Transition metal-catalysed directed C–H functionalisation with nucleophiles

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Abstract:

The quest for sustainable ways of introducing diverse functional groups onto complex scaffolds has made directed transition metal-catalysed C–H functionalisation reactions a main thrust within synthetic organic chemistry. These methodologies offer appealing opportunities for constructing carbon–carbon and carbon–heteroatom bonds by using a wide array of coupling partners. Strikingly, organometallic and X-based (X = N, O, S) nucleophiles, which are key reagents in cross-coupling reactions, remain underexploited in these transformations. However, as a result of fine-tuning the reaction conditions and a better understanding of the underlying mechanisms, these reagents have been recently incorporated into the synthetic toolkit of C–H functionalisations. This Review outlines a selection of recent advances in nucleophilic C–C and C–heteroatom bond-forming reactions via directed C–H activation. We focus on catalytic approaches involving organometallic nucleophiles and X-based (X = N, O, S) coupling partners and describe how the field has evolved towards innovative strategies that enhance the applicability and versatility of these transformations. In addition, we highlight synthetic challenges that remain unsolved and that could open exciting venues within this area.

Introduction

The discovery of sustainable methodologies that enable the access to highly demanded building blocks for modern life, from pharmaceuticals to agrochemicals, constitutes a key goal for the chemical community. In this context, since the second half of the 20th century, transition metal (TM) catalysis has unlocked innovative synthetic ways of forming chemical bonds.[1,2] An example of how these transformations can lead to major scientific advances in academia and industry is exemplified by the palladium-catalysed cross-couplings of organohalides with nucleophilic partners (Fig. 1a, left).[3] These reactions have changed the way chemists build C–C or C–heteroatom bonds in a reliable, predictable, and selective fashion. Indeed, Suzuki couplings or Buchwald-Hartwig aminations are among the top 20 most used reactions in drug discovery and development.[4] Despite their relevance in molecular synthesis, the synthetic community is eager to look for more sustainable strategies. In this context, directed TM-catalysed C–H functionalisation reactions have shown tremendous versatility to build value-added complex structures in a more environmentally friendly and atom-economical manner (Fig. 1a, right).[5,6] These strategies enable to control the site-selectivity of the C–H activation step by exploiting the coordinating ability of Lewis basic moieties in the substrates that act as mono- or bidentate directing groups (DGs).

Since the initial breakthrough by Murahashi in 1955 on C–H carbonylation,[7] and the renaissance of the field in 1993 by Murai,[8] these transformations have evolved, leading to synthetic landmarks in terms of efficiency, sustainability and structural complexity (Fig. 1b).[9,10] Although these reactions offer benefits compared to traditional cross-coupling reactions there remains a prevailing gap to close: the underutilization of nucleophiles as coupling partners. The first examples of nucleophilic C–C and C–X bond-forming reactions via C–H functionalisation were reported in the late 1990s-early 2000s (Fig. 1b),[11-13] yet this field remained rather limited for a long period of time. This is possibly a consequence of the diversity and complexity of the underlying reaction pathways (Fig. 1c). Most of the disclosed methodologies involved a base-assisted C–H metalation via a concerted metalation deprotonation or an electrophilic activation followed by a transmetalation step. While in some cases the reductive elimination (RE) occurs directly from the transmetalated product (low valent catalytic cycle), over the past decade, the necessity of triggering oxidative induced reductive elimination (ORE) events from high-valent

organometallic species to promote the couplings with nucleophiles has been uncovered. As a result of catalyst engineering and an increased mechanistic understanding, site-selective TM-catalysed nucleophilic C–H functionalisations have become a vibrant research area for the discovery of new retrosynthetic disconnections.

This Review covers the evolution of these nucleophilic couplings into sophisticated and powerful tools within synthetic organic chemistry. We have divided the selected examples into three categories according to the nature of the targeted nucleophile and the resulting bond-forming reaction (C–C, C–N or C–chalcogen), showing at the end of each section a brief recap of each reactivity. In addition, we highlight the implementation of innovative technologies along with key mechanistic intricacies that have enabled the rational design of reactivity patterns.

C–C bond-forming reactions

The scene for the catalytic construction of C–C bonds has been historically dominated by traditional cross-coupling reactions. However, in recent years, TM-catalysed directed C–H functionalisation using organometallic nucleophiles as coupling partners has gained momentum as a sustainable alternative to introduce carbon moieties on a wide variety of organic scaffolds. In this context, organoboron compounds are undoubtedly the most widespread reagents. Over the past years the utility of these organometallic nucleophiles has greatly increased, becoming versatile coupling partners for C–H arylations or alkylations. By analogy with Suzuki-Miyaura coupling, it is not surprising that, to date, palladium systems are the most explored catalyst for these C–H functionalisation strategies (Fig. 2). In this regard, Yu and co-workers have established these transformations in a prominent position. In 2006, Yu and co-workers developed the pyridine-directed alkylation of $C(sp^2)$–H and $C(sp^3)$–H bonds with methylboroxines and diverse alkylboronic acids (Fig. 2a).[14] This coupling proceeds under similar reactions conditions to the *ortho*-alkylation of oxazolines with SnR_4 previously described by the same research group, which constitutes the first example of Pd-catalysed nucleophilic C–C bond forming reaction via C–H activation.[15] While the methylation procedure occurred by combining $Cu(OAc)_2$ and benzoquinone, the alkylation with $AlkB(OH)_2$ only resulted in high yields when replacing the copper salt by Ag_2O. In 2007, Shi and co-workers applied similar reactions conditions for the Pd-catalysed $C(sp^2)$–H arylation of *N*-alkyl acetanilides

with commercially available ArB(OH)$_2$ (Fig. 2a).[16] In this particular case, the combination Cu(Otf)$_2$/Ag$_2$O was crucial for minimizing the boronic acid homocoupling. From a synthetic point of view, the substitution partner on the acetyl amides did not impact the coupling, but the use of aryl boronic acids with steric hindrance or electron-withdrawing groups decreased the reaction efficiency.

Yu and co-workers have also fulfilled the *ortho*-functionalisation of prevalent substrates in organic synthesis such as benzoic and phenylacetic acid derivatives (Fig. 2b). Their protocol involved the use of MeB(OH)$_2$ or PhB(OR)$_2$, in the presence of Ag$_2$CO$_3$ as oxidant and K$_2$HPO$_4$ as base.[17] Subsequently, the silver oxidant was replaced by air or O$_2$ in the C(sp^2)–H arylation of benzoic acids when using potassium aryltrifluoroborates as coupling partners (Fig. 2b).[18] This methodology enhanced the applicability of these transformations, being compatible with electron-deficient arenes. A related work disclosed the β-C(sp^3)–H functionalisation of *O*-methyl hydroxamic acid derivatives with aryl- and alkylboronic acids (Fig. 2b).[19] Initially, the C–C couplings were optimized in the presence of Ag$_2$O, but it was found that air could also serve as an efficient terminal oxidant. Notably, this work included the first examples of C(sp^3)–C(sp^3) bond formation in the context of TM-catalysed C–H activation. The practicality of this reaction was shown by the diversification of dehydroabietic acids. In 2015, the α-arylation of saturated azacycles and *N*-methylamines, assisted by thioamide directing groups was reported (Fig. 2c).[20] The exquisite monoselectivity of this protocol enabled the development of one-pot sequential diastereoselective heteroarylation to afford 2,5-diarylated pyrrolidines (>20:1 d.r.).

C(sp^2)–H bond functionalisations with arylboronic acid derivatives can also proceed at room temperature by engineering the corresponding Pd-based catalytic system (Fig. 2d). For example, in 2010, Lipshutz and co-workers reported the *ortho*-arylation of aromatic ureas under mild reaction conditions by increasing the electrophilic character of the Pd catalyst (Fig. 2d).[21] The use of a cationic palladium(II) catalyst, [Pd(MeCN)$_4$](BF$_4$)$_2$, not only accelerated the C–H bond-cleavage but also facilitated the transmetalation step. Subsequently, Gaunt and co-workers reported an alternative approach for enhancing the C–H cyclopalladation at room temperature (Fig. 2d).[22] To increase the strength of the chelating moiety, Gaunt and co-workers pre-installed an imine as surrogate of weakly coordinating carbonyl functionalities.[23] This strategy enabled the arylation of electron-deficient arenes with a wide variety of ArBF$_3$K.

The implementation of more sustainable alternative to metal-based oxidants have also contributed to the development of greener TM-catalysed C–H functionalisation processes.[24-26] In the context of nucleophilic couplings with boronic acid derivatives, Mei and co-workers disclosed in 2017 that the oxidative $C(sp^2)$–H alkylation of oximes can be triggered under electrochemical conditions (Fig. 2d).[27] In this case, the involvement of high-valent Pd^{III} or Pd^{IV} during the C–C bond-forming reaction was proposed, yet a $Pd^{II/0}$ catalytic cycle was not discarded.

Yu and co-workers have also designed strategies using chiral auxiliary ligands for developing highly enantioselective C–H activation/C–C couplings (Fig. 3). In 2008, promising preliminary results were obtained in the desymmetrization of prochiral $C(sp^3)$–H bonds using chiral mono-N-protected amino acid (MPAA) ligands (Fig. 3a).[28] Inspired by these results, the enantioselective C–H functionalisation of cyclopropanes with organoboron reagents by using N-arylamides as directing groups was reported (Fig. 3b). The systematic tuning of the MPAA (L_2) ligand and reaction conditions afforded an appealing synthetic route for accessing *cis*-substituted chiral cyclopropanecarboxylic acid under mild reaction conditions.[29] Subsequently, the group disclosed the use of a chiral mono-*N*-protected *a*-amino-*O*-methylhydroxamic acid (MPAHA, L_3) ligand to promote the asymmetric $C(sp^3)$–H coupling of cyclobutyl rings and acyclic amides with Ar–BPin.[30] During the optimization of the reaction conditions, a 4-cyano-2,3,5,6-tetrafluoroarylamide directing group was shown to provide high efficiency and enantioselectivity. Simultaneously, after an extensive ligand screening, the D-enantiomer of a MPAA (Ac-D-^{t}Leu-OH) was found to enable the arylation of γ-$C(sp^3)$–H bonds of triflyl-protected amines via $Pd^{II/0}$ catalysis (Fig. 3c).[31] More recently, an enantioselective version of the thioamide-directed $C(sp^3)$–H arylation[20] was developed by using a chiral phosphoric acid ligand (Fig. 3d).[32]

Despite palladium being the most widely-applied TM in catalysis, ruthenium catalysts have also demonstrated their potential for the C–H coupling of different molecules with organoboron reagents (Fig. 4a). In the early 2000s, Kakiuchi and co-workers demonstrated the capability of ruthenium catalysts for promoting the ligand-assisted direct arylation of aromatic ketones with arylboronates using

RuH$_2$(CO)(PPh$_3$)$_2$ (Fig. 4a).[33,34] Subsequently, inspired by these literature precedents, Sames and co-workers developed the Ru-catalysed α-arylation of pyrrolidines and piperidines using amidine as a directing group (Fig. 4a).[35] In these methodologies, the C–H bond-cleavage is proposed to proceed via oxidative addition to give an *ortho*-metalated Ru–H species. Complementary synthetic strategies have described the Ru-catalysed C–H arylation of amides via electrophilic C–H metalation when using [RuCl$_2$(*p*-cymene)]$_2$ as catalyst. For example, in 2015, Ackermann and co-workers reported the functionalisation of *N*-acyl anilines (Fig. 4a),[36] whereas a year later, Szostak and co-workers used disubstituted benzamides as starting materials (Fig. 4a).[37] Both procedures present wide functional-group tolerance with high regioselectivity. Interestingly, a mechanistic study from Chang and co-workers suggests that, in the presence of chemical oxidants, these C–H arylations involve an oxidatively induced reductive (ORE) process from high-valent ruthenium species.[38]

Nucleophilic C–C bond-forming reactions via site-selective C–H activation, have also been accomplished using Cp* complexes of the group 9 transition metals. In 2012, Cheng and co-workers reported the synthesis of phenanthridinones, key scaffolds in natural products and drugs, by the oxidative C–H coupling of *N*-methoxybenzamides with aryl boronic acids using [Cp*RhCl$_2$]$_2$.[39] This method enables the one-pot formation of C–C and C–N bonds under mild reaction conditions. More recently, Hu, Zhang and co-workers used [Cp*RhCl$_2$]$_2$ to perform the C–H vinylation of 2-phenylpyridine derivatives with pinacol vinylborate *en route* to access polycyclic alkaloids with inhibitory activities against cancer cells.[40] Remarkably, different Cp*TM systems have shown their potential for diversifying bioactive molecules via late-stage C–H methylation strategies (Fig. 4b). The introduction of methyl motifs into these complex architectures can dramatically affect their biological activity and physicochemical properties.[41] A collaboration between the research group of Ackermann and AstraZeneca (Johansson) has enabled a major breakthrough in the late-stage C–H methylation arena (Fig. 4b).[42] The authors reported the C–H coupling with trimethylboroxine of a myriad of substrates containing a wide range of directing groups using a Cp*Co^{III}-based catalyst. This work includes the successful derivatization of up to 15 drug-like molecules (for example, Sulfaphenazole or Diazepam). A year later, Pilarski and co-workers reported the first example of a mechanochemical protocol applied to the late-stage functionalisation of drugs (Fig. 4b).[43] This solvent-

free Cp*Rh-catalysed C–H methylation reaction provides high regioselectivity, functional group tolerance and short reaction times for functionalizing key heterocycles.

Organosilicon reagents have also displayed their synthetic applicability in TM-catalysed nucleophilic C–H functionalisation reactions (Fig. 4c). In 2007, Shi and co-workers reported the first palladium-catalysed direct C–C coupling with arylsilanes (Fig. 4c).[44] In this work, the *ortho*-arylation of acetanilides with ArSi(OMe)$_3$ is enabled by using an appropriate combination of inorganic salts, Cu(OTf)$_2$ and AgF. In 2009, this reactivity was extended to the functionalisation of alkenyl C–H bonds of cyclic enamides, by Loh and co-workers, using AgF as the sole additive.[45] In both examples, the authors proposed a Pd$^{II/0}$ manifold. In 2015, Yu and co-workers developed a ligand-controlled Pd-catalysed method for the β-C(sp^3)–H arylation of a wide variety of amide derivatives, including alanine- and ibuprofen-derived scaffolds (Fig. 4c).[46] The addition of a quinoline-based ligand was key to suppress the undesired side-reaction resulted from the triethoxyarylsilane homocoupling. Yu has also used amides as directing groups in the Cu-mediated C(sp^2)–H trifluoromethylation using the Ruppert-Prakash reagent (TMSCF$_3$) (Fig. 4c).[47] This protocol required stoichiometric quantities of Cu(OAc)$_2$ and Ag$_2$CO$_3$ for delivering high conversions. Catalysts based on other noble metals, such as Ru, Rh or Ir have also proven to efficiently promote the coupling with organosilanes. Similar to their previous work with organoboranes,[37] Szostak and co-workers have developed different Ru-catalysed C–H oxidative couplings with aryltrimethoxysilanes, in the presence of exogeneous oxidants. In 2017, the authors disclosed the direct arylation of diverse tertiary amides with excellent chemoselectivity and high functional tolerance (Fig. 4c).[48] In a follow-up paper, Szostak and co-workers reported the C–H arylation of indoles in aqueous media, a green and safer alternative to traditional organic solvents.[49] A few years earlier, Loh and co-workers used a similar strategy for the direct arylation of (hetero)arenes, including indoles, but using [Cp*RhCl$_2$]$_2$ as catalyst.[50] In 2018, Chang and co-workers expanded the substrate scope of the Hiyama-type cross-couplings to the Cp*Ir-catalysed functionalisation of benzamides (Fig. 4c).[51] In this work, the necessity of triggering an ORE event for affording the desired arylated product was identified. In addition, these results set the basis for their subsequent works with organoboron derivatives described above.[38]

Other combinations of transition metals and nucleophiles have also shown to be attractive options for constructing C–C bonds via C–H activation. In 2008, Nakamura and co-workers discovered that iron complexes can catalyse $C(sp^2)$–H arylations with in situ generated organozinc reagents.[52] Since then, these methodologies have been extended to the arylation or alkylation of $C(sp^2)$–H and $C(sp^3)$–H bonds with Grignard, organozinc, organoboron and organoaluminum reagents.[53] Hoover and co-workers have reported the Ni-catalysed oxidative decarboxylative (hetero)arylation of $C(sp^2)$–H bonds using silver nucleophiles as coupling reagents.[54] In this case, a silver salt was exploited to promote the decarboxylation of (hetero)aromatic carboxylic acid derivatives and generate in situ the transmetalating agent.[55] These methodologies use inexpensive and readily available carboxylic acid derivatives as raw materials and minimize the by-product formation and hence, offer interesting synthetic opportunities.

Organoboron compounds and palladium catalysis are the most powerful combination for the construction of C–C bonds through site-selective nucleophilic C–H functionalisation as evidenced by the numerous examples described above. Both alkyl and aryl boronic compounds could serve as nucleophilic partners and engage in the formation of $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp^3)$ bonds. Remarkably, examples of $C(sp^3)$–$C(sp^3)$ bond formation are also described albeit less investigated. To enhance the overall sustainability of the process, the use of stoichiometric amounts of chemical oxidants can be prevented by working under oxygen or air, as well as by implementing electrochemical protocols. The presence of chiral ligands, mostly mono-N-protected amino acids or hydroxamic acids, grants the formation of asymmetric scaffolds with high enantioselectivities. Among other metals is worth to mention ruthenium for its ability to promote the C–H activation in presence of diverse directing groups such as ketones, amidines, and benzamides. Cp*TM complexes demonstrated extraordinary functional group compatibility especially in the functionalisation of drug-like molecules. Organosilicon compounds displayed broad applicability as alternative nucleophiles for C–H functionalisation reactions catalysed by different transition metals such as Pd, Cu, Ru, Rh or Ir. Other nucleophiles such as, Grignard, organozinc and organoaluminium reagents are also effectively employed under iron catalysis.

C–N bond-forming reactions

Without any doubt, the C–N bond is one of the most relevant motifs within synthetic organic chemistry. Amines, amides, or N-containing heterocycles constitute prevalent fragments of bioactive molecules, natural products or materials. Therefore, the development of innovative and practical strategies that enable the formation of C–N bonds in an atom-economic fashion has received special attention. In this context, oxidative cross-dehydrogenative couplings (CDC) between C–H and N–H bonds and related transformations represent an appealing way to forge this type of bond.[56-57]

Direct CDC reactions have become an extremely powerful tool for the intramolecular synthesis of prevalent *N*-heterocycles. In these cases, the nucleophilic amino moiety of the substrate acts as both directing group and coupling partner. Since the pioneering work by Buchwald on $C(sp^2)$–H amination via a $Pd^{0/II}$ manifold,[13] the synthetic community has designed high-valent Pd catalysis to broaden the synthetic utility of CDC reactions and/or improve their reaction conditions (Fig. 5a). For example, in 2008, Gaunt and co-workers developed an alternative strategy, via a $Pd^{II/IV}$ catalytic cycle in the presence of $PhI(OAc)_2$, to synthesise carbazoles under mild reaction conditions (Fig. 5a).[58] The reaction proceeds with high efficiency at room temperature presumably owing to a facile reductive elimination event from a Pd^{IV} intermediate. As alternative to using stoichiometric amounts of oxidants, You and Cho merged photoredox and Pd catalysis to facilitate the synthesis of carbazoles (Fig. 5a).[59] In this work, an iridium photocatalyst was proposed to trigger the C–N bond-formation from an oxidised Pd^{III} species, formed by a single-electron-transfer (SET) process. In 2008, the Yu group developed the synthesis of lactams via Pd^{II}-catalysed intramolecular C–H amination using AgOAc and $CuCl_2$ as oxidants (Fig. 5a).[60] This transformation is proposed to occur via a $Pd^{II/IV}$ catalytic cycle. In the same year, the Yu group reported a tandem C–H iodination/amination route for the preparation of indolines and tetrahydroisoquinolines using Pd^{II}/Cu^I catalysts.[61] In 2009, a more general and versatile protocol for the synthesis of indolines in the presence of $Ce(SO_4)_2$ or N-fluoro-2,4,6-trimethylpyridinium triflate was reported (Fig. 5a).[62] The employment of this by-standing F^+ oxidant avoids alternative competitive reductive elimination events,[63,64] such as C–OAc, when using $PhI(OAc)_2$. The synthesis of benzazetidines, strained four-membered nitrogen-containing heterocycles, has been also accomplished by Chen and co-workers through intramolecular CDC processes starting from picolinamide-protected benzylamines (Fig. 5a).[65] The use of phenyliodonium dimethyl malonate, PhI(DMM), as oxidant

was key to facilitate the C–N bond-formation. Computational studies suggested that the reductive elimination step takes place from a bimetallic Pd^{III}–Pd^{III} complex instead of from a monomeric Pd^{IV} intermediate.

Apart from $C(sp^2)$–H/N–H couplings, intramolecular CDC cyclisations involving aliphatic C–H bonds are an attractive strategy for the construction of saturated N-heterocycles.[66] In this context, one of the major challenges is the susceptibility of metal–alkyl intermediates to undergo β-hydride elimination instead of $C(sp^3)$–N reductive elimination. However, the desired bond-forming process can be promoted through high-valent TM species by a diverse array of oxidants. Seminal examples were reported independently by Chen and Daugulis in 2012, using picolinamide (PA)-protected amines as substrates (Fig. 5b).[67,68] The former work disclosed the intramolecular amination of γ- and δ-$C(sp^3)$–H bonds to build azetidines and pyrrolidines, while the latter focused its attention exclusively on the formation of 5-membered ring structures. Starting materials bearing alternative bidentate directing groups, such as 8-aminoquinoline (AQ) or 2-pyridylmethylamine (PM) groups, also afford γ-lactams with high selectivity (Fig. 5b).[69]

Despite the significant synthetic advances accomplished in intramolecular CDC aminations by using directing groups, these approaches present an obvious disadvantage: the necessity of extra synthetic steps for their installation and removal. To address this limitation, the Gaunt group has taken advantage of the Lewis basicity of native functionalities, such as unprotected amines, to develop an elegant aziridination strategy (Fig. 5b).[70] This methodology provided strained nitrogen heterocycles via a rare four-membered palladacycle.

Apart from Pd systems, first-row metal-based catalysts, such as Cu,[71] Ni,[72] or Co,[73] have also demonstrated their synthetic applicability in intramolecular $C(sp^3)$–H amination reactions using AQ as chelating moiety (Fig. 5c). These reactions showed a wide substrate scope and notable complementary reactivities. While the Cu-catalysed reactions promoted the amination at β-benzylic over β-methyl C–H bonds, the nickel and cobalt systems favoured the functionalisation at β-methyl groups over β-methylene and γ-methyl C–H positions. Notably, Shi and co-workers extended the synthetic applicability of these methods to easily available linear triflamides through Ag catalysis.[74] This procedure targets primary C–H bonds over

secondary or tertiary ones. All these aminations required the presence of external oxidants to provide the corresponding products, presumably from high-valent TM intermediates.

Despite intermolecular TM-catalysed direct CDC aminations representing an appealing and sustainable alternative to Buchwald-Hartwig aminations, their synthetic applicability has been hampered by the dearth of reports when compared to the well-established cross-coupling reaction. Only sporadic works, mainly using Cu catalysts (Fig. 6a), have disclosed the participation of common nucleophilic nitrogen sources in directed C–H functionalisation reactions. Yu and co-workers reported a pioneering example in 2006 that described, among other transformations, the Cu-mediated coupling of 2-phenylpyridine with *p*-tolylsulfonamide.[75] A few years later, the Nicholas group accomplished the catalytic version of this reaction by using molecular oxygen as the terminal oxidant (Fig. 6a).[76] Other combinations of reagents have also been successfully exploited to forge new C–N bonds using copper-based systems. For example, Daugulis and co-workers discovered that AQ directing groups promote the functionalisation of benzamides with aliphatic cyclic and acyclic amines in good to excellent yields (Fig. 6a). While the initial reaction employed *N*-methylmorphorine *N*-oxide (NMO) as terminal oxidant,[77] further improvements have enabled the use of oxygen from air and expanded the scope to primary amines (Fig. 6a).[78] In 2014, the Yu group demonstrated that oxazoline could be also used as directing group in Cu-mediated C–H amination reactions, in which various sulfonamides, amides, and anilines act as amine donors in this reaction (Fig. 6a).[79] Subsequently, in 2018, Chang and co-workers expanded the scope of this reactivity by using aqueous ammonia as nitrogen source (Fig. 6a).[80] The synthetic utility of this coupling partner in the late-stage derivatization of biorelevant scaffolds was shown. The use of soft low-valent Cu(I) species, under stoichiometric and sub-stoichiometric reaction conditions, was crucial for preventing the strong NH_3 coordination.

Additional TM-based systems have been explored for unlocking novel intermolecular C–H amination couplings (Fig. 6b). For example, in 2011, Liu and co-workers developed a Pd-catalysed C–H amidation coupling of readily available aromatic ketones with sulfonamides and amides using the F^+ oxidant *N*-fluoro-2,4,5-trimethylpyridinium triflate (NFTPT) (Fig. 6b).[81] The key to success was the employment of Pd(OTf)$_2$, an electron-deficient palladium(II) complex, which facilitates the C–H bond-cleavage.[21] The

efficient coupling of different *N*-methyl arylsulfonamides discards the participation of nitrene intermediates in the reaction pathway. More recently, Ackermann and Lei concurrently developed electrochemical methods, using cobalt catalysts, for aminating substrates containing AQ and PyO (pyridine-1-oxide), respectively, with alkylamines (Fig. 6b).[82,83] Apart from the sustainable nature of the terminal oxidant, the protocol disclosed by Ackermann provided an additional synthetic advantage since optimal results were achieved when using a renewable solvent, γ-valerolactone (GVL).

Over the past decades, ligand-assisted transition-metal-catalysed C–H amination reactions have emerged as an attractive tool for building nitrogen-containing molecules. For intramolecular aminations, Pd(OAc)$_2$ has been shown to be one of the most commonly used catalysts, especially in C(sp^2)–N forming reactions. However, more sustainable first-row metals such as Cu, Co and Ni have shown their potential in intramolecular C(sp^3)–H aminations. For intermolecular C–H aminations, mainly Cu, Co and Pd have proved to be efficient in combination with a wide range of nitrogen sources such as sulfonamides, amides, anilines or aqueous ammonia. The most commonly used directing groups correspond to strongly coordinating moieties such as pyridine, 8-aminoquinoline and oxazoline, while the exploitation of prevalent weakly coordinating functionalities remains very limited.

C–O and C–S bond-forming reactions

Since the seminal reports of Sanford[12] and Yu,[75] considerable effort has been made to develop novel C–O and C–S bond-forming reactions via C–H functionalisation. In 2010, Yu and co-workers reported a Pd-catalysed intramolecular synthesis of dihydrobenzofurans using PhI(OAc)$_2$ as oxidant, via a high-valent Pd^{IV} species (Fig. 7a).[84] Notably, this method was applied to access architectures of great synthetic interest, such as spirocyclic compounds. Subsequently, Liu and co-workers expanded the scope of this reactivity by generating dibenzofuran derivatives using air as efficient terminal oxidant (Fig. 7a).[85] In contrast to Yu's work, a Pd$^{0/II}$ catalytic cycle was proposed to be responsible for the transformation.

By controlling the selectivity of the elimination event from Pd^{IV} intermediates,[86,87] Yu and co-workers unlocked the participation of free alkyl amines in γ-C(sp^3)–acyloxylation and alkoxylation processes. The authors used a transient directing group (TDG) in conjunction with *N*-fluoro-2,4,5-trimethylpyridinium

tetrafluoroborate as bystanding F^+ oxidant (Fig. 7b).[88] The power of this strategy was showcased in the late-stage diversification using drug molecules as coupling partners.

Copper-catalysed cross-dehydrogenative couplings have also been applied to the direct etherification of C–H bonds. For instance, Gooßen has exploited a bimetallic copper/silver cooperation for developing two methodologies for the *ortho*-alkoxylation of aromatic compounds (Fig. 7c).[89,90] The authors proposed the in situ generation of silver alkoxides species, which act as transmetalating agents. The first example, that targeted aromatic carboxylates, is particularly relevant from a synthetic point of view because it gives access to simple aryl ethers owing to a concomitant decarboxylation event during the reaction process. The second report enabled the functionalisation of 2-phenylpyridine derivatives.

Seeking for economical and greener C–O couplings, different research groups have employed electric current as a sustainable surrogate of chemical oxidants (Fig. 7d). Inspired by a seminal work by Kakiuchi on the electrochemical C–H halogenation of 2-phenylpyridines,[91] Mei and co-workers designed the first electrosynthetic Pd-catalysed protocol to promote $C(sp^3)$–O bond-forming reactions (Fig. 7d).[92] In this example, oxime substrates were functionalised with different oxyanion nucleophiles in a divided cell. Concurrently, Sanford disclosed a related electrochemical acetoxylation protocol that enabled the functionalisation of $C(sp^2)$−H and $C(sp^3)$−H bonds with tetramethylammonium acetate (TMAOAc) (Fig. 7d).[93] This reaction was efficiently carried out with substrates containing commonly used directing groups (for example, pyridine, pyrazole or oxime). The synthetic utility of merging electrosynthesis and direct C-O bond-forming reactions have been also demonstrated with other TM-based catalytic systems. In 2017, Ackermann and co-workers reported the $C(sp^2)$–H functionalisation of diverse molecules containing PyO as directing group with alcohols (Fig. 7d).[94] $Co(OAc)_2 \cdot 4H_2O$ was used as catalyst in conjunction with NaOPiv as sole additive. The versatility and robustness of the method was depicted by its broad functional group tolerance and its application to a gram-scale synthesis. More recently, Chang and co-workers have continued exploiting high-valent pathways to broaden the synthetic utility of Cp*TM-based catalytic system (Fig. 7d).[95] A Cp*Rh-catalysed electrolytic $C(sp^2)$–H acyloxylation protocol of readily available carboxylic acids was established. In addition, more complex derivatives such as natural products or drug candidates were also functionalised.

Apart from the early example reported by Yu in 2006,[75] additional TM-catalysed C–S bond forming reactions through C–H activation have been achieved using different S-based nucleophiles (Fig. 7e). For instance, Cp*Co^{III} compounds have proved to be efficient catalysts in C–S bond-forming reactions. In 2016, Glorius and co-workers reported the oxidative coupling of indoles with thiols under mild reaction conditions (Fig. 7e).[96] The authors proposed that an in situ generated cuprate complex, $[Cu(SPh)_2]^-$, is the transmetalating agent. Subsequently, Wang and co-workers employed a commercially available silver nucleophile, $AgSCF_3$, to develop the *ortho*-trifluoromethylthiolation of arenes containing traditional monodentate directing groups (Fig. 7e).[97] In contrast to the initial mechanistic proposals, recent experimental and computational studies suggest that these Cp*Co-catalysed C–S nucleophilic couplings involve oxidatively induced reductive elimination events, via high-valent cobalt intermediates.[98]

The construction of C–O bonds through C–H activation has proven to be effective with multiple TM-based catalysts such as $Pd(OAc)_2$, $Cu(OAc)_2$ or $Co(OAc)_2\bullet 4H_2O$, in combination with a wide range of nucleophilic coupling partners, including alcohols, carboxylic acids, acetates and borate esters. Even if the use of oxidants such as hypervalent iodine or F^+ oxidant was required in certain cases, more environmentally friendly terminal oxidants such air, O_2 or electric current have been employed successfully. For C–S bond forming reactions, there is still room for improvement because only two examples have been reported. In both systems, Cp*Co catalyst, stoichiometric amounts of chemical oxidants, and Cu- or Ag-based transmetallating agents are used.

Outlook

This Review Article has summarised the progress on the use of nucleophiles as coupling partners in TM-catalysed directed C–H functionalisation. Currently, these transformations offer an appealing alternative to traditional cross-coupling reactions for the controlled and selective formation of C–C and C–heteroatom bonds by merging a wide range of catalytic systems, organic scaffolds, and nucleophiles. Even though these C–H couplings are increasingly being used in organic synthesis, there are vast opportunities to move the field to the next stage in the coming years. The mechanistic knowledge already gathered will be critical to uncover novel reactivity patterns, via high-valent organometallic intermediates, that allow the design of

more complex and efficient catalytic processes. For fulfilling this ambitious goal, the combination of experimental studies, DFT calculations and mathematical modelling will be instrumental to identify design principles behind reactivity patterns. Moreover, the in-depth exploration of the synergistic cooperation between bimetallic systems offers interesting mechanistic and synthetic future prospects to enable transformations otherwise inaccessible by a single catalytic cycle.[55] The use of cost-effective and earth-abundant 3d transition metal catalysts or the implementation of electro- and photochemical redox strategies to replace the use of traditional chemical oxidants, have already shown to be truly promising to improve the sustainability of these reactions and should continue to be at the forefront of chemists´ endeavours. In this regard, the use of greener organic solvents, developing reactions in aqueous media or in solvent-free conditions, will reduce the environmental impact of these transformations, making them more appealing to be implemented at industrial level.[99] Moreover, the deployment of flow techniques will also enhance the sustainability of these transformations by easing catalyst recycling and process scale-up. In the context of site-selectivity, the development of nucleophilic C–H functionalisation reactions at distal *meta* or *para* positions remains underexplored and could open the doors to the synthesis of scaffolds with different substitution patterns.[100] In addition, the widespread exploitation as directing groups of prevalent functionalities, such as carboxylic acids, esters, amides or ketones, among others, will enhance the utility of these transformations, facilitating their translation to the late-stage diversification of complex molecules, which it is still limited. This will open exciting synthetic venues, especially in medicinal chemistry, streamlining the generation of new libraries of bioactive compounds. Indeed, the use of isotopically labelled nucleophilic coupling partners, which has not yet been investigated, could be appealing for drug discovery programs. Furthermore, the implementation of emerging technologies, such as high-throughput experimentation or machine learning, will trigger innovative and efficient nucleophilic C–H couplings thanks to the processing of large amount of data, including failed experiments from which insightful conclusion can be extracted. We hope that this Review will stimulate further developments towards more practical, elaborate and ground-breaking nucleophilic protocols.

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Author contributions

S.B., J.Z., S.L.-R., A.C. contributed to the literature search, the writing of the article and the preparation of the figures. M.H.P.-T. contributed to the literature search, the editing of the manuscript, coordinated the project and supervised the writing.
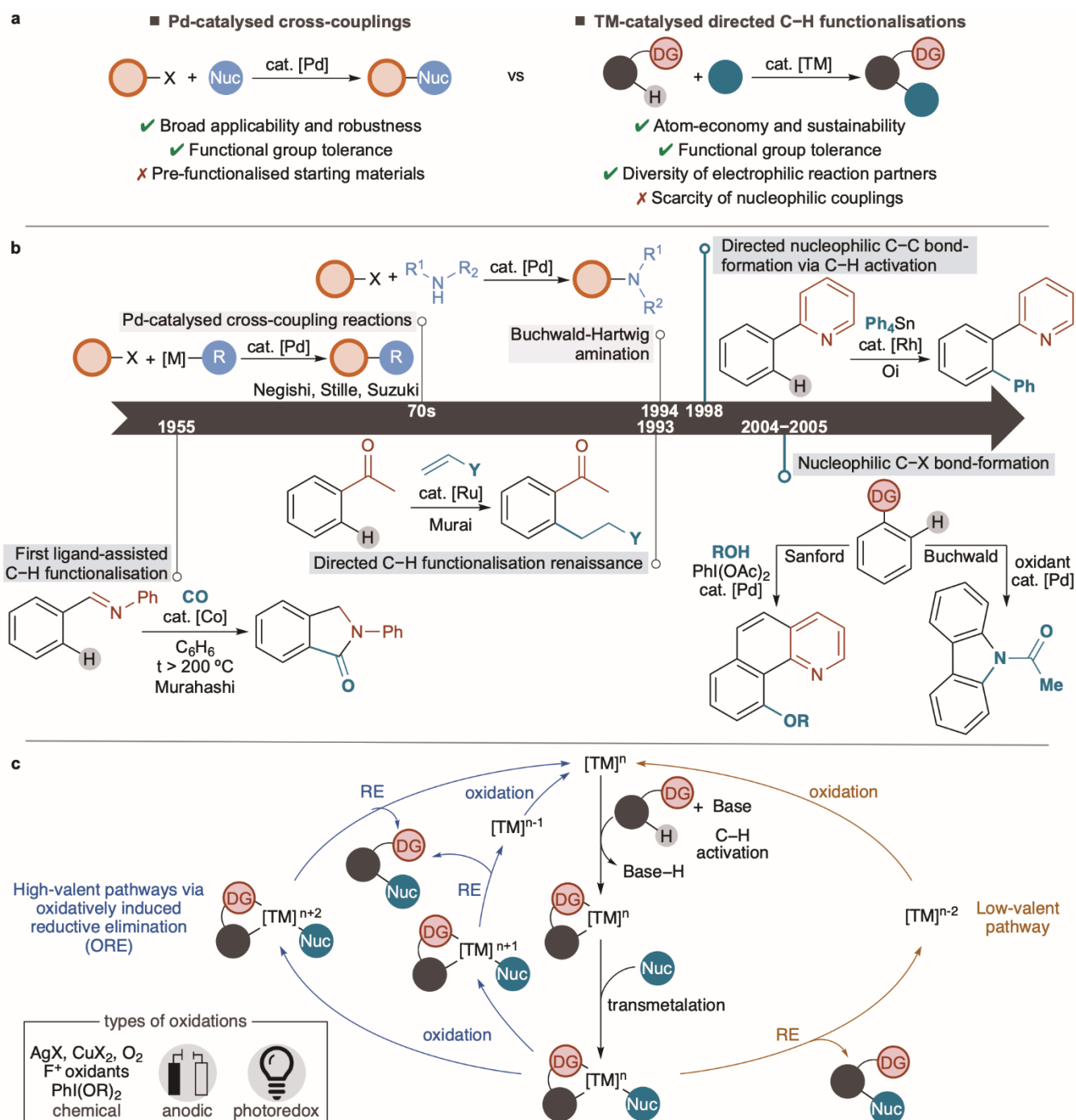
Competing interests

Additional information

FIGURES

Fig. 1| Evolution of site-selective TM catalysis: from cross-coupling to nucleophilic directed C–H functionalisation. a, Comparison between traditional Pd-catalysed cross-couplings and site-selective TM-catalysed

C–H functionalisations. **b,** Timeline describing major landmarks in these fields, in the context of C–C and C–X bond-forming reactions, highlighting in purple the seminal nucleophilic examples via directed C–H activation.[7,8,11,12,13] **c,** Simplified mechanistic scenarios proposed for nucleophilic directed C–H couplings. | DG, directing group; Me, methyl; Nuc, nucleophile; ORE, oxidatively induced reductive elimination; Ph, phenyl, RE, reductive elimination; TM, transition metal.
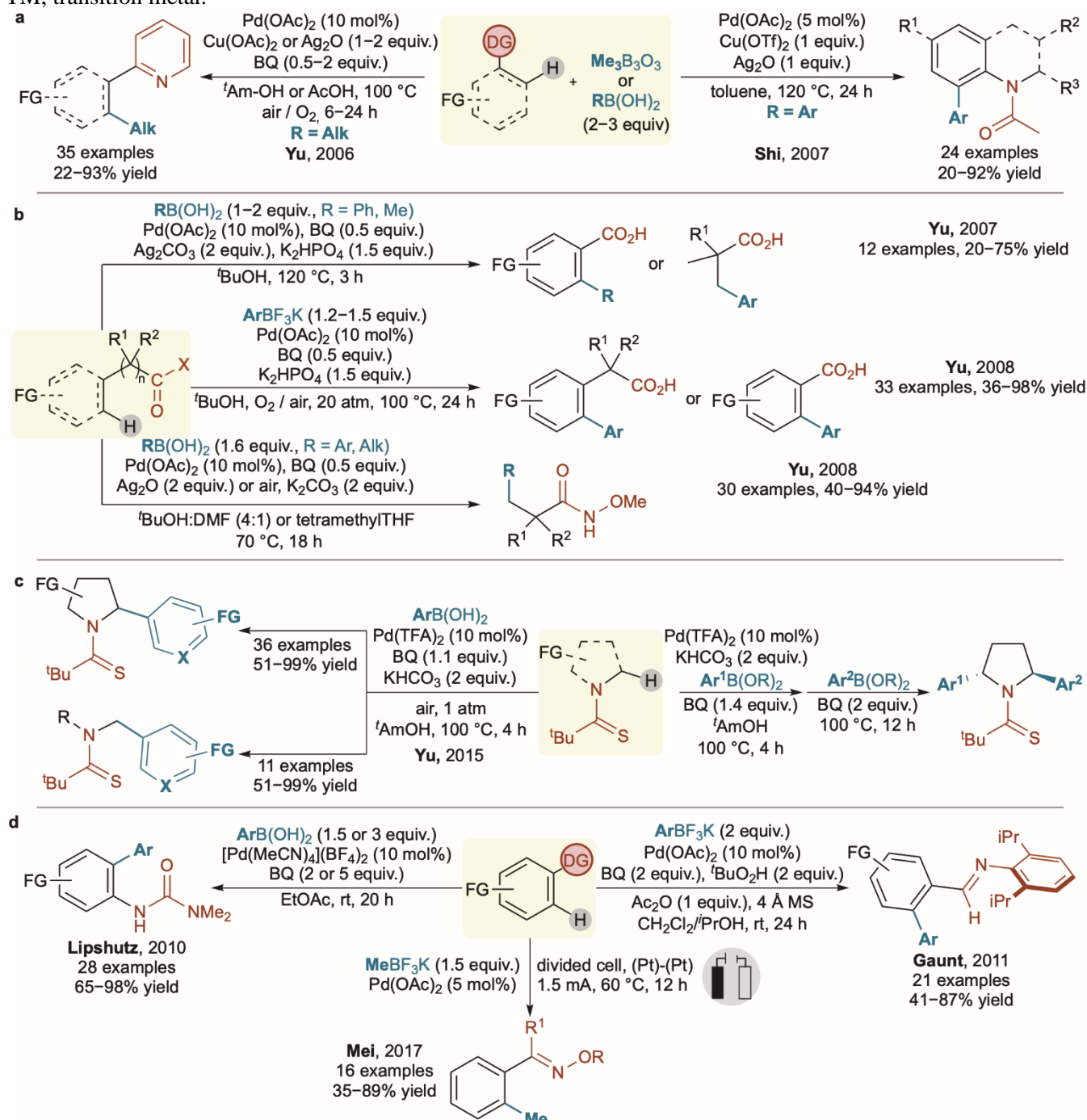

Fig. 2| Pd-catalysed C–H functionalisation with boronic acid derivatives. A, Early examples of C–H alkylation and arylation performed under oxidative conditions.[14,16] **b,** *ortho*-functionalisations of carboxylic acid derivatives that include the initial exploitation of aryltrifluoroborates and the first example of a C(sp^3)–C(sp^3) coupling in this field.[17,18,19] **c,** The high selectivity of an α-arylation of saturated azacycles and *N*-methylamines assisted by thioamide directing groups towards the corresponding monosubstituted products enables one-pot diastereoselective heteroaylation.[20] **d,** Oxidative C–C couplings are performed under mild reaction conditions by enhancing the C–H metalation step or by implementing electrochemical methods instead of using metal-based oxidants.[21,22,27] | Alk, alkyl; Ar, aryl; BQ, benzoquinone; DG, directing group; DMF, dimethylformamide; FG, functional group; ^{i}Pr, isopropyl; Me, methyl; MS, molecular sieves; OAc, acetate; ^{t}Bu, tert-butyl.
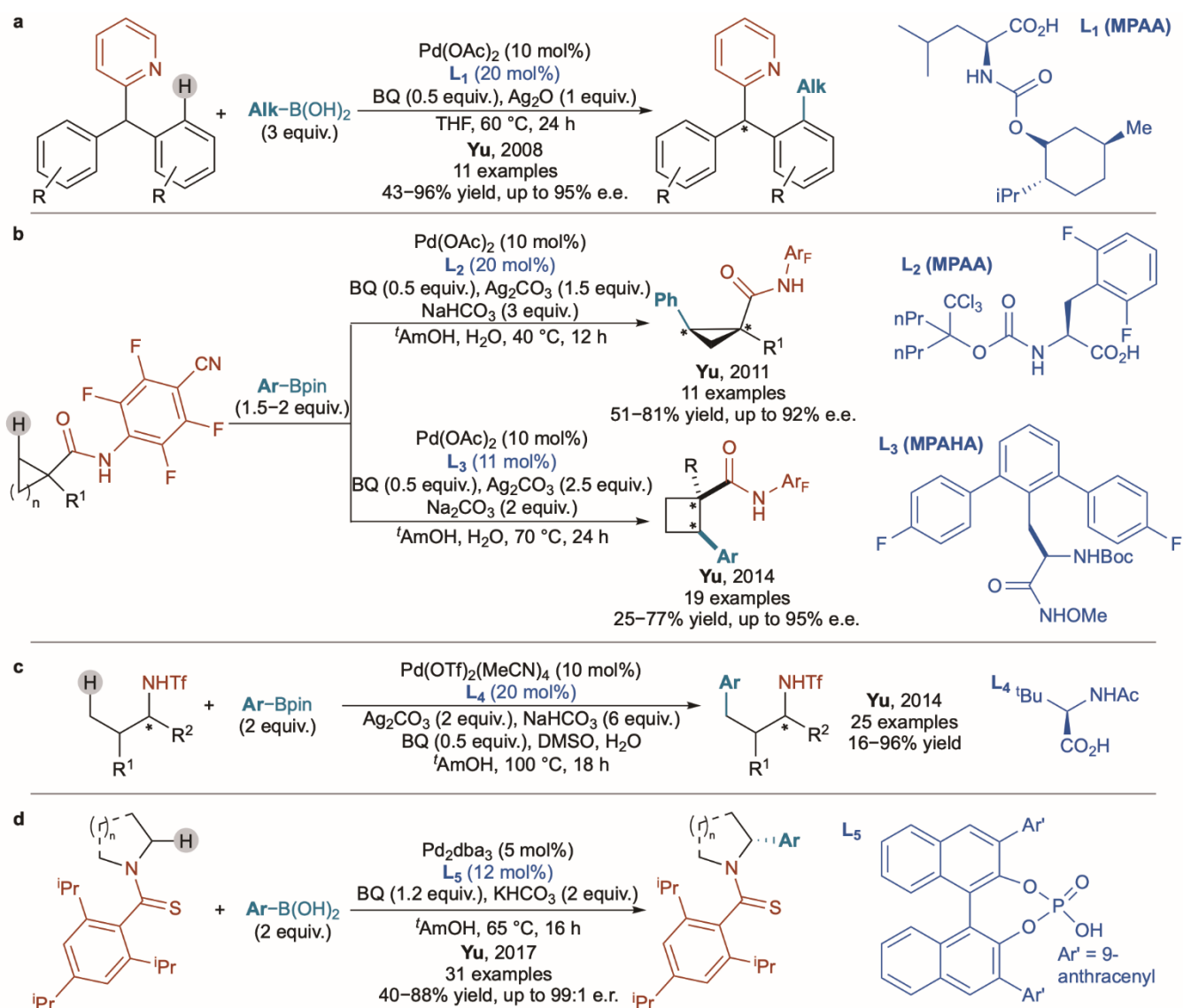
Fig. 3| Pd-catalysed enantioselective C–H functionalisation reactions with alkyl and arylboron reagents using chiral ligands. a, Desymmetrisation of prochiral C(sp³)–H bonds using monoprotected α-amino acids as ligands.[28] **b,** The enantioselective arylation of cycloalkanes containing electron-deficient amides as directing groups provides access to *cis*-substituted chiral cyclopropanecarboxylates and cyclobutanes with chiral quaternary stereocentres.[29,30] **c,** Arylation of γ-C(sp³)–H bonds in alkyl amines enabled by the D-enantiomer of a mono-N-protected amino acid ligand.[31] **d,** Thioamide-directed asymmetric C(sp³)–H arylation using a phosphoric acid ligand.[32] | Alk, alkyl; Ar, aryl; BQ, benzoquinone; dba, dibenzylideneacetone; DG, directing group; DMSO, dimethyl sulfoxide; e.e., enantiomeric excess; e.r., enantiomeric ratio; *i*Pr, isopropyl; L, ligand; MPAA, mono-*N*-protected amino acid; MPAHA, mono-*N*-protected *a*-amino-*O*-methylhydroxamic acid; Me, methyl; *t*Am, *tert*-amyl; *t*Bu, *tert*-butyl; Tf, trifluoromethylsulfonyl; THF, tetrahydrofuran.
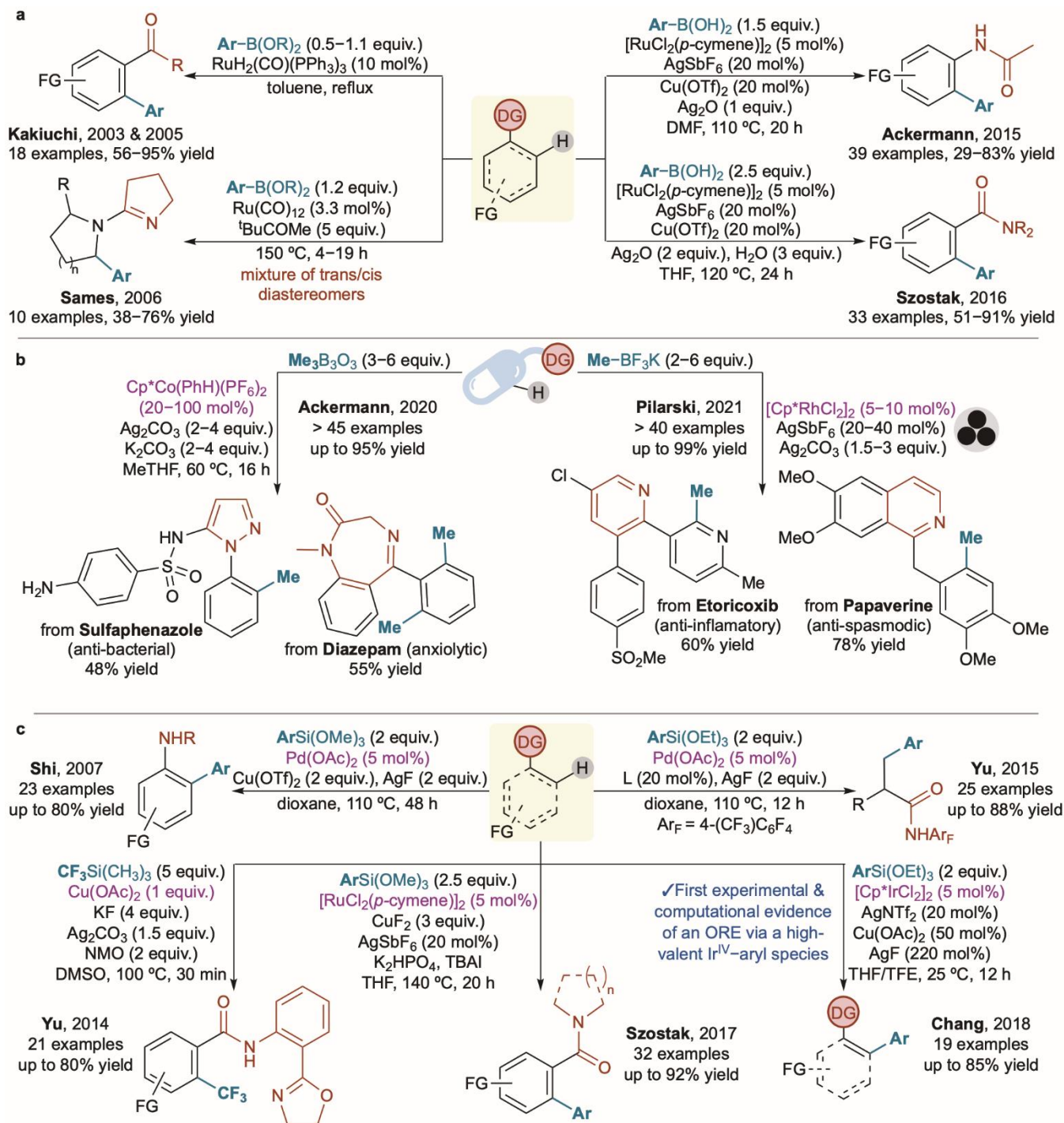
Fig. 4| Alternative approaches for TM-catalysed C–H activation/C–C couplings. a, Ru-catalysed C–H arylation reactions using boronic acid derivatives as coupling partners.[33,34,35,36,37] **b,** Late-stage C–H methylation by Cp*TM catalysts, including the first example of a mechanochemical protocol applied to LSF.[42,43] **c,** TM-catalysed directed C–H functionalisation with organosilicon nucleophiles.[44,46,47,48,51] | Ar, aryl; Cp*, pentamethylcyclopentadienyl; DG, directing group; DMSO, dimethyl sulfoxide; Et, ethyl; FG, functional group; L, ligand; LSF, late stage functionalization; Me, methyl; NMO, *N*-Methylmorpholine *N*-Oxide; ORE, oxidatively induced reductive elimination; *t*Bu, *tert*-butyl; Tf, trifluoromethylsulfonyl; TBAI, tetrabutylammonium iodide; TFE, trifluoroethanol; THF, tetrahydrofuran.
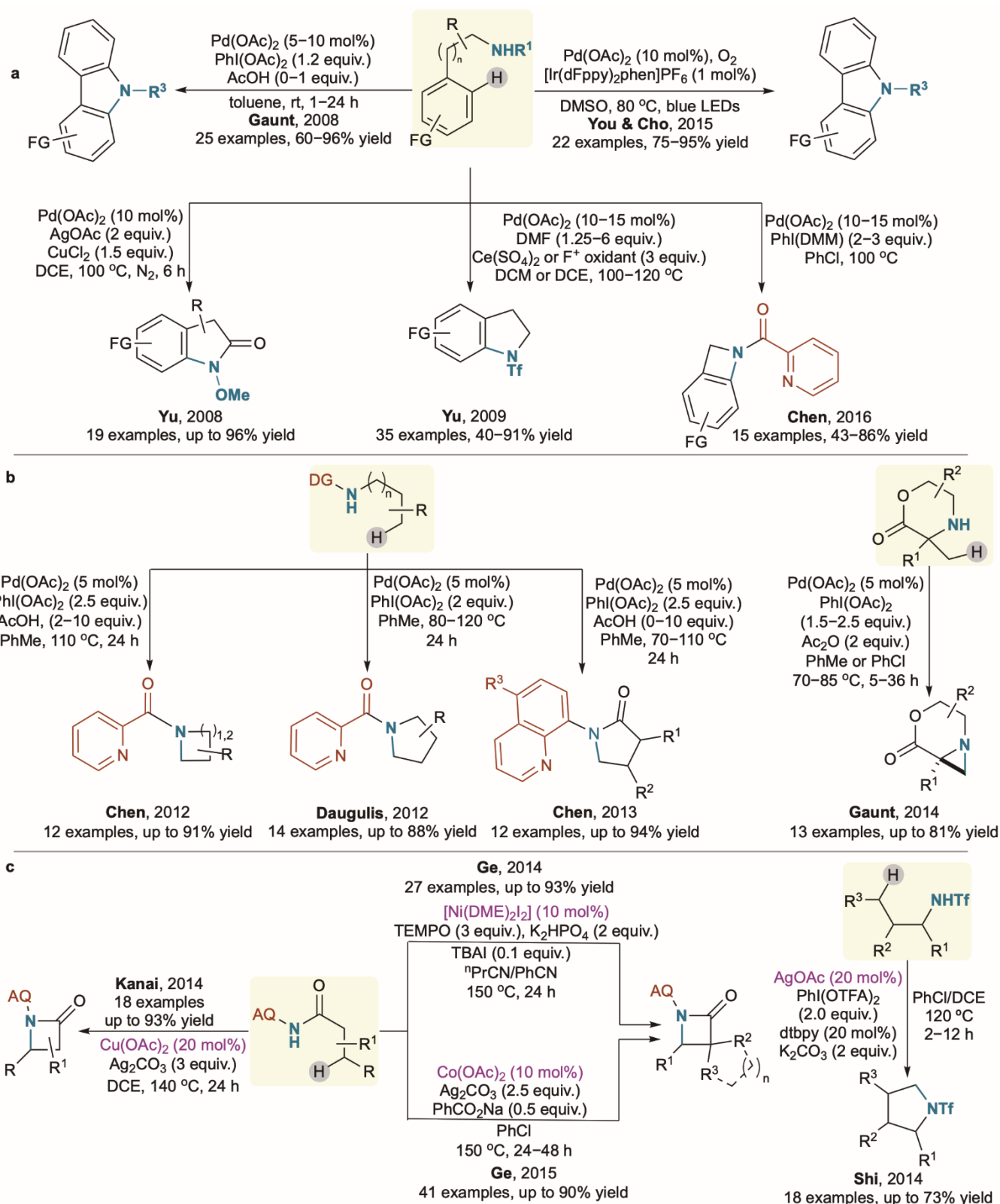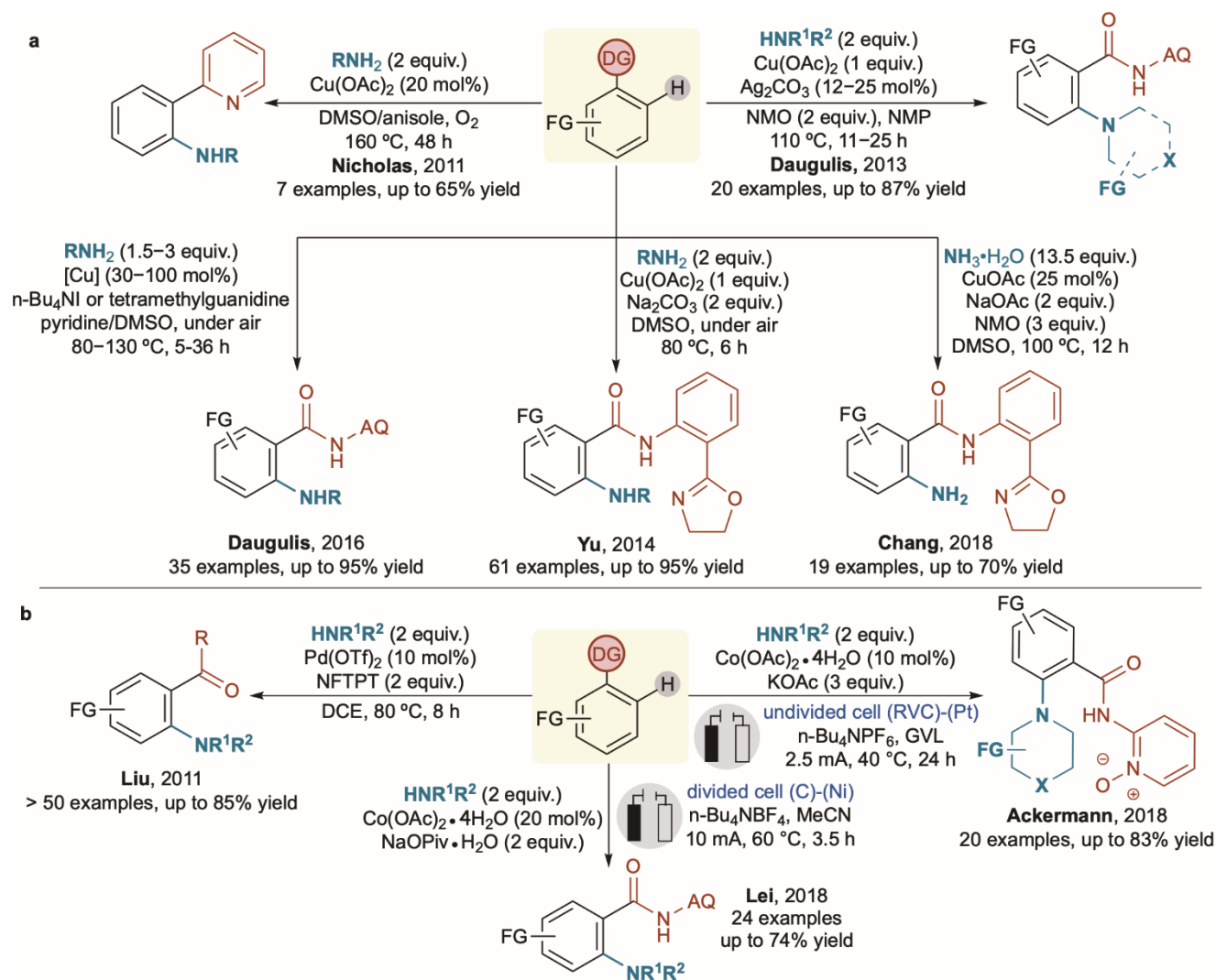
Fig. 5| Intramolecular oxidative cross-dehydrogenative couplings (CDC). a, Pd-catalysed C(sp²)–N bond-forming reactions via Pd[II/IV] catalytic cycles .[58,59,60,62,65] **b,** C(sp³)–H/N–H couplings catalysed by Pd(OAc)₂ using PhI(OAc)₂ as oxidant.[67,68,69,70] **c,** Intramolecular C(sp³)–N bond-formation with alternative TM catalytic systems.[71,72,73,74] | Ac, acetyl; AQ, 8-aminoquinoline; DCE, dichloroethane; DME, dimethoxyethane; dFppy, 2-(2,4-difluorophenyl)pyridine; DG, directing group; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; dtbpy, 4,4'-di-t-butyl-2,2'-bipyridine; FG, functional group; LED; light emitting diode; OTFA, trifluoroacetate anion; Ph, phenyl; PhI(DMM), phenyliodonium dimethylmalonate; Pr, propyl; TBAI, tetrabutylammonium iodide; TEMPO, (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl; Tf, trifluoromethylsulfonyl.
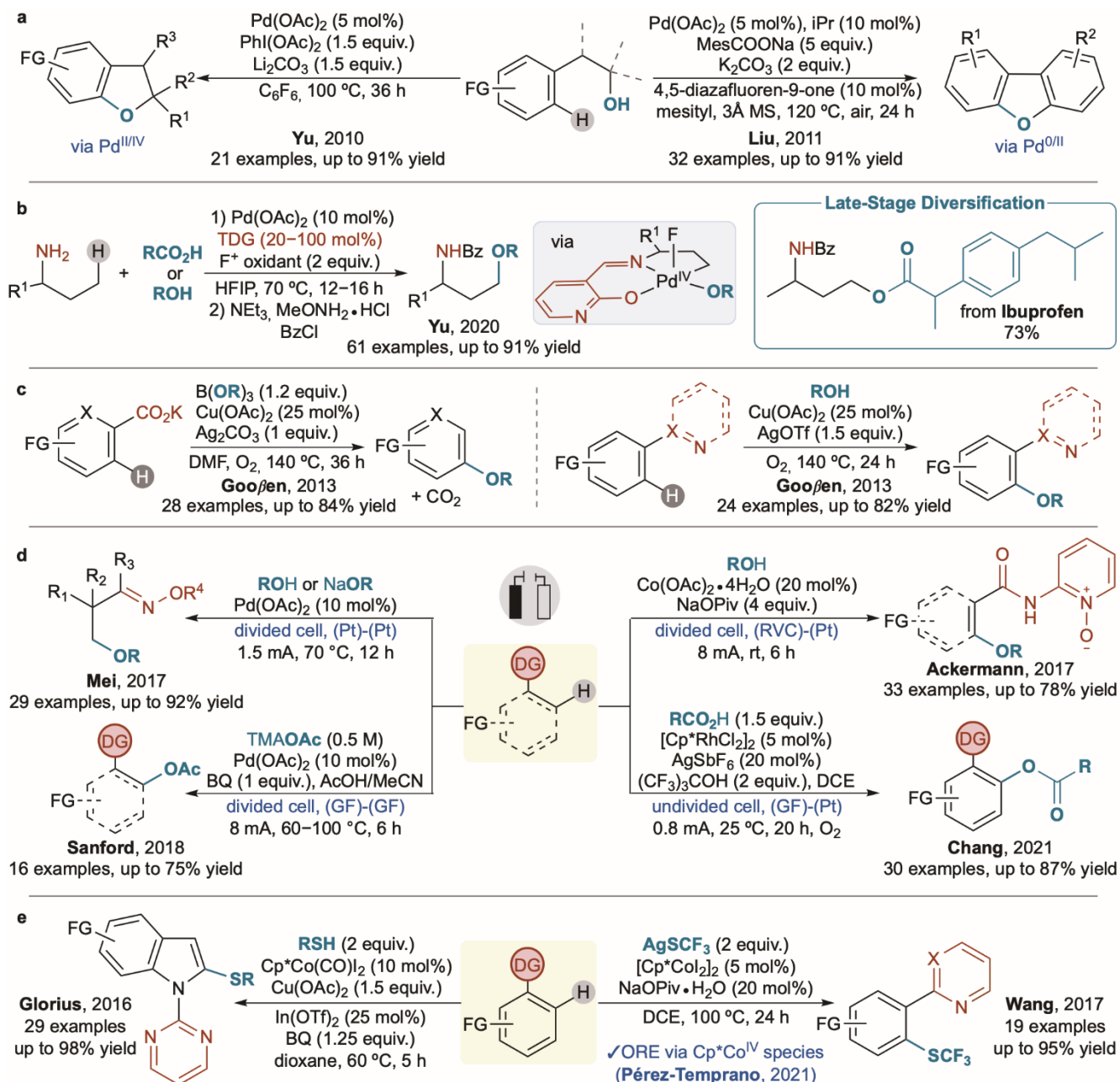
Fig. 6| Intermolecular C–H activation/C–N bond-forming reactions. a, Intermolecular C–H aminations catalysed by Cu-based systems.[76,77,78,79,80] **b,** TM-catalysed directed C–N bond-forming reactions.[81,82,83] | Ac, acetyl; AQ, 8-aminoquinoline; Bu, butyl; DCE, dichloroethane; DG, directing group; DMSO, dimethyl sulfoxide; FG, functional group; GVL, γ-valerolactone; Me, methyl; NFTPT, *N*-fluoro-1,3,5-trimethylpyridinium triflate; NMO, *N*-Methylmorpholine *N*-Oxide; NMP, *N*-Methyl-2-Pyrrolidone; OPiv, pivalate; RVC, reticulated vitreous carbon; Tf, trifluoromethylsulfonyl.

Fig. 7| TM-catalysed nucleophilic C–H activation/C–O and C–S bond forming reactions. a, Intramolecular C–O bond-forming reactions catalysed by Pd(OAc)$_2$.[84,85] **b,** Pd-catalysed C(sp^3)–H oxygenation of free amines via high-valent Pd^{IV} intermediates.[88] **c,** Cu-catalysed etherification of C–H bonds promoted by a bimetallic Cu/Ag cooperation due to the *in situ* formation of AgOR as transmetalating agents.[89,90] **d,** C–H oxygenation via electrochemical oxidation.[92,93,94,95] **e,** Site-selective C–H functionalisation with S-based nucleophiles.[96,97,98] | BQ, benzoquinone, Bz, benzoyl; Cp*, pentamethylcyclopentadienyl; DCE, dichloroethane; DG, directing group; DMF, dimethylformamide; FG, functional group; GF, Graphite; MS, molecular sieves; OAc, acetate; ORE, oxidatively induced reductive elimination; OPiv, pivalate; RVC, reticulated vitreous carbon; TDG, transient directing group; Tf, trifluoromethylsulfonyl.