeva and O. Daugulis, *Angew. Chem., Int. Ed.*, 2014, **53**, 10209–10212.
85 (*a*) L. Grigorjeva and O. Daugulis, *Org. Lett.*, 2014, **16**, 4684–4687; (*b*) L. Grigorjeva and O. Daugulis, *Org. Lett.*, 2014, **16**, 4688–4690.
86 (*a*) F. W. Patureau and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1977–1979; (*b*) H. Huang, X. Ji, W. Wu and H. Jiang, *Chem. Soc. Rev.*, 2015, **44**, 1155–1171; (*c*) J. Mo, L. Wang, Y. Liu and X. Cui, *Synthesis*, 2015, **47**, 439–459.
87 (*a*) T. Gerfaud, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2009, **48**, 572–577; (*b*) J. Wu, X. Cui, L. Chen, G. Jiang and Y. Wu, *J. Am. Chem. Soc.*, 2009, **131**, 13888–13889; (*c*) Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676–3677.
88 N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908–6909.
89 (*a*) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350–2353; (*b*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449–6457.
90 L. Xu, Q. Zhu, G. Huang, B. Cheng and Y. Xia, *J. Org. Chem.*, 2012, **77**, 3017–3024.
91 S. R. Neufeldt, G. Jiménez-Osés, J. R. Huckins, O. R. Thiel and K. N. Houk, *J. Am. Chem. Soc.*, 2015, **137**, 9843–9854.
92 (*a*) B. Li, H. Feng, S. Xu and B. Wang, *Chem. – Eur. J.*, 2011, **17**, 12573–12577; (*b*) B. Li, J. Ma, N. Wang, H. Feng, S. Xu and B. Wang, *Org. Lett.*, 2012, **14**, 736–739.
93 H. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 7318–7322.
94 (*a*) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 19592–19595; (*b*) M. Presset, D. Oehlrich, F. Rombouts and G. A. Molander, *Org. Lett.*, 2013, **15**, 1528–1531.
95 (*a*) T. K. Hyster, K. E. Ruhl and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 5364–5367; (*b*) S. Cui, Y. Zhang, D. Wang and Q. Wu, *Chem. Sci.*, 2013, **4**, 3912–3916.
96 (*a*) T. K. Hyster, L. Knorr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500–503; (*b*) B. Ye and N. Cramer, *Science*, 2012, **338**, 504–506; (*c*) B. Ye and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 7896–7899.
97 (*a*) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6033–6037; (*b*) Z. Zhou, G. Liu, Y. Shen and X. Lu, *Org. Chem. Front.*, 2014, **1**, 1161–1165; (*c*) J. Zhou, J. Shi, Z. Qi, X. Li, H. E. Xu and W. Yi, *ACS Catal.*, 2015, **5**, 6999–7003.
98 (*a*) T. Piou and T. Rovis, *J. Am. Chem. Soc.*, 2014, **136**, 11292–11295; (*b*) T. Piou and T. Rovis, *Nature*, 2015, **527**, 86–90.
99 (*a*) A. H. Sandtorv, *Adv. Synth. Catal.*, 2015, **357**, 2403–2435; (*b*) F. Bellina, *Top. Organomet. Chem.*, 2016, **55**, 77–102; (*c*) J.-F. Soulé and H. Doucet, *Top. Organomet. Chem.*, 2016, **55**, 103–118.
100 (*a*) N. R. Deprez, D. Kalyani, A. Krause and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 4972–4973; (*b*) Y. Zhu, M. Bauer and L. Ackermann, *Chem. – Eur. J.*, 2015, **21**, 9980–9983; (*c*) A. J. Reay, T. J. Williams and I. J. S. Fairlamb, *Org. Biomol. Chem.*, 2015, **13**, 8298–8309.
101 K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430–11433.
102 (*a*) G. Liu and Y. Wu, *Top. Curr. Chem.*, 2010, **292**, 195–209; (*b*) C. J. Engelin and P. Fristrup, *Molecules*, 2011, **16**, 951–969.
103 E. M. Stang and M. C. White, *Nat. Chem.*, 2009, **1**, 547–551.
104 C. Engelin, T. Jensen, S. Rodriguez-Rodriguez and P. Fristrup, *ACS Catal.*, 2013, **3**, 294–302.
105 A. J. Young and M. C. White, *Angew. Chem., Int. Ed.*, 2011, **50**, 6824–6827.
106 T. J. Osberger and M. C. White, *J. Am. Chem. Soc.*, 2014, **136**, 11176–11181.
107 A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas and M. Gulías, *J. Am. Chem. Soc.*, 2014, **136**, 7607–7610.
108 F. Hu and M. Szostak, *ChemCatChem*, 2015, **7**, 1061–1063.
109 M. J. Fuchter, D. K. Judge, M. Weimar and A. J. P. White, *Dalton Trans.*, 2013, **42**, 5615–5618.
110 P. Ricci, K. Krämer, X. C. Cambeiro and I. Larrosa, *J. Am. Chem. Soc.*, 2013, **135**, 13258–13261.
111 P. Ricci, K. Krämer and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 18082–18086.

112 M. Lafrance and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 16496–16497.
113 (*a*) J. Norinder, A. Matsumoto, N. Yoshikai and E. Nakamura, *J. Am. Chem. Soc.*, 2008, **130**, 5858–5859; (*b*) N. Yoshikai, A. Matsumoto, J. Norinder and E. Nakamura, *Angew. Chem., Int. Ed.*, 2009, **48**, 2925–2928; (*c*) N. Yoshikai, A. Matsumoto, J. Norinder and E. Nakamura, *Synlett*, 2010, 313–316; (*d*) L. Ilies, S. Asako and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 7672–7675; (*e*) N. Yoshikai, S. Asako, T. Yamakawa, L. Ilies and E. Nakamura, *Chem. – Asian J.*, 2011, **6**, 3059–3065; (*f*) L. Ilies, M. Kobayashi, A. Matsumoto, N. Yoshikai and E. Nakamura, *Adv. Synth. Catal.*, 2012, **354**, 593–596; (*g*) L. Ilies, E. Konno, Q. Chen and E. Nakamura, *Asian J. Org. Chem.*, 2012, **1**, 142–145.
114 Y. Sun, H. Tang, K. Chen, L. Hu, J. Yao, S. Shaik and H. Chen, *J. Am. Chem. Soc.*, 2016, **138**, 3715–3730.
115 B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1109–1113.
116 Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, *Org. Lett.*, 2011, **13**, 3232–3234.
117 O. M. Kuzmina and P. Knochel, *Org. Lett.*, 2014, **16**, 5208–5211.
118 F. Xie, Z. Zhang, X. Yu, G. Tang and X. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 7405–7409.
119 (*a*) F. Xie, Z. Qi and X. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 11862–11866; (*b*) F. Wang, X. Yu, Z. Qi and X. Li, *Chem. – Eur. J.*, 2016, **22**, 511–516.
120 (*a*) F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780–4787; (*b*) C. Feng and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2014, **53**, 2722–2726; (*c*) K. D. Collins, F. Lied and F. Glorius, *Chem. Commun.*, 2014, **50**, 4459–4461.
121 (*a*) M.-L. Louillat and F. W. Patureau, *Chem. Soc. Rev.*, 2014, **43**, 901–910; (*b*) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040–1052; (*c*) J. G. Kim, K. Shin and S. Chang, *Top. Organomet. Chem.*, 2016, **55**, 29–51.
122 (*a*) K.-H. Ng, Z. Zhou and W.-Y. Yu, *Org. Lett.*, 2012, **14**, 272–275; (*b*) C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2012, **14**, 656–659.
123 P. Patel and S. Chang, *Org. Lett.*, 2014, **16**, 3328–3331.
124 (*a*) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 9110–9113; (*b*) J. Ryu, K. Shin, S. H. Park, J. Y. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 9904–9908.
125 J. Ryu, J. Kwak, K. Shin, D. Lee and S. Chang, *J. Am. Chem. Soc.*, 2013, **135**, 12861–12868.
126 (*a*) S. H. Park, J. Kwak, K. Shin, J. Ryu, Y. Park and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 2492–2502; (*b*) T. M. Figg, S. Park, J. Park, S. Chang and D. G. Musaev, *Organometallics*, 2014, **33**, 4076–4085.
127 J. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2014, **53**, 2203–2207.
128 Y. Park, K. T. Park, J. G. Kim and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 4534–4542.
129 (*a*) J. Park and S. Chang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14103–14107; (*b*) H. Wang, G. Tang and X. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 13049–13052.
130 (*a*) H. Kim, K. Shin and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 5904–5907; (*b*) H. Kim and S. Chang, *ACS Catal.*, 2015, **5**, 6665–6669.
131 X.-S. Zhang, K. Chen and Z.-J. Shi, *Chem. Sci.*, 2014, **5**, 2146–2159.
132 S. Yu and X. Li, *Org. Lett.*, 2014, **16**, 1220–1223.
133 B. Zhou, J. Du, Y. Yang, H. Feng and Y. Li, *Org. Lett.*, 2013, **15**, 6302–6305.
134 W. Yang, J. Sun, X. Xu, Q. Zhang and Q. Liu, *Chem. Commun.*, 2014, **50**, 4420–4422.
135 R. Zeng, C. Fu and S. Ma, *J. Am. Chem. Soc.*, 2012, **134**, 9597–9600.
136 B. Ye and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135**, 636–639.
137 B. Ye, P. A. Donets and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 507–511.
138 S. Wu, R. Zeng, C. Fu, Y. Yu, X. Zhang and S. Ma, *Chem. Sci.*, 2015, **6**, 2275–2285.
139 H. Wang, N. Schröder and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 5386–5389.
140 (*a*) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17722–17725; (*b*) T. Gensch, S. Vásquez-Céspedes, D.-G. Yu and F. Glorius, *Org. Lett.*, 2015, **17**, 3714–3717.
141 R. Manikandan, P. Madasamy and M. Jeganmohan, *Chem. – Eur. J.*, 2015, **21**, 13934–13938.
142 S. Wu, X. Huang, W. Wu, P. Li, C. Fu and S. Ma, *Nat. Commun.*, 2015, **6**, 7946.
143 S. Yu and X. Li, *Org. Lett.*, 2014, **16**, 1200–1203.
144 S.-S. Zhang, J.-Q. Wu, Y.-X. Lao, X.-G. Liu, Y. Liu, W.-X. Lv, D.-H. Tan, Y.-F. Zeng and H. Wang, *Org. Lett.*, 2014, **16**, 6412–6415.
145 J.-Q. Wu, Z.-P. Qiu, S.-S. Zhang, J.-G. Liu, Y.-X. Lao, L.-Q. Gu, Z.-S. Huang, J. Li and H. Wang, *Chem. Commun.*, 2015, **51**, 77–80.
146 D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18566–18569.
147 S. R. Neufeldt and M. S. Sanford, *Adv. Synth. Catal.*, 2012, **354**, 3517–3522.
148 G. Maestri, M. Malacria and E. Derat, *Chem. Commun.*, 2013, **49**, 10424–10426.
149 C.-W. Chan, Z. Zhou and W.-Y. Yu, *Adv. Synth. Catal.*, 2011, **353**, 2999–3006.
150 (*a*) C. Zhou, P. Li, X. Zhu and L. Wang, *Org. Lett.*, 2015, **17**, 6198–6201; (*b*) N. Xu, P. Li, Z. Xie and L. Wang, *Chem. – Eur. J.*, 2016, **22**, 2236–2242.
151 Y. Huang, G. Li, J. Huang and J. You, *Org. Chem. Front.*, 2014, **1**, 347–350.
152 (*a*) A. N. Campbell and S. S. Stahl, *Acc. Chem. Res.*, 2012, **45**, 851–863; (*b*) W. Wu and H. Jiang, *Acc. Chem. Res.*, 2012, **45**, 1736–1748; (*c*) N. Gulzar, B. Schweitzer-Chaput and M. Klussmann, *Catal. Sci. Technol.*, 2014, **4**, 2778–2796; (*d*) O. Baslé, in *From C–H to C–C Bonds: Cross-Dehydrogenative-Coupling*, ed. C.-J. Li, Royal Society of Chemistry, 2015, pp. 197–218.
153 K. J. Stowers, A. Kubota and M. S. Sanford, *Chem. Sci.*, 2012, **3**, 3192–3195.
154 S. L. Zultanski and S. S. Stahl, *J. Organomet. Chem.*, 2015, **793**, 263–268.

155 Y. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 5827–5831.
156 (*a*) D. C. Fabry, J. Zoller, S. Raja and M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **53**, 10228–10231; (*b*) J. Zoller, D. C. Fabry, M. A. Ronge and M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **53**, 13264–13268; (*c*) D. C. Fabry, M. A. Ronge, J. Zoller and M. Rueping, *Angew. Chem., Int. Ed.*, 2015, **54**, 2801–2805.
157 S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230–7233.
158 Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai and J.-Q. Yu, *Nature*, 2014, **515**, 389–393.
159 Y. Dang, X. Deng, J. Guo, C. Song, W. Hu and Z.-X. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 2712–2723.
160 A. B. Weinstein and S. S. Stahl, *Catal. Sci. Technol.*, 2014, **4**, 4301–4307.
161 S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 5513–5517.

