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REVIEW SUMMARY

ORGANIC CHEMISTRY

Arene diversification through distal C(sp^2)–H functionalization

Uttam Dutta†, Sudip Maiti†, Trisha Bhattacharya, Debabrata Maiti*

BACKGROUND: Organic synthetic chemistry has facilitated the production of medicines, agrochemicals, food, polymers, dyes, and more through step- and atom-economical pathways. Most of these value-added products consist of complex molecular frameworks that can be constructed from simple starting materials by either functional group interconversion or installation of new functionality or coupling units. Incorporation of new functionality through direct replacement of a C–H bond, the most common constituent of organic molecules, has emerged as an attractive synthetic tool, particularly for its atom economy. However, to be useful, the process has to be highly regioselective to avoid costly time- and energy-intensive separations of similar product isomers.

For aromatic and heteroaromatic ring substrates, regioselective C–H functionalization implies the installation of a functional group selectively at *ortho*-, *meta*-, or *para*-positions one, two, or three carbons away from a substituent that is already present. Traditional approaches to achieving this goal have relied on subtle reactivity differences arising from steric and electronic effects associated with each substituent. Although electronically controlled C–H functionalization of arenes by Friedel-Crafts reactions has been known for over a century, such methods often suffer from poor selectivity and limited substrate scope. A quest to find a putative reaction path that would override intrinsic electronic or steric bias is therefore an active research area. In the last three decades, there have been notable advances in the realm of proximal *ortho*-C–H functionalization with the assistance of a coordinating directing group. However, accessing distal *meta*- and *para*-C–H functionalization of electronically and sterically unbiased arenes remained elusive until much more recently. The development of suitable synthetic methods that enable distal *meta*- or *para*-C–H functionalization with prominent selectivity remains an active challenge for researchers in the synthetic chemistry field.

ADVANCES: Steric and/or electronic influences can be manipulated through the design of suitable catalysts, ligands, or reagents that alter the traditional patterns of regioselectivity. Several approaches have been implemented in the past decade for the selective functionalization of *meta* and *para*-C–H bonds along these lines. These include (i) σ-bond activation–assisted remote C–H functionalization, in which initial ortho-cycloruthenation plays a crucial role; (ii) template-assisted remote C–H functionalization; (iii) the use of a bifunctional template for remote C–H activation of heteroarenes; and (iv) remote C–H functionalization enabled by noncovalent interactions such as ion pairing and hydrogen bonding. Pairing palladium with a transient mediator in conjunction with a precise directing group has also emerged as a viable approach. Finally, nondirected remote C–H activation protocols that rely on cooperative catalysis, ligand, or reagent control of regioselectivity have been reported.

OUTLOOK: Emergence of the aforementioned distal C–H functionalization techniques has recast numerous synthetic routes to producing value-added chemicals. One of the major challenges associated with increasing the practicality of this chemistry is to discover more environmentally benign, cost-effective, scalable, and sustainable catalytic systems with very high turnover number. Expanding the catalytic toolbox in this fashion will enable the synthetic modification of hitherto inaccessible sites of organic molecules and enhance the discovery and manufacture of pharmaceuticals, agrochemicals, and other desired materials. ■

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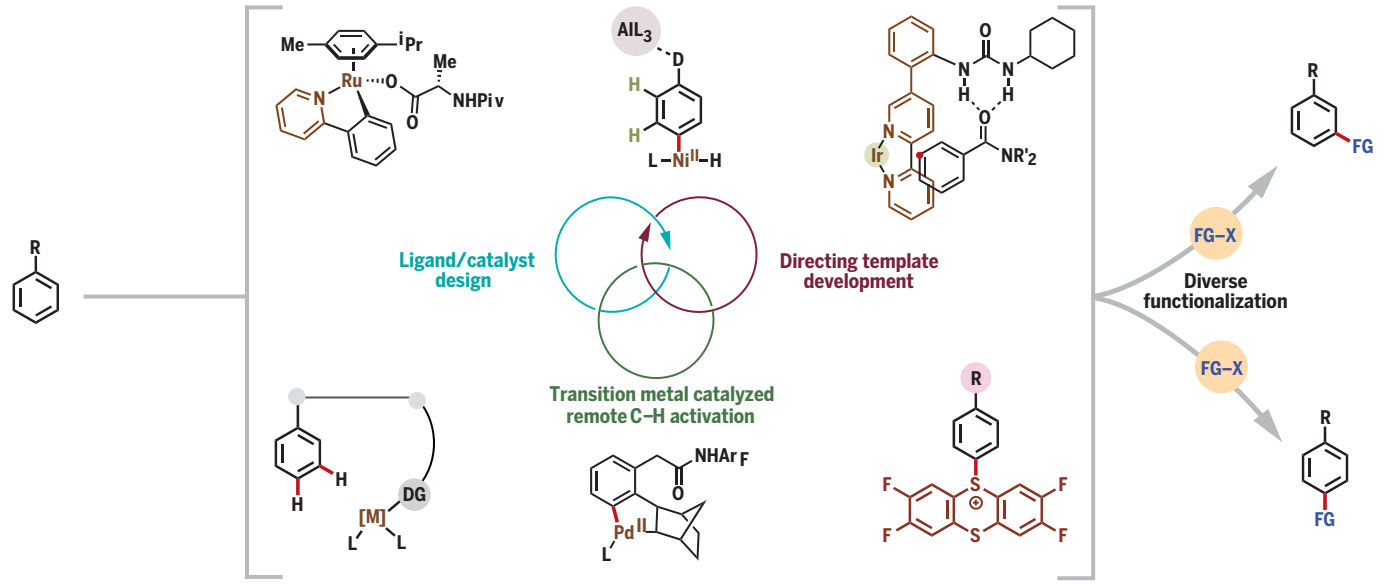

Distal C–H functionalization of arenes. Transition metal catalysts paired with an optimal ligand, directing group (DG), and/or mediator can add a functional group (FG) two or three carbons away from an existing group (R) on an aryl ring.

REVIEW

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Arene diversification through distal C(sp^2)–H functionalization

Uttam Dutta†, Sudip Maiti†, Trisha Bhattacharya, Debabrata Maiti*

Transition metal–catalyzed aryl C–H activation is a powerful synthetic tool as it offers step and atom-economical routes to site-selective functionalization. Compared with proximal *ortho*-C–H activation, distal (*meta*- and/or *para*-) C–H activation remains more challenging due to the inaccessibility of these sites in the formation of energetically favorable organometallic pretransition states. Directing the catalyst toward the distal C–H bonds requires judicious template engineering and catalyst design, as well as prudent choice of ligands. This review aims to summarize the recent elegant discoveries exploiting directing group assistance, transient mediators or traceless directors, noncovalent interactions, and catalyst and/or ligand selection to control distal C–H activation.

The advent of new chemical methodologies has enriched the repertoire of organic chemists to synthesize molecules with amazing complexity by modifying arene C–H bonds. By virtue of the near-universal preponderance of C–H bonds in aromatic systems, direct C–H functionalization techniques offer an opportunity for structural modification at any carbon center through step- and atom-economical pathways. Further, C–H functionalization may allow synthetic chemists to introduce a diverse range of functionalities to previously inaccessible carbon centers of complex molecules, providing analogs with potentially improved biological properties (Fig. 1A) (*1*). Despite the enormous potential of direct C–H functionalization, its widespread application is hindered considerably by regioselectivity issues. Although electrophilic aromatic substitution (S_EAr) reactions, in which regioselectivity is governed by the electronic nature of the substituents, has long been recognized as a powerful synthetic method to functionalize C–H bonds of arenes (Fig. 1B), achieving complementary *meta*-selective or *para*-selective functionalization, avoiding the formation of *ortho*-functionalized products, has been an active research area in the past decade. To override the innate site selectivity imparted by the starting substitution pattern, synthetic chemists devised various strategies to achieve distal C–H functionalization. The major challenge associated with the regioselective C–H functionalization of arenes is to distinguish the subtle reactivity difference of multiple C–H bonds. Although the transition metal–catalyzed activation of proximal C–H bonds is favored thermodynamically through the formation of conformationally rigid five-, six-, and even seven-membered metallacyclic intermediates, selectively targeting a C–H bond that is distant from existing functional groups remains an arduous task. Nevertheless, in recent years, several strategies have been developed to achieve the regioselective functionalization at remote *meta*- and *para*-positions of arenes. These include (i) σ-bond activation–assisted remote C–H functionalization, in which initial *ortho*-cycloruthenation plays a crucial role in favoring the electrophilic or radical coupling selectively at the *meta*- or *para*-position depending on the nature of chelating functional group (Fig. 1C) (*2*); (ii) template-assisted remote C–H functionalization (Fig. 1D); (iii) use of a bifunctional template for remote C–H activation of heteroarenes (Fig. 1E); and (iv) noncovalent interaction–enabled remote C–H functionalization (Fig. 1F) (*3*–*5*). The latter three approaches mainly rely on the direct release of the reactive metal center within close proximity to the remote C–H bond by incorporating a molecular bridge to constrain the distance and geometric relationship between the metal and the substrate. Further, the use of palladium and/or transient mediator cooperative catalysis in conjunction with a precise directing group has also emerged as a viable approach to activating remote C–H bonds (Fig. 1G) (*6*). Several approaches have also been developed for nondirected remote C–H activation in which regioselectivity is mainly governed by the catalysts, ligands, and/or reagents (Fig. 1H) (*7*). In this review, we aim to summarize chronologically the genesis, development, and applicability of these advances in regioselective *meta*- and *para*-C–H functionalization.

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σ-Bond activation–assisted *meta*- and *para*-C–H functionalization

As stated earlier, the electronically controlled S_EAr reaction is a powerful synthetic method to functionalize C–H bonds of arenes. Nevertheless, electronic properties of arenes could also be manipulated through C–H metalation. In 1994, Roper observed *para*-C–H nitration of phenyl in ruthenium complex **1** (Fig. 2A, i) (*8*). Later, a distinct regioselectivity pattern was observed by Coudret during halogenation of *ortho*-C–H ruthenated complex ***3*** (Fig. 2A, ii) (*9*). This functionalization was believed to proceed through S_EAr, with the selectivity governed by the Ru– C_{aryl} σ-bond, and was therefore called σ-bond activation–assisted C–H functionalization (*3*).

The potential application of these seminal reports involving stoichiometric Ru-arene complexes remained dormant until 2011, when the group of Ackermann observed the formation of *meta*-alkylated product, **7′** in 7% yield during their investigation of Ru-catalyzed *ortho*-C–H alkylation of **5** with primary alkyl halides (Fig. 2B, i) (*10*). Despite the mechanistic ambiguity and very low yield, this is considered the first report of catalytic σ-bond activation–assisted distal C–H functionalization. Contemporaneously, Frost and coworkers disclosed a catalytic *meta*-selective sulfonylation of 2-phenylpyridine with arylsulfonylchloride in synthetically useful yield (Fig. 2B, ii) (*11*). Consistent with the previous report by Roper and Wright, a S_EAr mechanism was posited to rationalize the *para*-selectivity with respect to the Ru–C_{aryl} σ-bond of **9**. Subsequently, *meta*-selective alkylation of arenes bearing *ortho*-directing groups was achieved by Ackermann in 2013 (Fig. 2B, iii) (*12*). That reaction was found to be retarded in the presence of TEMPO, a radical scavenger. Racemization of enantiomerically pure secondary alkyl halides was observed under the reaction conditions, adding support for homolytic cleavage of the C–Br bond. However, a competent catalytic cycle was yet to be conceived that could trigger subsequent developments in this domain.

Later in 2015, Ackermann (*13*) and Frost (*14*) concurrently reported *meta*-selective alkylation with tertiary alkyl halides that revealed an interesting mechanistic feature. Radical coupling between alkyl radical and *ortho*-ruthenated arene was proposed in lieu of classical electrophilic aromatic substitution. The Ru catalyst was suggested to play a dual role: reversible *ortho*-C–H ruthenation, followed by single-electron transfer to facilitate alkyl radical formation. According to the proposed mechanism (Fig. 2C), tertiary alkyl radical interacted with *ortho*-ruthenated organometallic species **B** to deliver intermediate **C**. Guided by electronic influence, selective coupling occurred at the *para*-position with respect to the Ru–C_{aryl} bond. Subsequently, redox re-aromatization, hydrogen abstraction and proto-demetalation followed to form the desired *meta*-alkylated compound.

This mechanistic disclosure prompted many useful synthetic developments. Because of the

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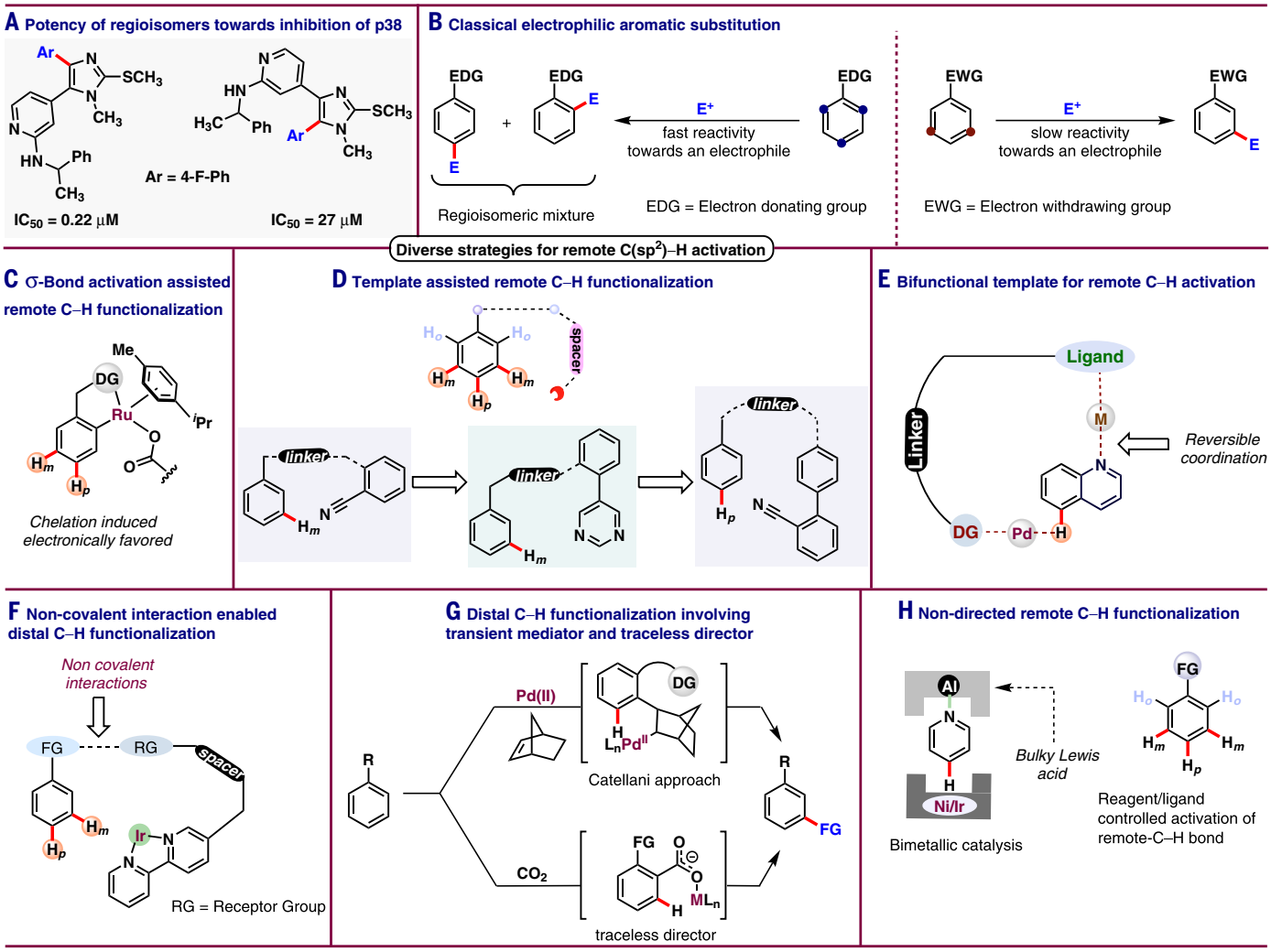

Fig. 1. Overview of diverse strategies for remote C(sp^2)–H activation. [M], transition metal; FG, functional group.

ubiquity of bromoarenes in cross-coupling reactions, regioselective bromination is one of the most desirable transformations. Ru–C_{aryl} σ-bond assistance was applied in *meta*-selective bromination of 2-phenylpyridine derivatives with tetrabutylammonium tribromide and *N*-bromosuccinimide, respectively, by Greaney (*15*) and by Huang (*16*) (Fig. 2D, i). In 2017, Li's group described the *meta*-selective alkylation of phenol derivatives using easily cleavable 2-phenoxypyridine as a substrate (Fig. 2D, ii) (*17*). The introduction of fluorine substituents is of paramount importance in pharmaceutical and agrochemical research for optimizing electronic properties and metabolic stability. In 2017, Ackermann's group reported *meta*-selective fluoroalkylation using a dual-ligand combination of electron-deficient triarylphosphine and carboxylate (Fig. 2D, iii) (*18*). Unlike secondary or tertiary alkyl halides, α-halocarbonyls are challenging coupling partners because of their affinity toward oxidative addition. Frost devised a *meta*-alkylation protocol using a relatively challenging α-halocabonyl coupling partner (Fig. 2D, iv) (*19*). Mechanistically, the desired *meta*-selectivity was achieved through cooperative catalysis of Ru(II) biscarboxylate and either a phosphine ligand or Pd(0) cocatalyst.

Direct C–H/C–H oxidative coupling through *meta*-selective benzylation of 2-phenylpyridine with toluene (**19**) was achieved by Zhao (*20*) and Shi (*21*) independently in 2017 (Fig. 2D, v). These studies used, respectively, di-tert-butylperoxide and heptafluoroisopropyl iodide ($^iC_3F_7I$) as a radical initiator. The regioselective switch from *ortho*- to *meta*-benzylation was demonstrated by Zhao when (±)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNDHP) was used as a ligand. A similar transformation was also reported by Ackermann using benzyl chlorides in conjunction with Ru(II) and a phosphine ligand (Fig. 2D, vi) (*22*).

Later, Greaney reported *meta*-selective carboxylation of arenes bearing various *ortho*-directing groups using CBr_4 as the C1 source (Fig. 2D, vii) (*23*). After the pioneering work by Roper, it took more than a decade to realize a Ru(0)–catalyzed *meta*-selective nitration of 2-phenylpyridine involving Ru–C_{aryl} σ-bond activation (Fig. 2D, viii) (*24*). A biscyclometalated Ru-complex, **25** was presented as an effective intermediate to couple with an in situ–generated nitro radical. In a recent report, our group demonstrated *meta*-selective nitration of 2-phenoxypyridine that was believed to follow a similar mechanism (*25*). Directing group removal produced *meta*-nitro phenol, a complementary outcome to the regioselectivity associated with Friedel-Crafts type nitration mechanisms. Progress in σ-bond activation–assisted C–H functionalization was substantially reinforced by the cooperation of phosphine and carboxylate ligands. The utility of a similar dual-ligand system was successfully exploited by Liang to harness three-component *meta*-selective coupling (Fig. 2E) (*26*).

In contrast to Ru–C_{aryl} σ-bond assisted *meta*-selective functionalization, *para*-C–H functionalization remained less explored. In 2017, Frost

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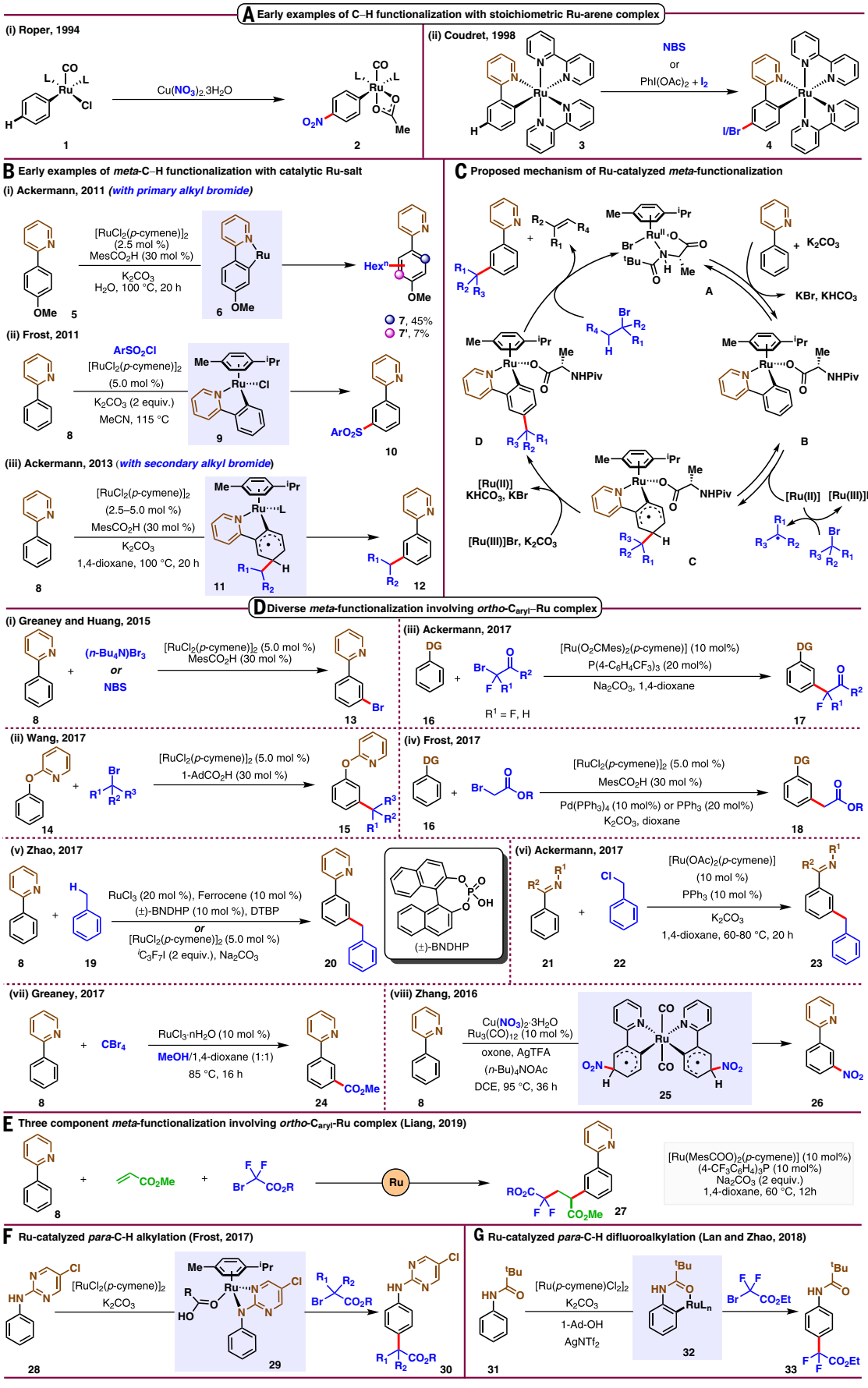

Fig. 2. σ-Bond activation–assisted *meta*- and *para*-C–H functionalization. NBS, *N*-bromosuccinimide; Mes, mesityl; *p*-cymene, 4-isopropyltoluene; DTBP, di-*tert*-butyl peroxide.

elaborated a complementary *para*-selective alkylation with 2-pyrimidinylaniline derivative, **28** (Fig. 2F) (*27*). A 4-membered cyclo-metallic species **29** was proposed to be responsible for the complementary *para*-selectivity. Computational studies revealed that in the presence of carbonate base, N–H ruthenation was preferred over C–H ruthenation (as observed in *meta*-C–H functionalization, assisted by acetate base). Mechanistically, the alkyl radical, generated from α-bromo esters, was preferentially coupled at the *para*-position of the redox active intermediate (**29**) to deliver the *para*-alkylated aniline derivatives (**30**). Later in 2018, Zhao *et al.* demonstrated a *para*-selective difluoromethylation of *N*-pivaloylaniline (**31**), in which C–H ruthenated 6-membered metalacyclic species **32** was proposed as the effective intermediate (Fig. 2G) (*28*). Control experiments revealed that the *ortho*-C–H ruthenation was crucial for the desired regioselectivity.

Remote-directing templates for C–H functionalization

Covalently attached directing templates for remote C–H functionalization

As discussed in the previous section, the σ-chelating ability of conventional *ortho*-directing groups could manipulate the electronic properties of apparently equivalent distal C–H bonds to attain regioselective functionalization. Despite substantial progress, these transformations often involve either a free radical pathway or a S_EAr mechanism to offer precise site selectivity, which in turn limits reaction scope substantially. One way to solve this problem could be the direct release of the reactive metal catalyst in close proximity to the targeted remote C–H bond. However, this approach requires the formation of a larger macrocyclic pretransition state (more than seven-membered) by the transition metal-directing group complex, leading to a thermodynamically disfavored cyclometalated intermediate. The key factors for the development of a remote-directing template should be (i) a simple reaction sequence for attachment and detachment of the directing template, (ii) compatibility of the directing template with the reaction conditions, (iii) coordination abilities of the directing group, and (iv) stability of the macrocyclic pretransition state. The precise spatial positioning of the directing group is also a requisite factor to selectively activate one of the many stereoelectronically similar remote-C–H bonds (*3*, *4*). To overcome these obstacles, Yu and coworkers developed an end-on template bearing a linear nitrile functionality as the directing group (Fig. 3A, i) (*29*). In this template, the specific combination of long tethering fragment and rigid, linear nitrile preferentially positions the Pd-catalyst proximal to the *meta*-C–H bond, disfavoring the competing *ortho*-palladation (for which the small cyclic pretransition state imposes high ring strain). The weak coordinating nature of nitrile group also assists in stabilizing the macrocyclic organometallic intermediate by releasing the ring strain in the pretransition state. The application of this rigid, U-shaped, template-based strategy was first realized in 2012 to achieve highly selective *meta*-C–H olefination of toluene and hydrocinnamic acid derivatives (*30*). In the case of toluene derivatives, the inclusion of bulky *tert*-butyl groups in the nitrile-containing end-on template assisted in constraining the macrocyclophane pretransition state through the Thorpe-Ingold effect (otherwise, the template-based assembly could suffer from increased conformational flexibility, leading to complete loss of both reactivity and selectivity). Whereas, a benzonitrile template ($\mathbf{T_2}$) was employed via an easily cleavable amide linkage to olefinate *meta*-C-H bond of hydrociannamic acid. Further computational studies by Yu, Wu, and Houk revealed that the crucial *meta*-C–H activation event actually occurs through a concerted metalation-deprotonation mechanism involving a heterodimeric [Pd(II)-Ag(I)] species (**35**) (*31*). The nitrile group coordinates to the silver center, which then places the palladium catalyst proximal to the *meta*-position of the arene through an acetate bridge. Subsequently, the same research group reported *meta*-C–H arylation and methylation of hydrocinnamic derivatives using an analogous U-shaped template ($\mathbf{T_2}$) (*32*). In all of these transformations, the use of a combination of mono-*N*-protected amino acid (MPAA) ligands and HFIP solvent was essential to achieve improved yields and selectivity. Building on these pioneering studies, in 2014, Tan developed an elegant silicon-tethered nitrile template ($\mathbf{T_3}$) for the *meta*-C–H olefination of benzyl alcohols (*33*). In 2014, our group developed an ester-tethered hydroxybenzonitrile template ($\mathbf{T_4}$) to accomplish *meta*-C–H olefination of phenylacetic acid derivatives (Fig. 3A, ii) (*34*). The presence of an electron–donating –OMe group enhanced the template efficacy by reducing the in situ transesterification with hexafluoroisopropanol. This method is operationally simple and involves a low-molecular-weight 2-hydroxy-5-methoxy benzonitrile template ($\mathbf{T_5}$) compared with the previous reports. In 2015, our group investigated the *meta*-C–H olefination of benzylsulfonyl ester derivatives using the commercially available 2-hydroxybenzonitrile ($\mathbf{T_4}$) directing group (DG) (*35*). A wide variety of mono-olefinated and di-olefinated products was furnished in excellent *meta*-selectivity under the optimized reaction conditions. Subsequently, our group further expanded this nitrile-based template–assisted strategy to enable diverse *meta*-C–H functionalization, including hydroxylation and acetoxylation of benzylsulfonic acid derivatives; olefination, silylation, and germanylation of arylsulfonates; olefination of biaryl phenols and carboxylic acids; olefination, acetoxylation, and hydroxylation of benzylphosphonate derivatives; and olefination of benzyl silanes (Fig. 3A, iii) (*36*–*39*). However, the direct *meta*-C–H functionalization of benzoic acid derivatives was elusive because of the inherent *ortho*-directing tendency of the carboxylate group, electron deficiency, and deleterious conformational flexibility of the macrocyclic pretransition state (*40*). In 2016, Li *et al.* developed an amide-linked, flexible, alkyl-tethered, nitrile-based template to achieve *meta*-C–H olefination and acetoxylation of benzoic acid derivatives (Fig. 3A, iv) (*41*). In the following year, Yu's group described *meta*-C–H olefination of benzoic acids using an analogous amide-linked nitrile template containing 2-cyanophenol as the directing group (*42*). Diversification of *N*-heterocyclic substrates represents a valuable synthetic transformation because of their abundance in many bioactive natural products. In 2014, Yu and coworkers described the *meta*-C–H olefination and acetoxylation of amine-containing substrates by introducing a new nitrile-containing template (**46**) (Fig. 3A, v) (*43*). Later, the same group used a modified U-shaped nitrile-based template to achieve *meta*-C–H olefination, arylation, and acetoxylation of indoline analogs (**47**) (*44*). In contrast to the established directional features of nitrile-based directing groups, a recent seminal report by Li and coworkers demonstrated the first example of carboxyl group directed *meta*-selective C–H arylation and olefination reactions (Fig. 3A, vi) (*45*). The key to achieving the desired selectivity was the suppression of the κ^1-coordination mode of the carboxylate, which would otherwise favor the undesired *ortho*-C–H activation. The κ^2-coordination mode of the carboxyl group actually directs the active palladium catalyst to the target *meta*-C–H bond and generates a cyclophane-like pretransition state.

Despite the success of nitrile-based templates, their weakly coordinating nature and incompatibility with harsh conditions motivated a search for an alternative robust directing group. To overcome these aforementioned difficulties, Yu's group exploited more strongly coordinating pyridine motifs in the directing template to effect *meta*-C–H iodination through a more tightly associated macrocyclophane pretransition state (*46*). In 2017, our group introduced an 8-nitroquinoline–based template to achieve *meta*-C–H alkenylation and acetoxylation of arenes (*47*). We proposed that in this template, strong σ-coordinating 8-nitroquinoline offers a bidentate coordination mode to the reactive Pd center, leading to the formation of a stable palladacycle. Although this work shows the potential of a bidentate-directing group to functionalize distal position of arenes, providing flexibility to the macrocyclic pretransition state is a challenging task.

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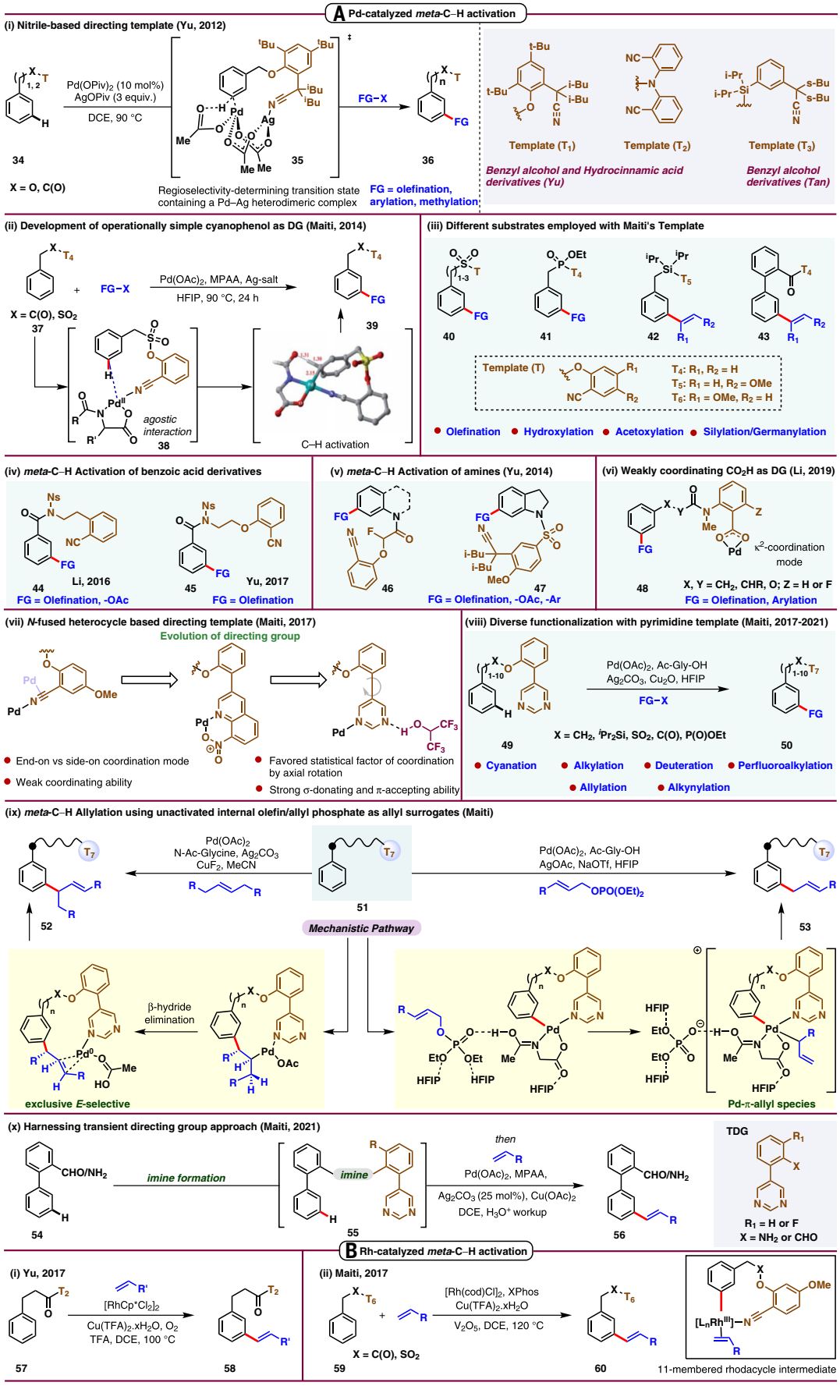
Fig. 3. Covalently attached directing templates for *meta*-C–H functionalization. Piv, pivaloyl; HFIP, hexafluoroisopropanol; OTf, triflate; MeCN, acetonitrile; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; Cp*, 1,2,3,4,5-pentamethylcyclopentadienyl; Ar, aryl; DCE, 1,2-dichloroethane.



Subsequently, our group designed a biphenyl pyrimidine–based template (**T7**) to achieve *meta*-C–H alkylation and alkenylation of arenes using allyl alcohol as a coupling partner (Fig. 3A, viii) (*48*). Subsequently, we disclosed *meta*-C–H cyanation of arenes bearing diverse functionality using a similar pyrimidine-based template (*49*). The superiority of this biphenyl pyrimidine–based template could be ascribed to three factors: (i) Its strong σ-coordination leads to a more tightly associated cyclophane-like pretransition state, (ii) the energetically low-lying π-orbitals of the pyrimidine ring render the Pd center electropositive, and (iii) irrespective of axial rotation across the biaryl motif, the directing *N*-atom of the pyrimidine ring remained close to the desired *meta*-C–H bond (Fig. 3A, vii). Building on this strategy, our group expanded the scope of *meta*-C–H functionalization to allylation, perfluoroalkenylation, deuteration, and alkynylation of a wide variety of arenes, including pharmaceutical agents (Fig. 3A, viii) (*50*–*52*). This pyrimidine-based template was also successfully applied to functionalization of the *meta*-C–H bond of arenes containing long alkyl chains. Efficacy of the pyrimidine-directing group was further elaborated in our recent study in which the concept of covalently labile imine linkage formation between substrate and directing template was introduced to functionalize *meta*-C(sp^2)–H bonds of biphenyl aldehydes and amines. This protocol offered an opportunity to avoid the additional synthetic steps involved in directing template attachment and detachment (Fig. 3A, x) (*53*).

Thus far, we have described the wide applicability of the template-directed strategy in enabling diverse remote site-selective C–H functionalizations by Pd catalysis. In search of an alternative catalytic platform, Yu and coworkers developed an Rh(III)-catalyzed *meta*-selective C–H alkenylation reaction for aniline, carboxylic acid, and indoline derivatives using a modified nitrile template (Fig. 3B, i) (*54*). Our group reported a Rh(III)-catalyzed *meta*-C–H olefination reaction for a wide variety of cyanophenol template–anchored benzylsulfonyl ester and phenyl acetic acid ester derivatives, which further demonstrates the applicability of this strategy for other metals (Fig. 3B, ii) (*55*). The desired site selectivity for this process was governed by the formation of an 11-membered rhodacyclic intermediate.

Since the pioneering report by Yu's group in 2012, the covalently linked template strategy has proven highly effective for regioselective transformations at the *meta*-position. In 2015, our group developed a recyclable silyl ether–linked *para*-substituted biphenyl cyano-based template (**63**) to achieve *para*-C–H activation (Fig. 4A). Initially, *para*-selective C–H olefination and acetoxylation of toluene derivatives and olefination of phenols were achieved using this D-shaped template (Fig. 4B) (*56*, *57*). Subsequently, we realized that the steric and electronic modulation of the directing template was necessary to introduce other functionality selectively at the *para*-position (Fig. 4C). We found that the inclusion of two methoxy groups in the nitrile- containing arene ring increased the reactivity as well as the directing ability of the nitrile group toward the *para*-C–H bond. We reported the *para*-C–H silylation (**67**) and ketonization (**68**) of diverse arenes using this second-generation template (Fig. 4D) (*58*, *59*). Very recently, we also demonstrated that this D-shaped assembly was successful in delivering *para*-C–H olefinated products with Rh catalysis (Fig. 4E) (*60*). In 2019, Yu and coworkers reported the *para*-C–H acetoxylation of electron deficient benzoic acid derivatives (**70**) using an amide-linked biphenyl cyano-based template (Fig. 4F) (*61*).

Noncovalent interaction enabled remote-C–H functionalization

The use of directing groups has become imperative to selectively functionalize the distal C–H bonds of arenes. However, covalently attaching a directing group is step intensive, requiring prefunctionalization installation and postfunctionalization removal. Noncovalent interactions routinely induce selective transformations in asymmetric organocatalysis and in enzymatic catalysis (*62*, *63*). There has been a recent upsurge in merging noncovalent interactions with transition metal catalysis to promote site-selective C–H activation chemistry. In principle, three factors play pivotal roles for noncovalent interaction–enabled, transition metal–catalyzed site-selective C–H functionalization: (i) molecular recognition, (ii) stabilization of the transition state, and (iii) substrate concentration (*64*). Noncovalent interactions are relatively weak, displacement of the product by the substrate occurs readily in a catalytic cycle.

As far as arene C–H borylation is concerned, the regioselectivity of this process is extremely interesting and rather distinctive (*65*). Unlike classical arene chemistry, in which electronics are the key controlling element for regioselectivity, iridium-catalyzed C–H borylation is generally governed by the steric demand of the substituents. Thus, achieving regioselectivity by overriding the intrinsic steric preference in C–H borylation of arenes is a major challenge. In this context, noncovalent interactions have emerged as strong drivers for the development of modified borylation strategies to manipulate regioselectivity beyond simple steric control. Although most examples centered on proximal directing strategies for *ortho*-selective borylation, the last few years have witnessed an upsurge in the application of noncovalent interactions to accomplish iridium-catalyzed borylation at more remote *meta*- and *para*-positions (Fig. 5A).

In the current scenario, five different catalytic systems are capable of borylating arene *meta*-C–H bonds with excellent regioselectivity. The pioneering *meta*-selective C–H borylation not dictated by sterics was reported by Kuninobu, Kanai, and coworkers in 2015 using an elegant H-bonding interaction motif (Fig. 5B) (*66*). In this strategy, the authors used a modified bipyridine ligand **74** bearing a urea-based hydrogen bond donor unit to interact with an H-bond acceptor unit on the arene substrate, bringing the reactive iridium metal center in close proximity to the desired *meta*-C–H bond. A wide range of arenes bearing H-bond acceptor groups such as amides, phosphonates, phosphonic diamides, and phosphine oxides were compatible under the optimized reaction conditions to afford *meta*-C–H borylated products with excellent selectivity. The conventional iridium-catalyzed borylation conditions using 4,4′-di-*tert*-butyl-2,2′-dipyridyl as a ligand showed poor regioselectivity for all of these substrates.

The second approach to *meta*-C–H borylation has relied on the in situ generation of imines from the corresponding aromatic aldehydes and a secondary B–N interaction (Fig. 5C) (*67*). The electron-rich 3,4,7,8-tetramethylphenanthroline proved the optimal ligand and provided the desired *meta*-C–H borylated products in high selectivity. Although the origin of this observed *meta*-selectivity remains unclear, it is proposed that in the transition state, a dative bond between the *B*-atom of the pinacolatoboron and the *N*-atom of the imine facilitates encapsulation of the imine substrate into the pocket of the tris(boryl)iridium complex (**77**) and thus places the *meta*-C–H bond over the iridium center.

Another noncovalent interaction between ion pairs was introduced by Phipps' group to achieve *meta*-C–H borylation of charged substrates (Fig. 5D). The *meta*-selectivity was rationalized through a transition state, **79,** in which the ion-pair interaction between the appended sulfonate group (anionic counterpart) of a bipyridine ligand and the aromatic quaternary ammonium salt regulates the substrate-catalyst orientation in such a way that the tris(boryl)iridium-bipyridine complex comes close to the desired *meta*-C–H bond (*68*). This same sulfonate-substituted bipyridine ligand was also capable of acting as a proficient hydrogen bond acceptor (**82**) to direct iridium-catalyzed borylation selectively at the *meta*-position of arenes bearing trifluoroacetyl-protected amines as hydrogen bond donors (Fig. 5E) (*69*). The regioselectivity of conformationally strained substrates was very poor, which could be attributed to the fact that some extent of conformational relaxation in the substrate was required to enable a fruitful hydrogen-bonding interaction with the ligand. In 2019, Phipps' (*70*) and Smith's (*71*) groups independently

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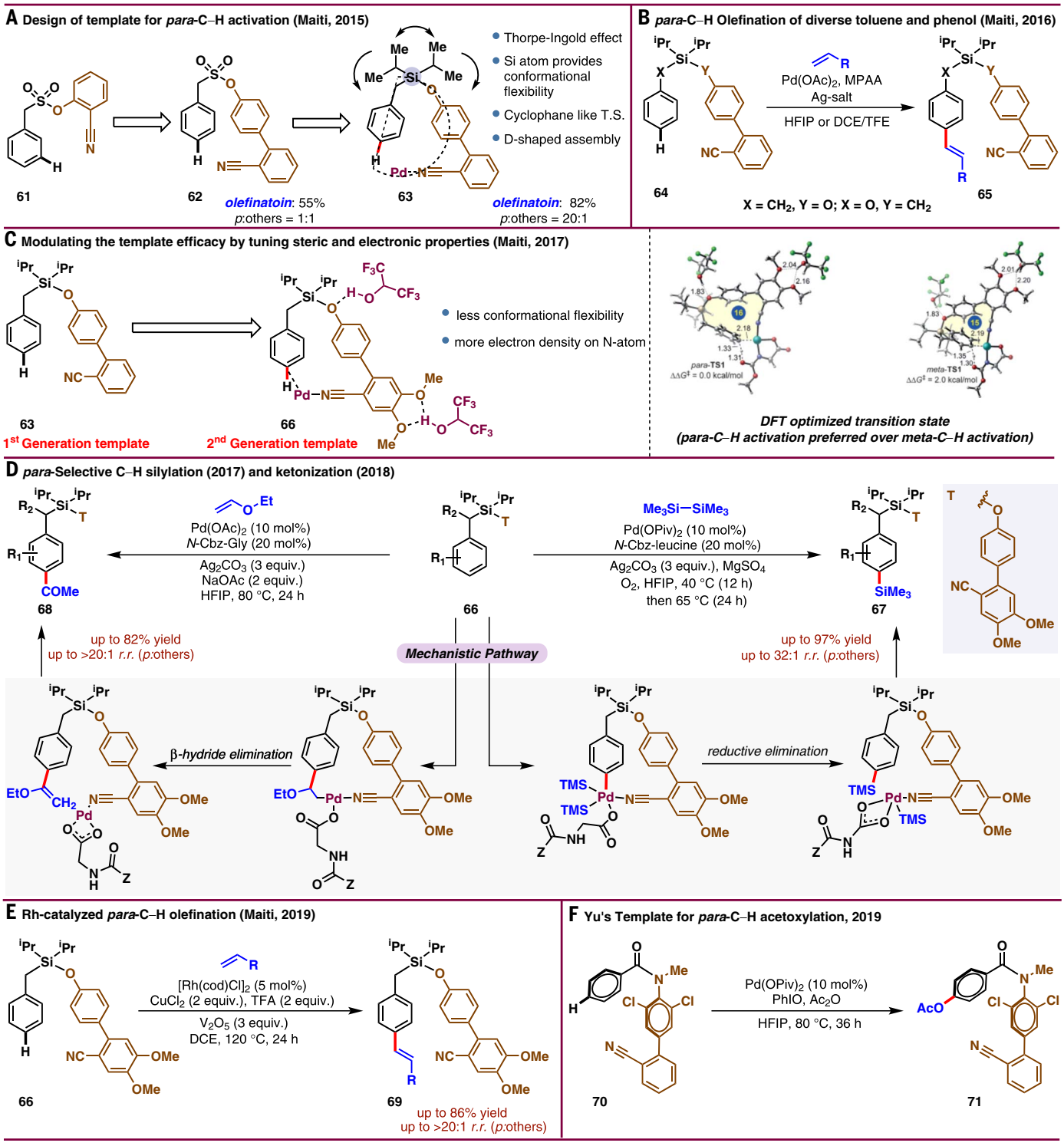

Fig. 4. Covalently attached directing templates for *para*-C–H functionalization. Me, methyl; *i*-Pr, isopropyl; Cbz, benzyloxycarbonyl; cod, 1,5-cyclooctadiene; TFA, trifluoroacetic acid; V_2O_5, vanadium pentoxide.

disclosed the use of ion-pairing interactions in an alternate way to control distal site selectivity. Ion-pairing interactions between the anionic substrates and the cationic counterion, which was unfunctionalized and sufficiently bulky to exert steric shielding at the *ortho*- and *meta*-positions, induced *para*-selectivity with conventional borylation catalysts (Fig. 5F). Recently, Phipps' group reported an asymmetric *meta*-C–H borylation method through desymmetrization of geminal diaryl motif **88** bearing an H-bond donor site (such as a benzhydrylamide or diarylphosphinamide) through a combination of ion-pair interactions and H-bonding interactions simultaneously (Fig. 5G) (*72*). The sulfonate-substituted bipyridine ligand was used to align the substrate for *meta*-C–H borylation through H-bonding,

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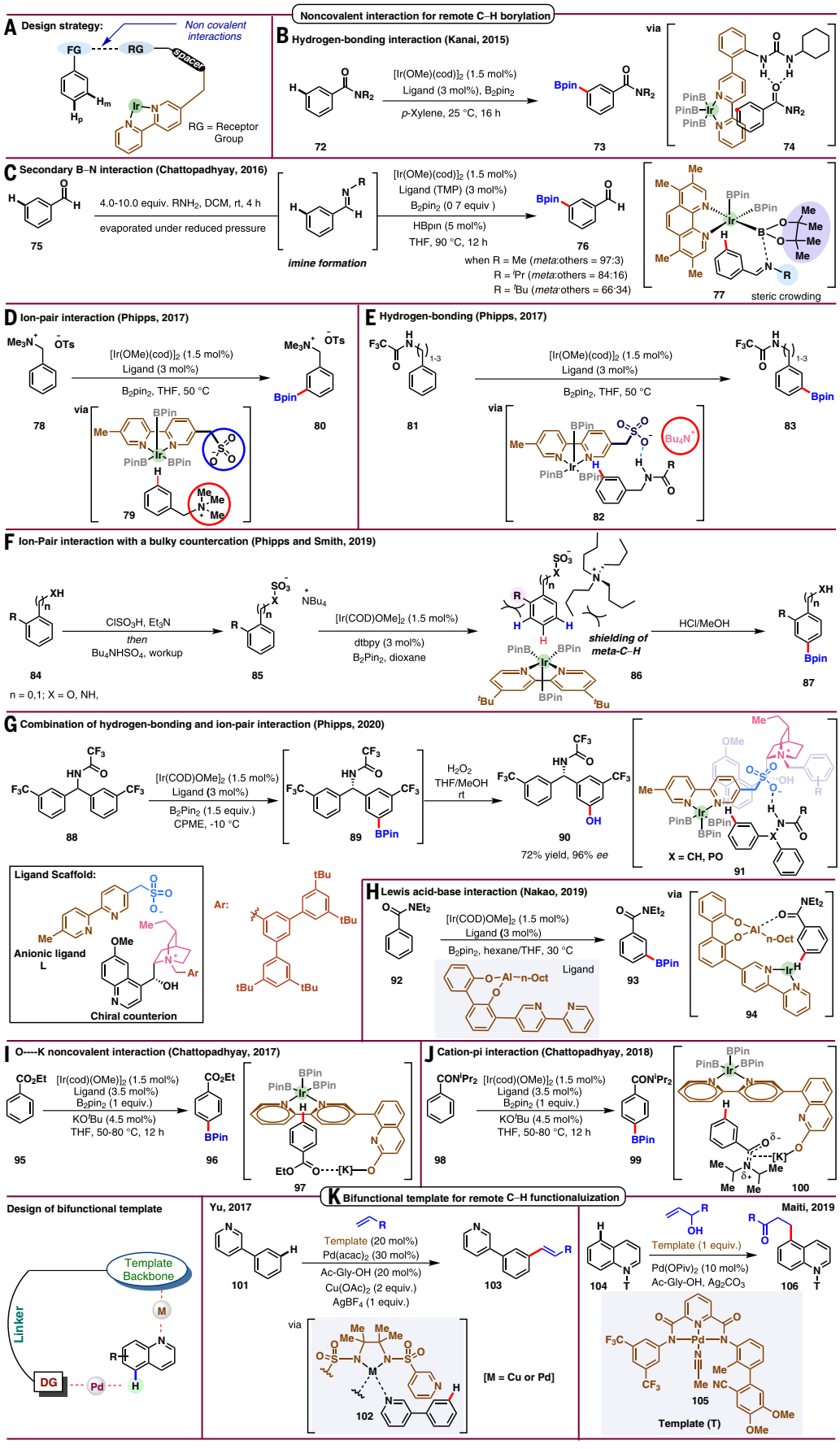

Fig. 5. Noncovalent interaction–enabled remote C–H functionalization. Bpin, pinacolatoboron; dtbpy, 4,4′-di-*tert*-butyl-2,2′-dipyridyl; CPME, cyclopentyl methyl ether; ^{t}Bu, *tert*-butyl.

and the chiral counter-cation derived from quinine was responsible for long-range asymmetric induction by ion pairing with the anionic ligand.

Nakao and coworkers exploited a bipyridine-type ligand containing an alkylaluminum biphenoxide moiety as the strong Lewis acidic counterpart to offer *meta*-selective C–H borylation of *N*,*N*-diethylbenzamides (Fig. 5H) (*73*). It was proposed that a Lewis acid-base interaction is responsible for this high level of observed selectivity.

For *para*-selective arene C–H borylation, the first distinct strategy beyond simple steric control was reported by Chattopadhyay and coworkers. They introduced an L-shaped ligand containing both a bipyridine unit and a quinolone moiety to afford *para*-C–H borylation of diverse arenes and heteroarenes bearing ester functionality in excellent selectivity (Fig. 5I) (*74*). In the presence of KO^{t}Bu as a base, the tautomerization of the 2-quinolone moiety generated the corresponding potassium aryloxide form that could recognize the carbonyl oxygen atom of the ester through an O-K···O=C noncovalent interaction and thus provide desired *para*-selectivity. The same ligand was also applied to achieve *meta*-C–H borylation of benzamides. In this case, the regioselectivity was mainly governed by cation-π interactions between the potassium cation and the amide π-electron cloud (Fig. 5J) (*75*).

Despite substantial progress, noncovalent interactions are mainly used to control regioselectivity in the context of Ir-catalyzed C–H borylation chemistry. Although Pd catalysis can offer diverse functionalization at distal positions of arenes, the use of noncovalent interactions is restricted because of the need for harsh reaction conditions that might be incompatible with weak noncovalent interactions.

Yu and coworkers developed a bifunctional template–mediated approach to functionalize the distal C–H bond of heteroarenes (Fig. 5K). In this catalytic scaffold, two metal centers act in a cooperative manner: One metal (either Cu or Pd) helps to confine the substrate orientation by reversibly coordinating with its heteroatom, and the second metal (Pd) assists in activating the targeted C–H bond. Initially, this strategy was applied to achieve *meta*-C–H olefination of 3-phenylpyridines using a catalytic amount of bis-sulfonamide scaffolds bearing two C3 pyridyl groups (*76*). They also demonstrated remote, site-selective C–H olefination of quinolines and other heterocycles, although a stoichiometric nitrile-based bisamide template and palladium were required for this process. Considering more diverse functionalizations, the recent report by our group of alkylation using allyl alcohols as coupling partners points to the potential generality of this approach (*77*).

Pd(II)/norbornene cooperative catalysis strategy for remote C–H functionalization

As illustrated earlier, a rapid paradigm shift in distal C–H functionalization of arenes was observed through putative design of a template and/or directing group that maintains optimal positioning between the target C–H bond and the metal-bound anchoring unit. The process involves a highly energy-demanding, large macrocyclic pretransition state. A complementary strategy involving a transient mediator that facilitates Pd-relay chemistry has emerged as a productive research field in recent years. The Pd-relay process in conjunction with norbornene (NBE) as transient mediator is famously named after Prof. Marta Catellani, who introduced the methodology (*78*). Initially, this methodology was exploited for *ipso*- and *ortho*-di-functionalizations of aryl halides (*6*). A related concept was brilliantly introduced by the Yu group to achieve *meta*-selective C–H alkylation of phenyl acetamide (Fig. 6A, i) (*79*). The catalytic process is initiated with amide-directed *ortho*-palladation (**A**). Subsequent NBE coordination and 1,2-migratory insertion relays the Pd to the next *meta*-C–H bond (Fig. 6A, ii). The β-hydride elimination path, as observed in traditional Heck coupling, is prevented because of the unavailability of β-hydrogen in the planar, *syn*-conformation. Upon a second C–H activation at the *meta*-position, intermediate **B** undergoes oxidative addition with the coupling partner (R-X). Reductive elimination (**C** to **D**) and β-carbon elimination (**D** to **E**) leads to NBE extrusion. Finally, protodepalladation furnishes the desired *meta*-C–H functionalization. Undeniably, a complex catalytic cycle is operational to effect the desired *meta*-selective functionalization. Because this catalytic cycle consists of threefold active aryl-palladium intermediates, a slight deviation from the optimal condition could lead to the formation of the unintended side products [e.g., direct *ortho*-functionalization (**A** to **G**), cyclobutane (**H**) formation from **B**]. Therefore, the appropriate choice of ligand is crucial to restrict side product formation by modulating the relative reactivity of these palladacycles. Initial experiments involving pyridine ligands facilitated 1,2-migratory insertion of NBE into the presumptive *ortho*-palladacycle intermediate, albeit yielding the cyclobutene **H** to a greater extent. However, electron-donating 2-alkyl pyridines seemed to be extremely proficient for the *meta*-alkylation over the formation of **H**. Yu's group highlighted the crucial role of the pyridine-based ligand (**109**) that promoted the *meta*-selective alkylation suppressing the related side reactions. Concurrent *meta*-selective arylation through Pd-NBE cooperative catalysis was reported by Dong (Fig. 6A, iii) (*80*). A tertiary amine group was recruited as *ortho*-DG to trigger the initial *ortho*-C–H palladation. A combination of $AsPh_3$ ligand and acetate cocktail was essential to achieve high yield and *meta*-selectivity. In the following years, diverse classes of substrates, including anilines, phenols, heterocyclic anilines, 2-benzyl heterocycles (*81*), β-arylethylamine (*82*), aromatic alcohols (*83*), phenethylamines (*84*), phenylacetic acids (*85*), benzylsulfonamides (*86*), benzyl alcohols, and even pseudo-aldehydes (*87*) (Fig. 6A, iv) were successfully used for *meta*-selective functionalizations through Pd-NBE cooperative catalysis. Thus far, *meta*-selective alkylation, arylation, alkynylation, amination, and chlorination were achieved.

The tantalizing possibility of Pd-NBE cooperative catalysis was further explored for stereoselective *meta*-C–H functionalization by Yu and coworkers in 2018 (*88*). Stereoselective *meta*-arylation of diarylmethylamines and homobenzylamines (**117**) was demonstrated through Pd-(+)-NBE-CO_2Me [where (+)-NBE-CO_2Me refers to methyl (1S,4R)-bicyclo[2.2.1] hept-2-ene-2-carboxylate] mediated desymmetrization (Fig. 6A, v). Apart from relaying the Pd catalyst from the *ortho*- to the *meta*-position, the chiral NBE-CO_2Me triggered chiral differentiation between two *ortho*-C–H palladated intermediates. Therefore, the dual role of catalytic chiral NBE-CO_2Me set an elegant example in the regime of enantioselective distal C–H functionalization. (*R*)-BNDHP (1,1′-binaphthyl-2,2′-diyl hydrogen phosphate) (**125**) acted solely as an additive to improve the yield and selectivity while the chiral NBE-CO_2Me dictated the enantioselective outcome. The study also demonstrated the efficacy of Pd-(+)-NBE-CO_2Me cooperative catalysis in resolving a racemic mixture of secondary amines through kinetic resolution. The methodology took a further leap when Catellani-type reactivity was extended from *meta*- to the farthest *para*-C–H bond in the Yu group's report of *para*-selective arylation of hydrocinnamic acid derivatives relying on Pd-NBE cooperative catalysis (*89*). This elegant approach of Pd/NBE cooperative catalysis combining with remote directing template was also utilized for the first time to achieve C6 arylation of iso(quinolines) and C7 arylation of tetrahydroisoquinolines. Contemporaneously, our group presented *para*-arylation of sulfonate, phosphonate and phenol-based scaffolds (**126**) by attaching our previously developed *meta*-directing group, **128** (Fig. 6A, vi) (*90*). The *meta*-directing group was expected to promote *meta*-C–H activation and subsequent Pd relay prompted the *para*-C–H arylation. Arguably, this strategy unveiled a possibility to reach the distal *para*-position of an arene bypassing the formation of a 16- to 17-membered cyclophane intermediate.

Traceless directing group strategy for *meta*-C–H functionalization

Traceless directing group strategies rely on a subtle balance between stability of the directing

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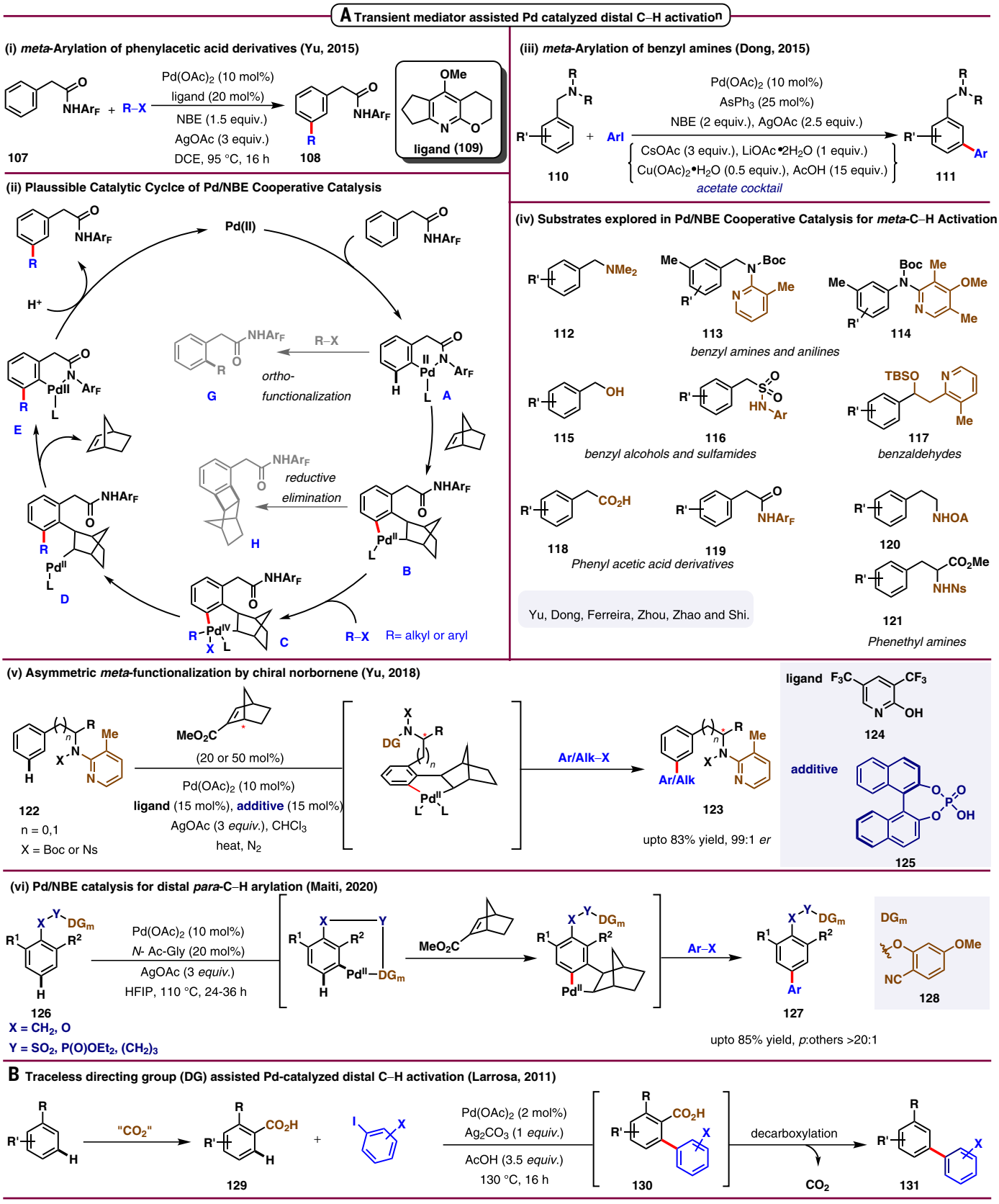

Fig. 6. Transient mediator and traceless directing group–assisted distal C–H functionalization. AcOH, acetic acid.

group to ensure proximal C–H activation and facile postsynthetic cleavage of the same group in a single synthetic setup. Directing ability, accessibility, relative stability, and facile removal strategies positioned the carboxylic acid group as a promising candidate in bringing this concept to fruition. In 2011, Larrosa and coworkers applied carboxylic acid as a traceless directing group for distal *meta*-C–H arylation of arenes under Pd catalysis (Fig. 6B) (*91*). Strategically, the carboxylic acid was introduced *ortho* to the original aryl substituent and then acted as a directing group to functionalize the adjacent carbon; decarboxylation then formally furnished *meta*-functionalized products. In addition to the direct use of benzoic acid in regulating *meta*-C–H activation through a relay mechanism, in situ carboxylation involving a continuous source of carbon dioxide was also applied for the same purpose (*92*).

Catalyst, ligand, and reagent controlled remote C–H functionalization

As alluded to in the previous sections, the distal C–H functionalization of arenes was successfully achieved with the assistance of directing groups. In parallel, substantial effort has been devoted toward nondirected distal C–H functionalization that overrides the inherent electronic bias of the substrate. Substitution-controlled distal C–H functionalizations, for example, *meta*-selective C–H borylation of 1,2- or 1,3-disubstituted benzenes (*93*, *94*) where regioselectivity is governed by electronic and/or steric effects of the substituents, are not included in this section (Fig. 7A). Instead, we mainly focus on the design of catalysts, ligands, reagents that play a pivotal role in determining the regioselective outcome. A specialized strategy involving "cooperative nickel/aluminum catalysis" was pioneered by Hiyama and Yap in 2010 for C4-H alkylation and alkenylation of pyridine (*95*). Cooperative catalysis was also applied in 2016 by Nakao to promote *para*-selective alkylation of aromatic amides and ketones. Sterically encumbered Lewis acid [$(2,6\text{-}^{t}Bu_2\text{-}4\text{-}Me\text{-}C_6H_2O)_2AlMe$, (MAD)] and *N*-heterocyclic (NHC) ligand (IPr) were carefully designed to execute the desired regioselective transformation (Fig. 7B) (*96*). The NHC-ligated Ni catalyst was selectively guided to the *para*-C–H bond as O-coordination of benzamides or ketones to MAD sterically shielded the *ortho*- and *meta*-C–H bonds. In 2015, Itami reported *para*-selective borylation of monosubstituted arenes in which steric governance of ligand was highlighted as the key factor in controlling the regioselectivity (Fig. 7C) (*97*). The sterically congested Xyl-MeO-BIPHEP ligand was designed to drive regioselective C–H activation. Mechanistic elucidation revealed that the active catalyst, tris-boryl-Ir(III), was coordinated by Xyl-MeO-BIPHEP, which is spatially oriented through π–π interactions to surround the Ir(III) center (**139**) (*98*). The geometric disposition of the ligand produces a small cavity for the arene to interact with the catalyst. Therefore, the less hindered *para*-C–H bond was selectively activated through a "metal-assisted σ-bond metathesis" transition state.

Ligand-controlled regioselective C–H olefination of arenes, in which the arene was used as the limiting reagent, was reported by Yu's group in 2017 using a 3,5-bis(trifluoromethyl) pyridin-2-ol ligand (*99*) (Fig. 7D, i). Density functional theory calculations suggested **141** as the preferred transition state, in which one of the 2-pyridone ligands coordinated to Pd(II) through a κ^2-mode and the other coordinated exclusively through the nitrogen center. The second ligand acted as an internal base to facilitate C–H activation through a "concerted metalation deprotonation" mechanism. Detailed investigation of relative Gibbs free energies revealed that the presence of the 2-pyridone ligand lowered the C–H activation energy compared with acetate base, and the initial rate of the reaction was enhanced 1.4-fold. Thus, this catalytic system offered improved reactivity to streamline distal *meta*- and/or *para*-selective arene-limited C–H olefination. Concurrently, van Gemmeren used a mixture of *N*-acetyl glycine and a pyridine-based ligand to effect a similar transformation (*100*). Ligand accelerated regioselective C–H cyanation of arenes has recently been accomplished independently by Ritter (*101*), van Gemmeren (*102*), and Yu (*103*) (Fig. 7D, ii). Whereas Ritter and van Gemmeren's groups recruited a dual ligand system consisting of MPAA and a pyridine-quinoline-quinoxaline derivative in conjunction with Pd-catalyst for arene limited selective C–H cyanation, 2-pyridones were highlighted as effective ligands by Yu for the same transformation. Nevertheless, a moderate level of regioselectivity was observed for distal *meta*- and/or *para*-position in all these catalytic systems. The regioselectivity was imparted collectively by the steric and electronic influence of the ligand system.

Recently, in 2019, the group of Fernández-Ibáñez disclosed a *para*-selective olefination of aniline derivatives by exploiting a Pd/S,O catalytic system (Fig. 7D, iii) (*104*). Although the regioselectivity was controlled by electronic effects, the presence of electron-withdrawing substituents also effected *para*-olefination of anilines in good yields. Various *N*-substituted anilines smoothly delivered *para*-olefinated products. The positive role of the 2-isopropyl-2-(phenylthio)acetic acid ligand in influencing the reaction rate was supported by kinetic experiments. With C–H activation as the rate determining step of the present protocol, the k_H/k_D value decreased in the presence of the ligand, providing strong support for a ligand accelerated C–H activation mechanism.

Catalyst development has played a pivotal role in fostering atom and step economy in synthesis. A bis-cationic Pd catalyst, **148**, coordinated by an amine-*N*-oxide ligand, was successfully used by Ritter's group to effect C–H imidation of arenes using N-fluorobenzenesulfonimide (Fig. 8A, i) (*105*). An unusual step involving Pd(II) oxidation, enabled by the amine-*N*-oxide-ligand, was proposed to be rate limiting. Later in 2016, the developed catalyst **148** in conjunction with $Ru(bpy)_3(PF_6)_2$, was successfully applied to highly *para*-selective C–H amination of arenes by the same group (Fig. 8A, ii) (*106*). The *para*-selective amination was posited to proceed through a radical addition mechanism. High electron affinity of $TEDA^{2+\bullet}$ [TEDA, *N*-(chloromethyl)triethylenediamine] was envisioned to induce arene-to-radical charge transfer in the transition state, which facilitated the *para*-selective addition to the arenes. The protocol was amenable to various substituted arenes with distinct electron properties.

Nicewicz's group disclosed a photoinduced regioselective arene C–H amination involving N-heterocycles as aminating reagent and acridinium as photocatalyst (**152**) in 2015 (Fig. 8B) (*107*). It was postulated that an arene cation radical ($Ar^{+\bullet}$) was formed through photoinduced electron transfer from the arene to the excited state of the photocatalyst. Subsequently, $Ar^{+\bullet}$ could form a σ-adduct with the amine, undergo deprotonation, and then re-aromatization to deliver the desired products. In later years, a similar concept was further capitalized on by the same group to incorporate diverse functionality in a regioselective fashion.

An excellent example of reagent-controlled, site-selective C–H functionalization is the thianthrenation of arenes, demonstrated by Ritter's group (Fig. 8C). They envisaged the potential of an "electrophilic persistent sulfur-based radical" that would couple with arenes in a site-selective fashion to furnish thianthrenium salts **153**. Compound **153** was then used to synthesize a wide variety of functionalized arenes **154** through either photoredox catalysis or transition metal catalyzed cross-coupling (*108*).

The influential role of reagents on the reactivity pattern of a substrate or the mechanistic path of a reaction was nicely demonstrated in a recent study by Altman and coworkers (Fig. 8D) (*109*). This study highlighted the switch from conventional decarboxylative benzylation to *para*-C–H alkylation using an amine base. The base-promoted re-aromatization of **158** through formal 1,5-hydrogen migration was proposed to rationalize the observed *para*-selective alkylation (**159**). In the absence of base, **157′** delivered the decarboxylative benzylation product (**160**).

Thus far, we have discussed various nondirected, regioselective distal C–H functionalizations of arenes enabled by catalysts, ligands,

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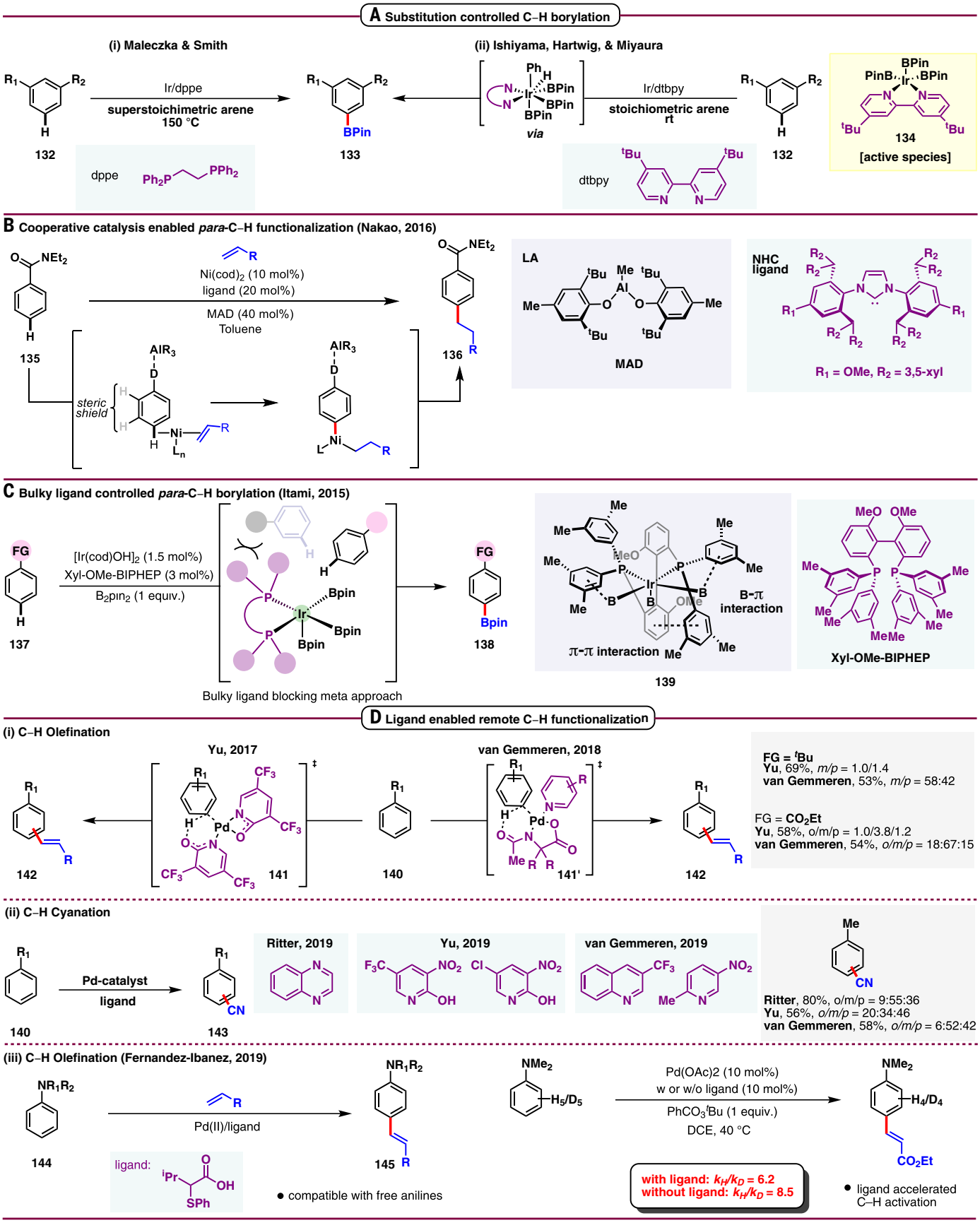

Fig. 7. Ligand-controlled distal C–H functionalization. dppe, 1,2-bis(diphenylphosphino)ethane; D, donor unit.

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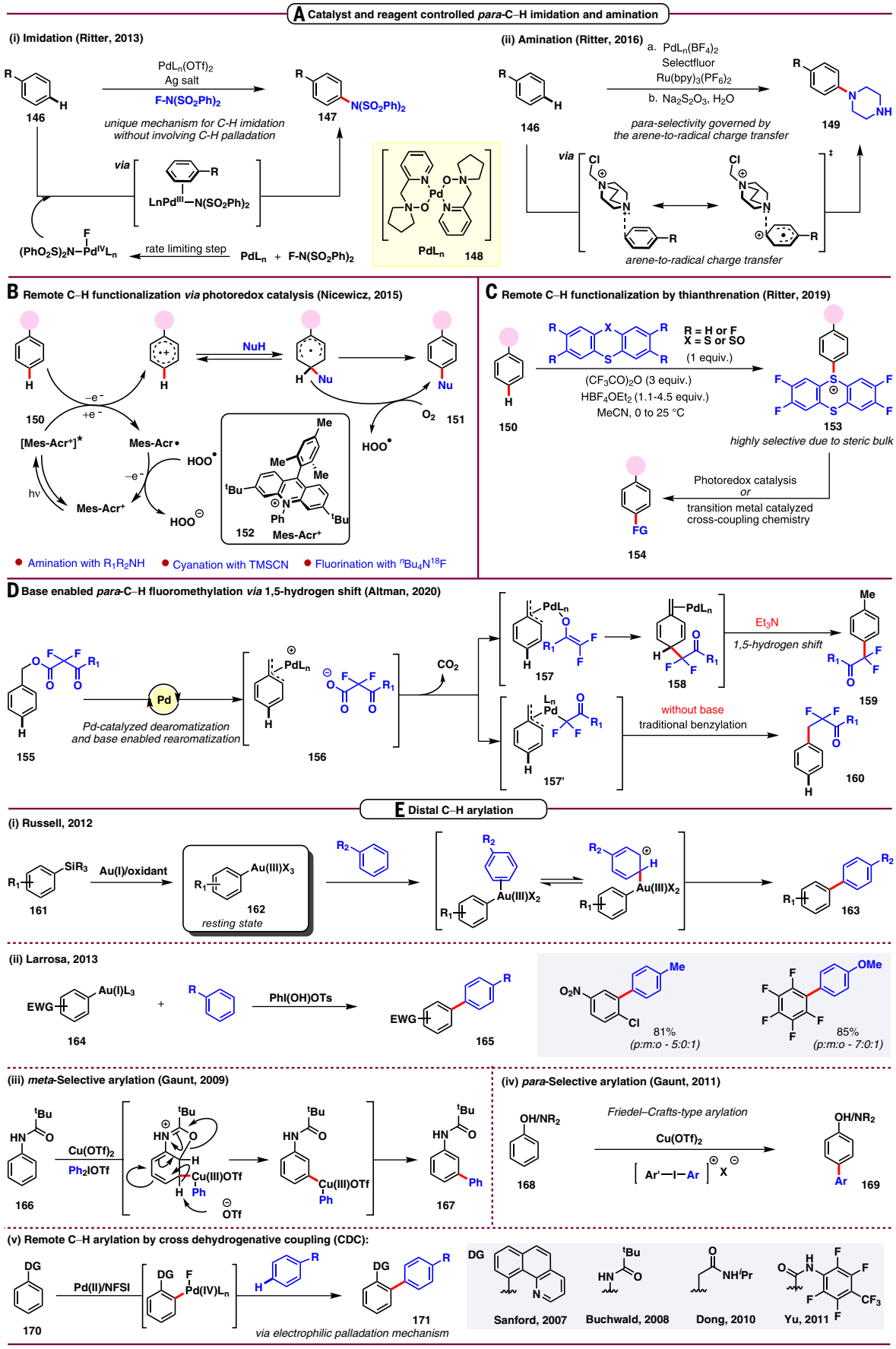

Fig. 8. Reagent-controlled distal C–H functionalization. bpy, 2,2'-bipyridine; OTs, tosylate.

and reagents. Direct C–H arylation of arenes is one of the most desirable transformations in organic synthesis to access biaryls, which are prevalent in natural products, agrochemicals, and pharmaceuticals. Depending on the nature of the coupling partners, direct arene C–H arylation can be classified as oxidative coupling, nonoxidative coupling, or cross-dehydrogenative coupling. Several groups have contributed to the design and development of protocols for site-selective direct C–H arylation. Here, we only discuss recent reports with promising *meta*- and *para*-selectivity. Russell's group devised a gold-catalyzed method for oxidative cross coupling between aryl silanes and arenes in 2012 (Fig. 8E, i) (*110*). The site selectivity of the coupling was consistent with the S_EAr pattern. A redox active Au(I)/Au(III) catalytic cycle involving precatalyst activation, two consecutive electrophilic aurations, reductive elimination, and catalyst reoxidation was proposed. The Au(I)/Au(III) redox cycle was further adapted by Larrosa *et al.* to enable selective coupling of electron-rich and electron-deficient arenes (Fig. 8E, ii) (*111*). It was hypothesized that the electron-deficient arene would selectively form the arene-Au(I) salt, which could be transformed to an arene-Au(III) complex upon addition of an oxidant. Subsequent coupling with electron-rich arenes was facilitated with this arene-Au(III) complex. A copper-catalyzed *meta*-selective C–H arylation of pivanilides was reported by Gaunt in 2009 (Fig. 8E, iii) (*112*). Although the exact mechanism remained unclear, Friedel-Crafts–type cupration was believed to be operative selectively at the *meta*-position. However, in a subsequent report in 2011, the same group disclosed that similar *meta*-C–H arylation could be achieved even in the absence of Cu catalyst, albeit in lower yield. Therefore, the exact role of Cu is yet to be elucidated (*113*). In 2011, Gaunt and coworkers also devised an elegant method for *para*-selective arylation of electron-rich phenol and aniline derivatives under copper catalysis (*114*). Despite the notable *para*-selectivity, the protocol is only applicable to electronically biased phenol and aniline derivatives (Fig. 8E, iv). *Para*-selective direct C–H coupling between two arenes or cross-dehydrogenative coupling was explored with the assistance of a chelating directing group (Fig. 8E, v) (*115*–*118*). In this strategy, arenes bearing *ortho*-directing groups were selectively added to the *para*-C–H bond of electron-rich arenes.

Outlook

The field of remote C(sp^2)–H functionalization has achieved pronounced advances in terms of designing directing templates and understanding the reactivity of transition metal catalysts in specific ligand frameworks. One of the major challenges associated with increasing the practicality of this chemistry is to discover more environmentally benign, cost-effective, scalable, and sustainable catalytic systems with very high turnover number. We hope this review will inspire readers to expand the catalytic toolbox, enabling the synthetic modification of hitherto inaccessible sites of organic molecules and enhancing the discovery and manufacture of pharmaceuticals, agrochemicals, and other desired materials.

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Arene diversification through distal C(sp)-H functionalization

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Targeting distal C–H bonds in arenes

The Friedel-Crafts reaction is among the oldest in organic chemistry. For well over a century, chemists have relied on electronic effects intrinsic to aryl rings to append substituents at specific sites along the periphery. However, only in the past decade have they devised catalytic techniques that over-ride these preferences so that new groups usually drawn to the neighboring sites of an existing substituent instead wind up two or three carbons away. Dutta *et al.* review progress in this field, highlighting elaborate directing groups and mediators as well as sophisticated ligand design.

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