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Transition metal-catalyzed site- and regio-divergent C–H bond functionalization

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Recent advances in transition metal-catalyzed C–H bond functionalization have profoundly impacted synthetic strategy. Since organic substrates typically contain several chemically distinct C–H bonds, controlling the regioselectivity of C–H bond functionalization is imperative to harness its full potential. Moreover, the ability to alter reaction pathways to selectively functionalize different C–H bonds in a substrate represents a greater opportunity and challenge. The choice of catalysts, ligands, solvents, and even more subtle variations of the reaction conditions have been shown to allow the formation of regioisomeric C–H functionalization products starting from the same precursors. This review describes recent advances in transition metal-catalyzed divergent C–H bond functionalization that highlight its potential in organic synthesis.

1. Introduction

Catalytic processes that selectively provide a single product among other possible products and isomers are of central academic and synthetic interest. Among these processes, transition metal-catalyzed C–H bond functionalization has emerged over the last two decades as an increasingly important synthetic strategy.[1] Over this period, numerous catalytic C–H bond functionalization reactions have become sufficiently selective, economical, broad in scope, and predictable to compete as alternatives to more established synthetic methods, such as C–X/C–M cross couplings. A versatile and reliable strategy for regioselective C–H bond functionalization is the use of a directing group (DG).[2] Through coordination of a DG to a transition metal catalyst, the proximity effect dictates the regioselective functionalization of a specific C–H bond. In spite of its successes, this approach suffers from limitations. Since organic substrates possess several distinct and potentially reactive C–H bonds, not only must the synthetic chemist identify a DG that is selective for one of those sites, but additional steps are typically required to install the DG onto the substrate and later remove it from the product.

Expanding the synthetic toolbox to allow for the selective functionalization of the different C–H bonds in a given substrate without the need for the introduction of separate DGs

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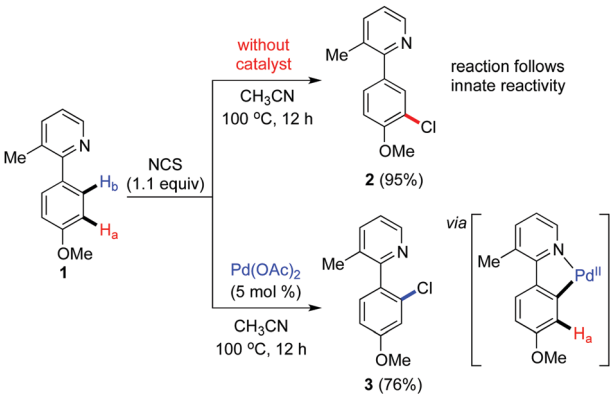
has been a long-standing goal in organic methodology. Since research efforts have moved away from transformations based on *ortho*-metalated intermediates and more towards the functionalization of less easily accessed remote C–H bonds, advances in transition metal-catalyzed C–H functionalization have now made it possible to rapidly access to regioisomeric products from a common starting material. These methods are particularly appealing in combinatorial campaigns to diversify a fragment pool.

This review presents, with a mechanistic focus, how C–H functionalization regioselectivity can be redirected, by subtle changes in catalysts, solvents, additives, and reaction conditions, to obtain regioisomeric products form the same starting materials.[3] Recent successes in this area have been reported most commonly in the divergent functionalization of sp^2 C–H bonds in arenes, heteroarenes, and alkenes, but also less commonly of sp^3 C–H bonds of alkyl groups. The examples, taken from the literature up to the beginning of 2017, also include reactions where functionally equivalent starting materials that differ only by their spectator or protecting groups are selectively converted through divergent C–H functionalization into pseudo-isomeric products. Finally, divergent catalytic methods that result in the selective functionalization of indoles at positions 2- through 7- are showcased to demonstrate the power of state-of-the-art divergent C–H bond functionalization methods.

2. *ortho*-Directing groups override innate C–H functionalization reactivity

Electronic preference *vs.* directed C–H functionalization

Electrophilic aromatic substitution (S_EAr) is a prototypical example of regioselective functionalization of arene C–H bonds that is governed by the inherent electronic properties of the substrate. As students are taught in introductory organic chemistry classes, in the absence of sterically overriding substituents, the regioselectivity of S_EAr in a substituted benzene ring is dependent on the presence of electron-donating groups, which are *ortho*/*para*-directing, or electron-withdrawing groups, which are *meta*-directing. Transition metal-catalyzed C–H functionalization can overcome this innate reactivity, allowing for the activation of a C–H bond not predicted by this conventional analysis. Sanford *et al.* reported an excellent example of DG-guided Pd-catalyzed C–H bond halogenation (Scheme 1).[4] In the absence of catalyst, the arene **1** follows its innate reactivity profile to afford the product chlorinated *ortho* to the electron-donating methoxy group, **2**. In contrast, in the presence of a Pd catalyst, the catalytic pathway overrides the innate electronic preference through a DG-guided cyclometalation[5] in *ortho* to the directing pyridyl group, leading to the selective formation of a regioisomeric product that is chlorinated *meta* to the electron-donating methoxy group, **3**.



Scheme 1

Pd and Ir catalyst-controlled C4/C8-arylation or alkynylation of isoquinolones. Transition metal-catalyzed C–H functionalization also often follows an electronic preference for the most electron-rich position that is analogous to electrophilic

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Sang-gi Lee

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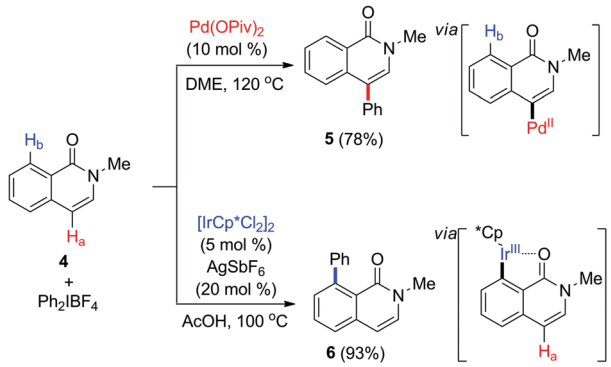
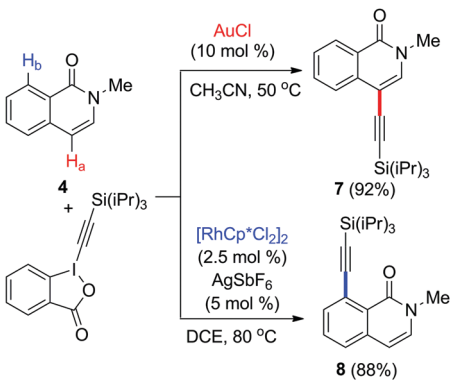


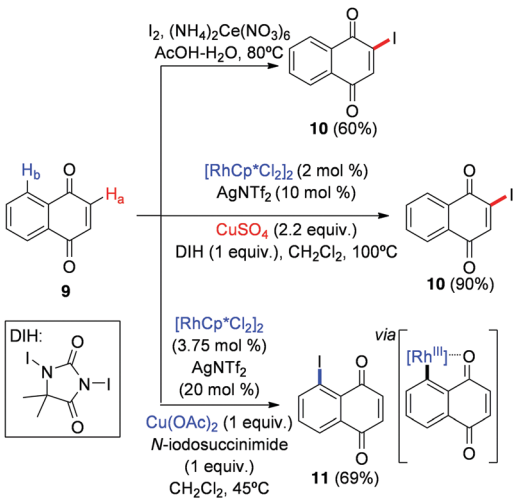
Scheme 2

aromatic substitution reactions. This innate reactivity can just as easily be redirected with the assistance of a DG. For instance, in 2015, Hong and co-workers reported a catalyst-controlled C4/C8 site-selective C–H arylation of isoquinolones **4** using aryliodonium salts as the coupling partners (Scheme 2).[6] A C4-selective arylation is successful *via* a postulated electrophilic palladation pathway to give **5**. A complete reversal of selectivity is observed using an Ir catalyst, where the amide carbonyl group acts as a DG to result in arylation exclusively at the 8-position to give **6**. The electronic preferences and directing ability of isoquinolones **4** have allowed the Patil group to extend this chemistry with the introduction of a C4-selective alkynylation that employs an electrophilic gold catalyst giving **7**, and of a C8-selective alkynylation that employs the affinity of the amide group for a cationic rhodium catalyst giving **8** (Scheme 3).[7]

Rh catalyst-controlled C2/C5-halogenation of naphthoquinones. Closely related results were reported in 2016 by da Silva Júnior, Bower, and co-workers for the regioselective iodination or bromination of 1,4-naphthoquinone **9** and its derivatives (Scheme 4).[8] Electrophilic halogenation of the parent 1,4-naphthoquinone **9** intrinsically favors the formation of the C2-halogenated product **10**.[9] However, in the presence of a cationic Rh catalyst and $Cu(OAc)_2$ additive, treatment of **9** with *N*-haloimides results in a selective iodination (or bromination) at the 5-position to give **11**. The reversal in selectivity is attributed to a reversible cyclometalation at the 5-position directed by the adjacent carbonyl group, and trapping of the resulting intermediate by



Scheme 3

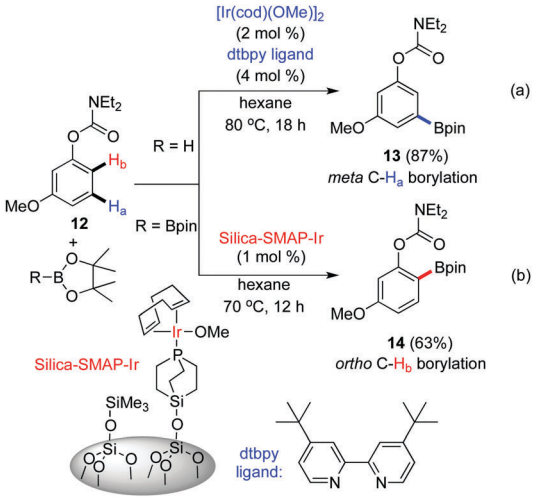


Scheme 4

the electrophilic halogenation agent. Interestingly, the nature of the Cu(II) salt additive is critical, as switching from $Cu(OAc)_2$ to $CuSO_4$ restores the innate regioselectivity.

Steric preference *vs.* directed C–H functionalization

Catalyst/ligand-controlled *ortho*- and *meta*-borylation of phenylcarbamates. Transition metal-catalyzed C–H borylations are useful methods for the construction of C–B bonds.[1h,10] In general, for Ir centers that are coordinated to bidentate nitrogen ligands such as bipyridines, the reaction is regioselective for the least sterically hindered C–H bond. For instance, Marder, Snieckus *et al.* regioselectively introduced a pinacolboronate ester group (Bpin) at the *meta*-position of **12** to give **13** (Scheme 5a).[11] In the case of monosubstituted benzene derivatives, bulkier bisphosphine ligands were also shown to further improve *para*:*meta* selectivity on the basis of steric preference for the former.[12] Similarly, coordination by bulky Lewis acids also increases *para* selectivity in the Ir-catalyzed C–H borylation of Lewis basic benzamides and pyridines.[13] By contrast, Sawamura *et al.*

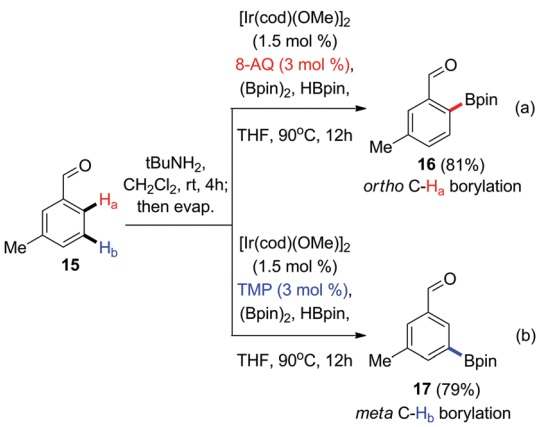


Scheme 5

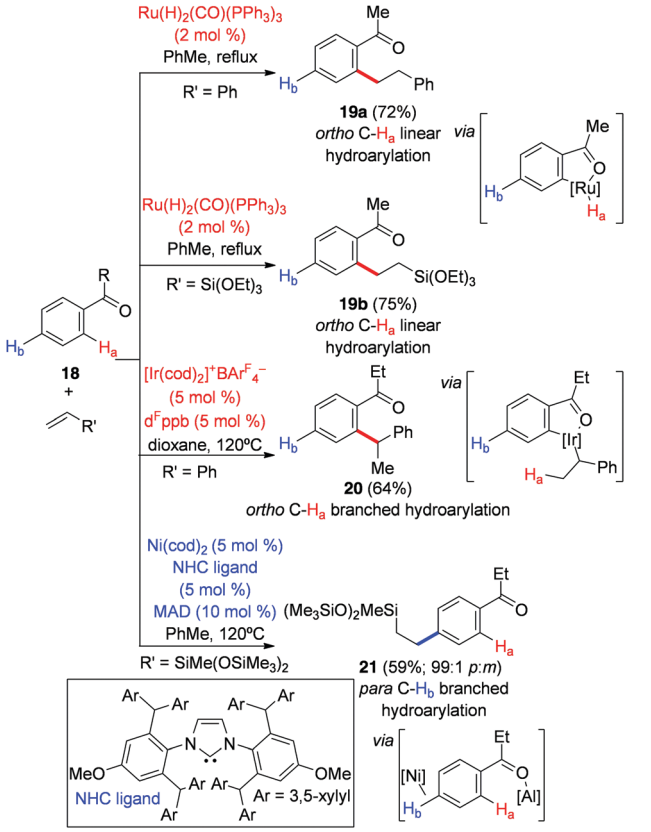
successfully achieved a selective *ortho* C–H borylation of **12**, affording **14** (Scheme 5b), by employing a silica-supported monodentate phosphine-ligated Ir complex (silica-SMAP-Ir).[14] The reversal of regioselectivity in the latter case is consistent with the involvement of the carbamate as an *ortho*-DG, and also occurs with other DGs such as esters.[15] It is plausible that coordination of the DG to the Ir center is a consequence of the inability of Ir to form bis(phosphine) complexes when the phosphine ligands are sparsely distributed on the silica surface, opening up a coordination site at the Ir center. Less common bidentate monoanionic P,Si- and N,B-ligands have also been used in place of bidentate nitrogen ligands to free a coordination site at Ir, favoring C–H borylation reactions *ortho* to DGs.[16]

Catalyst/ligand-controlled *ortho*- and *meta*-borylation of aromatic aldehydes *via in situ*-generated imines. A similar strategy was reported in 2016 by Bisht and Chattopadhyay to achieve the Ir-catalyzed divergent *ortho* or *meta* borylation of benzaldehydes **15** (Scheme 6).[17] The aldehyde carbonyl, a comparably poorer DG, is first converted *in situ* to a more apt imine *ortho* DG.[18] The latter is readily hydrolyzed back to the benzaldehyde during the reaction workup. With a hemilabile ligand such as 8-aminoquinoline (8-AQ) or a flexible diimine ligand, the DG is able to coordinate to the Ir center, and direct the C–H borylation at the *ortho* position to afford benzaldehyde **16**. By contrast, in the presence of a rigid bidentate ligand such as 3,4,7,8-tetramethyl-1,10-phenanthroline (TMP), coordination of the imine DG to the Ir center is prevented, and the borylation occurs at the least sterically hindered *meta* position, giving **17**. The authors have also proposed the involvement of secondary interactions between the imine DG and a boryl ligand on Ir to rationalize high *meta*:(*para* + *ortho*) selectivities in unsubstituted, 2- or 4-substituted benzaldehydes.[19]

Catalyst/ligand-controlled *ortho*- and *para*-alkylation of aromatic ketones and amides with alkenes. In one of the landmark reports of C–H functionalization leading to C–C bond formation, the Murai group disclosed the ruthenium-catalyzed hydroarylation of alkenes, which proceeds with *ortho* selectivity due to the directing action of carbonyl groups.[20] For example, when aromatic ketone **18** is reacted with a styrene derivative or



Scheme 6



Scheme 7

vinylsilane in the presence of a Ru catalyst, the linearly *ortho* alkylated product **19** is obtained (Scheme 7).

The Bower group demonstrated in 2014 that branched *ortho* alkylated products such as **20** are instead exclusively obtained by reacting aromatic ketones (*e.g.* **18**) with styrenes in the presence of a cationic Ir catalyst featuring the weakly coordinating anion $BAr^F{}_4^-$ (Ar^F = 3,5-$(CF_3)_2C_6H_3$) and the electron-deficient wide bite-angle ligand 1,4-bis(di(pentafluorophenyl)phosphino)-butane (d^Fppb).[21] These conditions were found to promote a chemoselective reductive elimination from the branched alkyliridium(III) intermediate over that from the linear isomer.

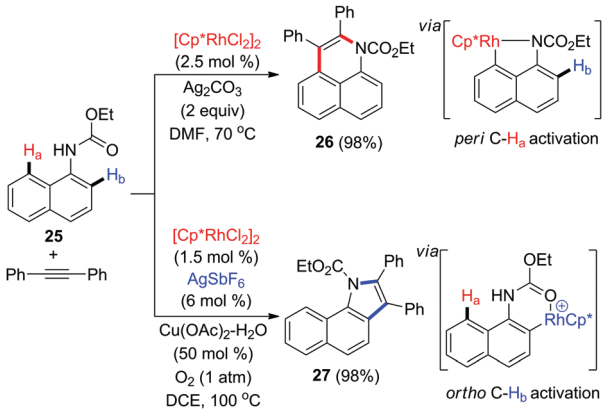
Moreover, Sakaki, Nakao, and co-workers showed in 2016 that the regioselectivity for the aromatic alkylation reaction is redirected away from the *ortho*-directing influence of the ketone towards the *para* position by reacting ketones with alkenes in the presence of the bulky Lewis acid catalyst MAD [(2,6-*t*Bu_2-4-Me-$C_6H_2O)_2$AlMe] and a Ni(0) catalyst coordinated to an exceptionally bulky N-heterocyclic carbene (NHC) catalyst.[22] For instance, reaction of **18** with a vinyl silane gives the linearly *para* alkylated ketone **21** with high selectivity ($p:m$ = 99:1). In this transformation, coordination of the sterically hindered Lewis acid to the carbonyl oxygen not only blocks the approach of the bulky catalyst to the *ortho* or *meta* hydrogens of **18**, but also preferentially electronically activates the *para* C–H_b bond over the *meta* C–H towards attack by the electron-rich Ni catalyst.[23] It should be noted that the scope of the latter Ir- and Ni-catalyzed alkylations, in addition to ketones, includes benzamides but

excludes benzoate esters. Nevertheless, the scope of Ni-catalyzed *para*-alkylations was later extended by the Nakao group to sulfonamides and sulfones.[24]

Specificity of C–H functionalization reaction conditions

Catalyst-controlled divergent C–H activation/alkyne annulations. In spite of their remarkable aptitude to direct catalytic C–H functionalization, DGs may lead to divergent regioselectivity as a function of the specific catalyst employed and the intricacies of the reaction conditions.[1g,2a] For example, Lam *et al.* reported a divergent aryl sp^2 C–H functionalization of 3-aryl-4-hydroxyquinolin-2-ones, such as **22**, that contain two distinct, non-adjacent sites of initial C–H functionalization, where product selectivity was empirically observed to proceed through catalyst control (Scheme 8).[25] By using the Pd–NHC complex PEPPSI-IPr as the precatalyst, an oxidative alkyne annulation provided spiroindene **23** exclusively *via* C–H_a bond activation. In contrast, a Ru-based precatalyst, $[RuCl_2(p\text{-cymene})]_2$, results in the activation of the C–H_b bond to afford benzopyran **24** as the major product. Although selectivity for **24** under Ru catalysis may be the consequence of a kinetic preference for the formation of the 5-membered metalacycle, an explanation for the reluctance of Pd to form the 5-membered metalacycle over the 6-membered one awaits further investigation.

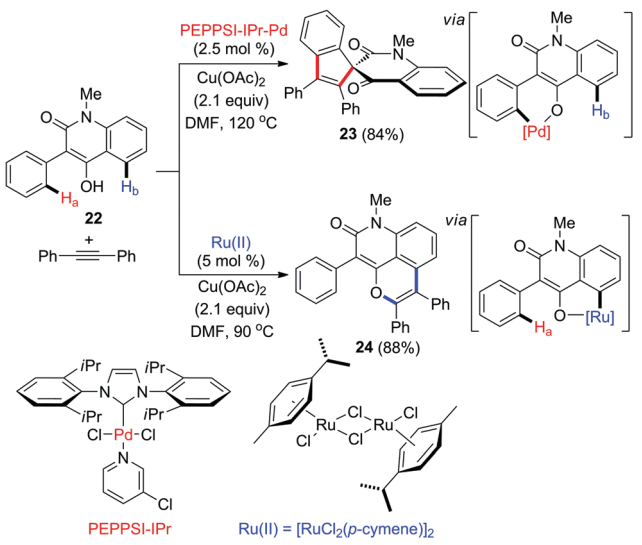
A second example is offered by Jin and co-workers, who demonstrated the Rh(III)-catalyzed divergent C–H activation/alkyne annulation of naphthyl carbamate **25** (Scheme 9).[26] In the presence of a neutral Rh(III) catalyst in polar DMF, the *peri* C–H bond is activated to form a Rh-N rhodacycle intermediate that ultimately gives benzoquinoline **26**. In contrast, the Lewis acidic cationic Rh(III) catalyst that is presumably generated *in situ* by the addition of $AgSbF_6$ activates the *ortho* C–H bond in dichloroethane solvent to furnish the benzo-fused indole derivative **27**. The authors propose that N-coordination of the carbamate is favored for the neutral Rh complex, leading to *peri* annulation through the 5-membered metalacycle, but that



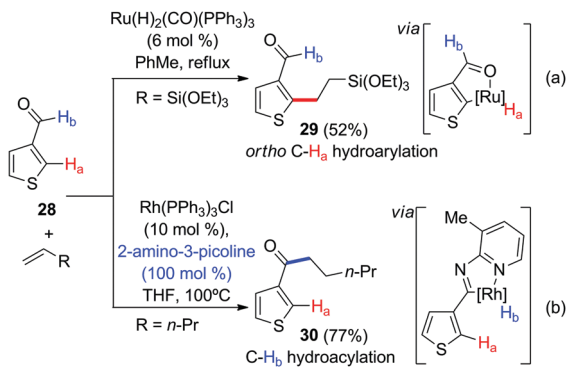
Scheme 9

O-coordination is favored for the more electrophilic and/or oxophilic cationic Rh complex, favoring directed *ortho*-functionalization through the 6-membered metalacycle.

Catalyst-controlled divergent C–H *ortho*-hydroarylation *vs.* hydroacylation of alkenes with benzaldehydes. The original Murai *ortho*-hydroarylation reaction[20] has been extended to substrates bearing DGs beyond aryl ketones,[1b] including other carbonyl derivatives such as aromatic imines[27] and some electron-rich or sterically hindered aldehydes.[28] For instance, thiophene-3-carbaldehyde **28** is reacted with triethoxyvinylsilane in the presence of a Ru catalyst to afford the *ortho*-hydroarylation product **29** (Scheme 10a). However, as demonstrated by the Jun group,[29] the facile formation of aldimines between aldehydes and primary amines can be harnessed to favor hydroacylation reactions in place of *ortho*-hydroarylations (Scheme 10b). Hence, when thiophene-3-carbaldehyde **28** is reacted with 1-pentene in the presence of the Wilkinson's Rh catalyst and 2-amino-3-picoline, the hydroacylation product **30** is obtained in place of the corresponding *ortho*-hydroarylation product.[30] Whereas selectivity in the *ortho*-hydroarylation is believed to arise from the 5-membered ruthenacycle obtained by *ortho*-metalation, selectivity for the hydroacylation is driven by a more favorable Rh chelate with the picoline imine. The latter intermediate also prevents unproductive decarbonylation side-reactions that are commonly encountered in reactions of aldehydes with transition-metal catalysts.



Scheme 8

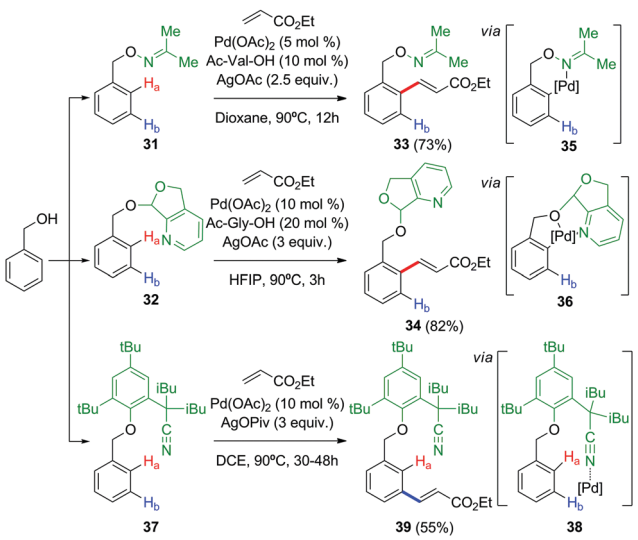


Scheme 10

3. Directing group influence beyond *ortho*-metalation

meta-Selective directing groups

The directing group strategy is especially powerful in the functionalization of C–H bonds located in close proximity to the DG, in particular C–H bonds in *ortho* to the DG in the case of arene substrates. The primacy of these reactions is related to the facile formation of 5-, 6-, or more rarely 7-membered cyclometalated intermediates.[2,5] Given the lack of direct approaches for the functionalization of arenes in the *meta* position to other substituents, considerable efforts have been spent towards the development of DG to regioselectively achieve these C–H functionalizations.[31] The first great success in this area was the demonstration in 2012 by the Yu group of a *meta*-selective oxidative alkenylation of benzyl alcohol derivatives through a DG strategy (Scheme 11).[32] It has been shown that benzyl alcohols are readily converted to derivatives bearing directing sp^2-hybridized nitrogens, such as acetone oxime **31**[33] or the pyridine acetal **32**.[34] Under Pd catalysis, these DGs can affect their *ortho*-selective oxidative alkenylation to provide substituted cinnamic esters **33** and **34**. The *ortho*-selectivity in these transformations is consistent with the formation of the corresponding palladacycle intermediates **35** and **36**. By contrast, the rigid nitrile-based DG **37** introduced by the Yu group favors a cyclophane-type transition state in which the U-shape of the DG and the linear coordination of the nitrile group (*e.g.* **38**) direct the Pd catalyst away from the *ortho* hydrogen H_a, towards the *meta* hydrogen H_b. As a result oxidative alkenylation with this DG is *meta*-selective, giving the substituted cinnamate ester **39**. Computational studies have indicated that a concerted metalation–deprotonation (CMD) transition state is likely involved in the C–H activation step, and that involvement of a dimeric $Pd_2(OAc)_4$ or heterodimeric $PdAg(OAc)_3$ complex significantly lowers the energy of the transition states leading to the *meta* products.[35]



Scheme 11

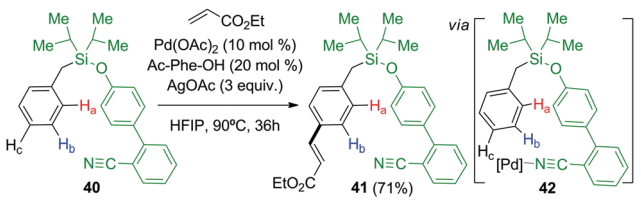
The DGs can readily be cleaved from products **33** and **34** by reductive cleavage of the N–O bond and acidic methanolysis, respectively, to reveal the corresponding *ortho*-alkenylated benzyl alcohols. The DG in **39** must however be cleaved by hydrogenolysis to provide the alkenylated toluenes. To overcome this limitation, several groups have introduced a series of new *meta*-DGs that are either more synthetically accessible and/or can be cleaved to reveal more convenient synthetic handles.[32,36] Together with the development of these new *meta*-DGs, the introduction of *N*-acylated amino acid ligands (also known as monoprotected amino acids, or MPAA), and the use of hexafluoroisopropanol (HFIP) either as a solvent or as an additive have, since these earlier reports, considerably broadened the scope of substrates and the number of C–H functionalizations amenable to *meta* direction.[36d,e,37]

para-Selective directing groups

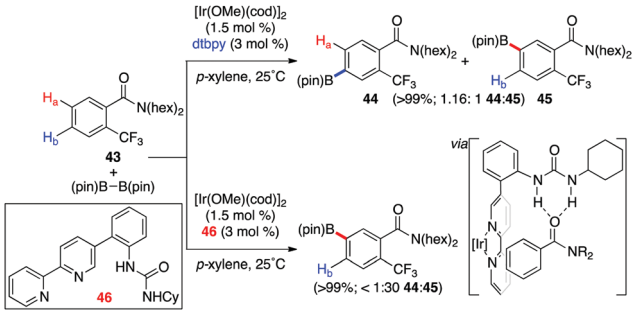
In 2015, the Maiti group introduced an extended silane-linked nitrile DG that enables the *para*-selective alkenylation and acetoxylation of benzylsilanol derivatives under Pd catalysis (Scheme 12).[38] The design of this templating ligand shares similar features with previously introduced *meta*-DGs, including a linearly coordinating nitrile group and geminal bulky groups on a tetragonal atom of the linker harnessing the Thorpe–Ingold effect to favor intramolecular reactivity. Hence, when silane-linked nitrile **40** is reacted with ethyl acrylate under typical Pd-catalyzed oxidative alkenylation conditions, the *para*-substituted cinnamic ester derivative **41** is obtained as the major product over other possible regioisomers (*p* : others = 8 : 1). A pre-organized intermediate **42**, reminiscent of the *meta* analogue **38**, is proposed to account for the regioselectivity of this transformation. Although the Tamao oxidation of the resulting benzyldialkylsilyl ether (*e.g.* **41**) was not demonstrated for these specific substrates,[36h,39] such oxidative cleavage should provide a divergent synthesis of either the *ortho*-, *meta*-, or *para*-functionalized benzyl alcohols when combined with the use of the removable DGs shown in Scheme 11. More recently, the same group has also introduced a silane-linked nitrile that acts as a *para*-DG for the C–H functionalization of phenol derivatives.[40]

meta-Direction through non-covalently bound directing groups

In spite of their demonstrated ability to direct the regioselectivity of an arene C–H functionalization to the *meta* or *para* position, these newly introduced DGs suffer from important disadvantages. The designer DGs can require multi-step syntheses, making them uneconomical on a practical scale. Furthermore, this approach requires additional steps to install, and eventually to



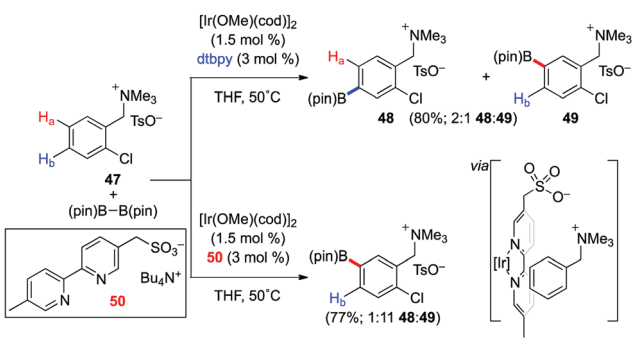
Scheme 12



Scheme 13

cleave the DGs. As an alternative to this covalently-linked DG approach, Kuninobu, Kanai, and co-workers have introduced a *meta*-selective Ir-catalyzed C–H borylation of arenes bearing hydrogen bond-accepting substituents (amides, esters, phosphonates, phosphonic diamides and phosphine oxides) that relies on non-covalent interactions between the catalyst's ligand and the substrate (Scheme 13).[41,42] For example, when amide **43** was reacted with bis(pinacolato)diboron (B_2pin_2) in the presence of an Ir catalyst and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) ligand, the C–H borylation proceeds quantitatively at the least sterically hindered 4- and 5-positions to yield a mixture of boronate esters **44** and **45** in a 1.16 : 1 ratio. However, in the presence of the designer bipyridine urea ligand **46**, the reaction becomes highly selective (**44** : **45** < 1 : 30) for a C–H borylation at the 5-position, which sits *meta* to the amide group. Scalability up to gram-quantities was demonstrated for the synthesis of **45**. The authors' design and rationale rest on the reversible double hydrogen-bonding of the amide substrate with the Ir catalyst ligated with **46**, which localizes the Ir center in close proximity to the *meta* C–H bond.[43] The same group has later reported a designer bipyridine ligand bearing a Lewis acidic boronic ester group to direct the selective *ortho*-borylation of Lewis basic aryl sulfides through acid–base interactions.[44]

A second example of Ir-catalyzed divergent borylation that relies on non-covalent interactions was introduced in 2016 by the Phipps group (Scheme 14).[45] As for other 1,2-disubstituted benzene derivatives such as **43**, the selectivity of Ir-catalyzed borylation of benzylammonium salt **47** under typical conditions (Ir(I)/dtbpy) is governed by sterics. A regioisomeric mixture is obtained where C–H functionalization *meta* to the chlorine substituent, giving **48**, was favoured by 2 : 1 over C–H functionalization *meta* to the ammonium group giving **49**. Switching the neutral bipyridine ligand for the anionic bipyridinesulfonate ligand **50** results in an inversion of the selectivity to favor functionalization *meta* to the ammonium group (1 : 11 **48** : **49**). Reversal of the selectivity has been rationalized by ion pairing between the anionic sulfonate and the cationic ammonium, which brings H_a in closer proximity to the reactive Ir center. Control experiments where the ammonium group is replaced by a neutral dimethylamine or *tert*-butyl groups have shown no *meta*:*para* regioselectivity, offering support to the hypothesis that ion-pairing is responsible for the observed regioselectivity.



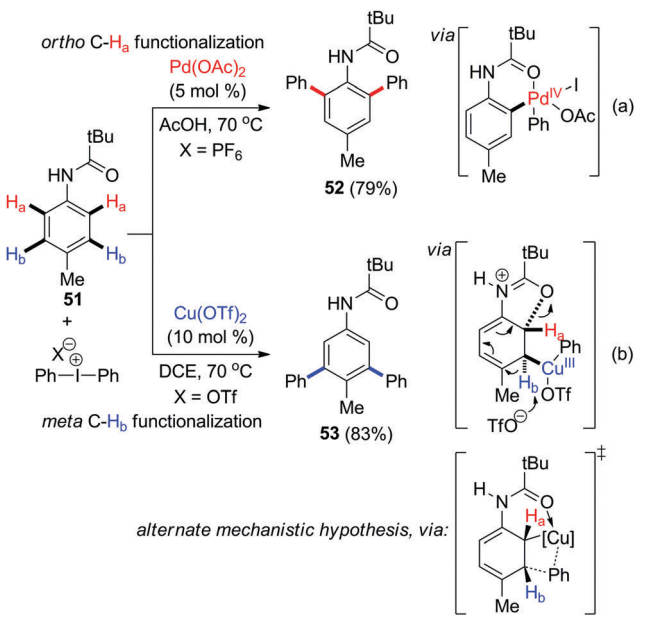
Scheme 14

Electronic polarization by a directing group

Directing groups, as shown in the examples above, can localize a transition metal center in proximity to a reactive C–H bond to accomplish its regioselective functionalization. It has also been demonstrated that DGs can less often play another role by electronically polarizing the substrate to result in a unique reactivity pattern.

Catalyst-controlled *ortho*- and *meta*-arylation of anilides. A pair of divergent anilide arylation reactions exemplify the dichotomy between the typical metal-coordinating action of a DG and the less common electronic polarization of the substrate by the same DG. Daugulis *et al.* demonstrated that the $Pd(OAc)_2$-catalyzed arylation of electron-rich pivalanilides **51** with diaryliodonium salts occurs in carboxylic acid solvent to give the *ortho* C–H functionalized **52** exclusively.[46] The same results are obtained with aryl iodides alongside AgOAc in place of diaryliodonium salts. The authors suggested a mechanism proceeding through a Pd(IV) intermediate to afford upon reductive elimination the *ortho* (relative to the anilide) substituted product (Scheme 15a).

In contrast, Gaunt *et al.* discovered that the arylation regioselectivity can be altered by employing a $Cu(OTf)_2$ precatalyst to

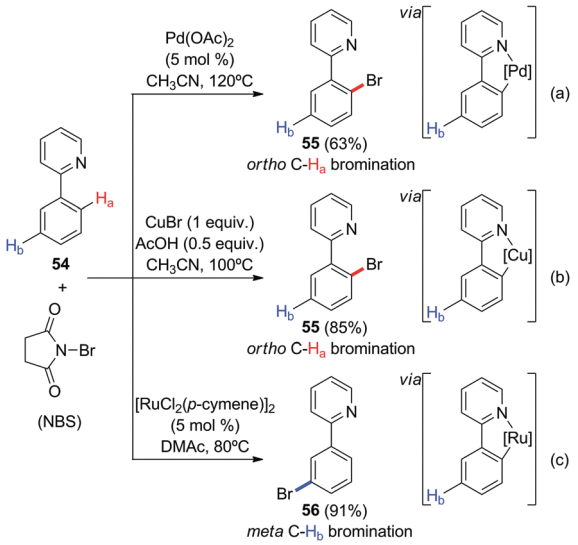


Scheme 15

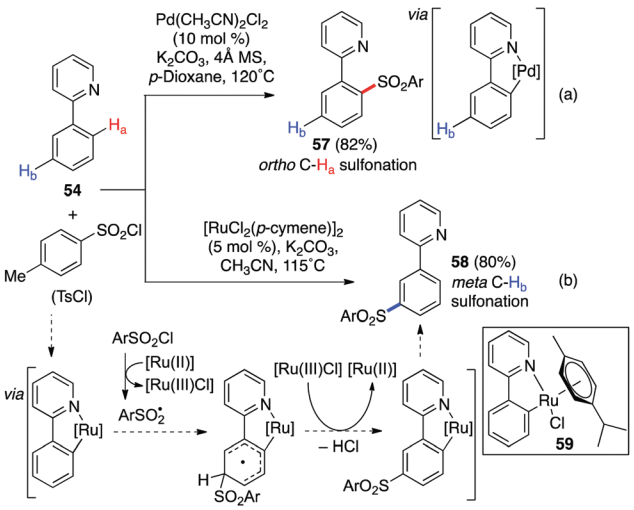
afford the *meta*-arylated product **53** (Scheme 15b).[47] This result is notable for its contrast with the regioselectivity expected for either a DG-guided process (*ortho*) or a classical electrophilic aromatic substitution pathway (*ortho*/*para*). The authors originally proposed a Cu(I)/Cu(III) cycle for this transformation where the active Cu(I) species, formed by the reduction or disproportionation of the Cu(II) precatalyst, oxidatively adds to the diaryliodonium salt to generate an arylcopper(III) species. This highly π-Lewis acidic arylcopper(III) intermediate coordinates to the aromatic ring to result in oxy-cupration upon intramolecular nucleophilic attack of the carbonyl oxygen at the *ortho*-position. Re-aromatization and reductive elimination complete the catalytic cycle to afford the *meta*-arylated product. However, their assessment conflicts with a recent computational investigation.[48] According to the latter, selectivity for the *meta*-arylated product results from a carbamate-directed electrophilic attack of the arylcopper(III) species at the *ortho* position that evolves into a Heck-type carbocupration of the anilide. Re-aromatization through the abstraction of a proton and cleavage of the C–Cu bond then provides the *meta*-arylated product and regenerates the Cu(I) catalyst.

Catalyst-controlled *ortho*- and *meta*- bromination and sulfonation of phenylpyridines. Transition metals themselves have been shown to act as DGs by electronically polarizing the reactive substrate. This property has been synthetically exploited in catalytic cycles that involve cyclometalated Ru complexes of aromatic imines as intermediates.[31b,d,49] In these reactions, the aromatic imine acts as a DG to promote the transformation of an *ortho* aryl C–H bond into a new C–Ru σ bond. The resulting intermediate displays an apparent increased π-nucleophilicity at the position *para* to the new C–Ru bond,[50] and therefore *meta* to the original aromatic imine DG. After functionalization occurs from the metalated intermediate, the subsequent protolysis of the C–Ru bond finally affords the remotely functionalized arene. An example of this divergent catalysis is shown in the selective bromination of phenylpyridine **54**, which can be selectively *ortho*-brominated with *N*-bromosuccinimide (NBS) either in the presence of a Pd catalyst,[4] or in the presence of a Cu catalyst,[51] to give **55** (Scheme 16a and b). These reactions, which exemplify typical DG-guided reactions, have also been reported for closely related substrates and brominating agents *via* Cu,[52] Co,[53] and Rh catalysis,[54] among others. However, when **54** is reacted with NBS in the presence of a Ru catalyst, the *meta*-brominated regioisomer **56** is instead obtained (Scheme 16c).[55] The complete reversal of the selectivity has been attributed to the electronic influence of the cyclometalated Ru intermediate, which remotely directs bromination at the distal position.[56]

This divergent reactivity manifold is not limited to aromatic bromination reactions and can extend to catalytic C–H alkylation, sulfonation, and more recently nitration reactions.[31,57] For instance, the Dong group reported that, under the influence of a Pd catalyst, 2-phenylpyridine **54** reacts with *p*-toluenesulfonyl chloride (TsCl) and a carbonate base to afford the *ortho* C–H sulfonated **57** (Scheme 17a).[58] Indirect mechanistic studies carried out by the Dong group have highlighted the possible involvement of a *ortho*-metalated Pd(II) chelate intermediate,



Scheme 16



Scheme 17

which is then oxidized into a Pd(IV) sulfinate by TsCl before the formation of the new C–S bond through reductive elimination.[59] By contrast, the Frost group discovered that when the same 2-phenylpyridine **54** is treated with TsCl in the presence of a Ru catalyst and a carbonate base, a reversal of selectivity occurs to provide the *meta* sulfonated isomer **58** in place of **57** (Scheme 17b).[60] As for the above Ru-mediated *meta* bromination of **54**, evidence points toward the involvement of an *ortho*-cyclometalated Ru chelate as a key intermediate, which polarizes and activates the phenyl ring at the position *para* to the C–Ru σ bond. Furthermore, the preformed complex **59** reacts with TsCl under the identical reaction conditions to quantitatively afford **58**, and **59** is also a competent pre-catalyst for the conversion of **54** into **58**. The Frost group has more recently combined this Ru-mediated *meta*-selective C–H sulfonation with a Cu-mediated *ortho*-selective C–H bromination and a Suzuki–Miyaura cross-coupling to rapidly construct polycyclic heteroaryl sulfones.[61]

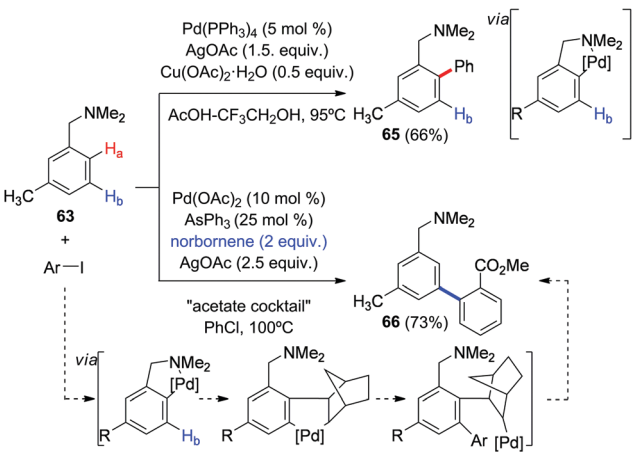
Although S_EAr mechanisms were first suggested for the reaction of the cyclometalated Ru intermediates, evidence for odd-electron species has been uncovered, indicating preferential π-addition of a radical on the aryl group in *para* to the C–Ru bond (*e.g.* Scheme 17, bottom).[55a,60b,62]

Transient directing groups

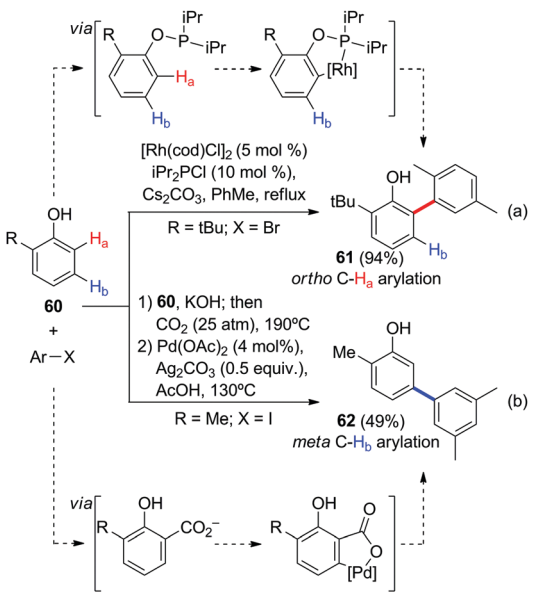
The majority of directing groups are covalently bonded to their substrates. Unless these DGs are an inherent constituent of the target of a synthesis, the additional steps that may be required to install, and then remove these DGs represent a limitation to this approach. In some instances, however, it is possible to circumvent these drawbacks with the use of transient, traceless DGs, which also can provide divergent reactivity pathways.[63]

Divergent C–H arylation of phenols controlled by transient directing groups. Transient directing groups have provided for a divergent synthesis of arylated phenols *via* C–H functionalization (Scheme 18). Building on earlier examples,[64] Bedford, Caffyn, Prashar, and co-workers reported an *ortho* selective Rh-catalyzed C–H arylation of phenols with aryl halides that employs a phosphorus-based transient DG (Scheme 18a).[65] In this transformation, the phenoxide – generated by the action of cesium carbonate on the phenol **60** – first reacts with the chlorodialkylphosphine to generate a transient phosphinite. The latter acts as an *ortho*-DG in the cyclometalation of the arene with the Rh catalyst. After the arylation has occurred, a base mediated transesterification of the phosphinite group liberates the *ortho* C–H arylation product **61**. The Larrosa group used instead carbon dioxide as a traceless DG in a one-pot relay *meta* arylation of phenols (Scheme 18b). When a phenoxide is first reacted under high temperatures and carbon dioxide pressure,[66] a Kolbe–Schmitt reaction produces the corresponding salicylate, which acts as an *ortho* DG for the cyclometalation of the Pd catalyst *meta* to the phenol group.[67] Following the *meta* arylation step, a decarboxylation ultimately occurs to afford the product **62**.[68]

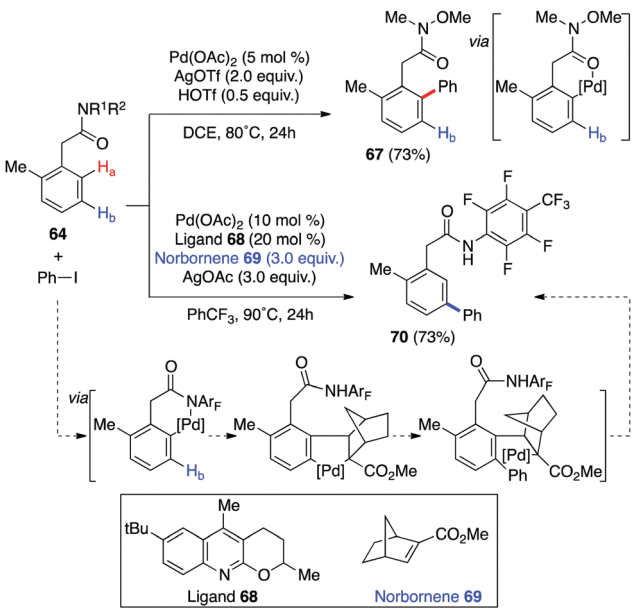
Divergent C–H arylation of benzyl amines and arylacetic amides controlled by transient directing groups. Following the pioneering work of Catellani,[69] Lautens,[70] and others,[71] several groups have sought to exploit the reversible carbopalladation of certain alkenes, in particular norbornene, by arylpalladium(II) intermediates to redirect the regioselectivity of C–H functionalization reactions catalyzed by this metal. Two examples of such C–H arylations that employ norbornene as a transient DG are shown in for benzyl amines **63** and arylacetic amides **64** in Schemes 19 and 20. When benzyl amine **63** is reacted with an iodoarene in the presence of a Pd catalyst and silver and copper acetates as additives, the *ortho* C–H arylation product **65** is obtained since the benzyl amine group is a potent DG in the initial cyclopalladation.[72,73] By contrast, when benzyl amine **63** is reacted with an iodoarene in the presence of a Pd catalyst,



Scheme 19



Scheme 18



Scheme 20

norbornene, and a 'cocktail' of acetates (the Ag(I), Cs(I), Li(I), Cu(II) acetates and acetic acid), the regioselectivity of the C–H arylation is altered to furnish the *meta* isomer **66**.[74] The formation of this regioisomer has been rationalized by an amine-directed *ortho*-palladation that is followed by an insertion into the π-bond of norbornene. The forced proximity of the resulting intermediate facilitates the formation of the 5-membered palladacycle through C–H_b activation, which then reacts with the iodoarene to result in the *meta*-arylated alkylpalladium(II) species. The final product **66** is then obtained through a β-aryl elimination followed by protolysis of the aryl–Pd bond.

These divergent catalytic C–H arylation reactions have similarly been implemented for arylacetic amides **64** (Scheme 20). Building on the C–H arylation of benzamides reported by the Daugulis group,[75] Wang and co-workers demonstrated that the Weinreb amides of arylacetic acids are suitable *ortho* DGs to effect their C–H arylation with iodoarenes in the presence of a Pd catalyst, silver salts, and trifluoromethanesulfonic acid, resulting in biaryl derivatives such as **67**.[76] The Yu group exploited the Catellani-type reversible insertion of the key cyclometallated arylpalladium(II) intermediate into the π-bond of norbornenes to redirect the regiochemistry of this arylation to the *meta* position.[77] Under highly optimized conditions, the *p*-trifluoromethyltetrafluorophenyl amides of arylacetic acids are *meta* arylated with an iodoarene in the presence of a Pd catalyst, silver acetate, the quinoline ligand **68**, and norbornene **69** to afford biaryl derivatives such as **70**. In particular, the use of **69** in place of the parent norbornene greatly expands the scope of this transformation with respect to the iodoarene. This reaction has also been expanded to allow for the *meta*-alkylation of arylacetic amides with alkyl halides,[77] and later for the arylation, alkynylation and chlorination of diverse C–H substrates including anilines, heterocyclic amines, and phenol derivatives, among others.[78] The reversible insertion of arylpalladium(II) complexes into the π-bond of norbornene was also exploited to alter the regioselectivity of Pd-catalyzed amination reactions of aryl halides in favor of the *ortho* isomer (through C–H substitution), as opposed to the more frequently encountered *ipso* functionalization (through C–X substitution).[79]

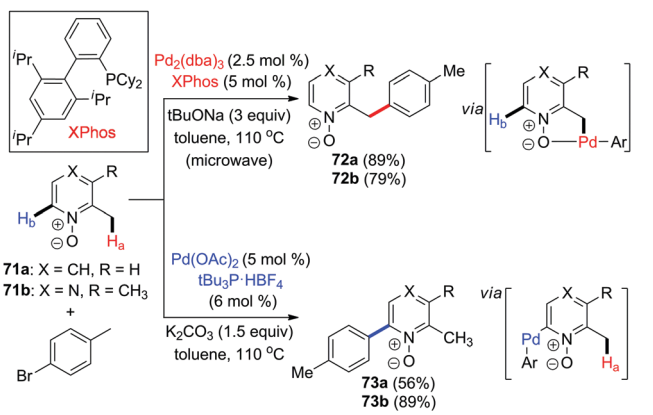
4. Control of regioselectivity without directing groups

In spite the ubiquity of the directing group approach in catalytic C–H functionalization schemes, achieving divergent catalysis is far from being limited to DG-based strategies. Redirection of the product selectivity away from a substrate innate's reactivity pattern by bifurcation of the catalytic reaction pathways has been successfully used to create divergent transformations. Given the prevalence of redox-neutral C–H/C–X couplings among transition metal-catalyzed transformations, it is no surprise that the choice of the base employed to remove HX can have important consequences on the regioselectivity of a transformation. In the simplest case, two different C–H bonds of sufficiently different Brønsted acidity can be differentiated by employing a base with strength such that only one C–H bond is efficiently functionalized. In more complex cases, the choice of a base can favour one reaction pathway among many in a more subtle fashion.

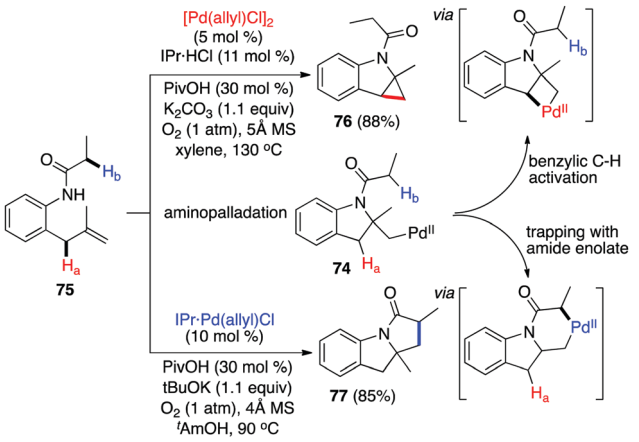
Differences in C–H acidity

Base-controlled divergent Pd-catalyzed sp^3 C–H/sp^2 C–H arylation of azine *N*-oxides. Fagnou *et al.* developed catalytic systems for the selective arylation of either the *ortho* sp^2 C–H or the benzylic sp^3 C–H bond of a 2-alkylated azine *N*-oxide, such as that of picoline and pyrazine *N*-oxides **71** (Scheme 21).[80,81] In the presence of a $Pd_2(dba)_3$/XPhos catalyst system and a strong *tert*-butoxide base, the rather acidic benzylic C–H_a bond is palladated with the assistance of the oxygen atom of *N*-oxides as a DG to afford **72**. In contrast, the combination of $Pd(OAc)_2$ with the sterically bulky electron-rich tBu_3P ligand and a weaker carbonate base, the benzylic C–H_a bond remains untouched. Under the latter conditions, the *ortho* sp^2 C–H_b bond is activated, *via* a postulated CMD transition state, to form an arylPd(II)-complex on the way to the heterobiaryl **73**. Selective *ortho* sp^2 C–H arylation of a pyridine *N*-oxide in the presence of an acidic benzylic C–H bond was recently reported by Tsukano, Takemoto, Hirama, and co-workers in the synthesis of the complanadines A and B.[82]

Base-controlled divergent Pd-catalyzed sp^3 C–H functionalization *via* σ-alkylPd(II)-intermediates. There has been a great interest in the use of catalytically generated Pd-complexes for domino reactions to construct complex polycycles.[83] Among recent examples, Yang and co-workers reported a divergent sp^3 C–H functionalization of σ-alkylPd(II)-intermediates **74**, formed through an aminopalladation of **75**. The transformation proceeds with $[Pd(allyl)Cl]_2$ and a NHC ligand precursor, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl), or with the corresponding preformed NHC–Pd catalyst, to afford cyclopropanated indolines **76** or benzo-fused pyrrolizidines **77** (Scheme 22).[84] The chemoselectivity of the reaction is governed by the choice of base and solvent polarity. In a nonpolar solvent, with a milder carbonate base, the σ-alkylPd(II) intermediate is found to activate the benzylic sp^3 C–H bond, presumably *via* a concerted metalation–deprotonation transition state forming a palladacyclobutane intermediate, resulting in the fused cyclopropane **76** after



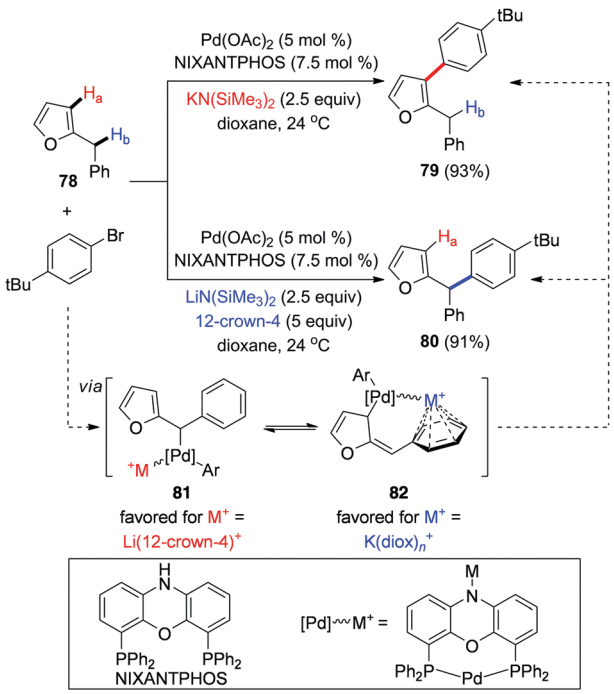
Scheme 21



Scheme 22

reductive elimination. In the presence of strong base in a polar solvent, however, the amide enolate traps the σ-alkylPd(II) intermediate **74** to give **77** selectively following reductive elimination. Related divergent reactions involving σ-alkylPd(II) intermediates have also been reported by Xu, Loh, and co-workers.[85]

Base-controlled divergent Pd-catalyzed sp^3 C–H/sp^2 C–H arylation of 2-benzylfurans. In 2016, Thompson, Walsh, and co-workers reported a divergent C–H functionalization of 2-benzylfurans **78** where selectivity for either the benzylic or the 3-furyl C–H is similarly governed by the choice of base, yet where pK_a differences are not the critical factor favoring one regioisomer over another (Scheme 23).[86] When **78** is reacted with a bromoarene in the presence of a NIXANTPHOS–Pd complex and potassium bis(trimethylsilyl)amide as a base, the 3-arylated



Scheme 23

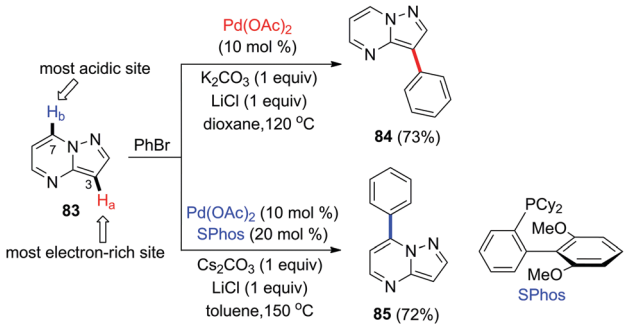
furan **79** is obtained selectively. However, when the potassium base is replaced with its lithium analogue and 12-crown-4 as an additive, arylation instead proceeds at the benzylic position to give **80**. Both of these deprotonative cross-coupling processes are analogous to the more widespread Buchwald–Hartwig arylation of enolates. Hence, oxidative addition of a Pd(0) complex into the bromoarene and subsequent transmetalation with the resonance-stabilized benzylic anion, obtained by deprotonation of **78** with the strong amide base, provides a common benzyl(aryl)Pd(II) complex, such as **81**. Reductive elimination, which here governs the **79**:**80** selectivity, occurs with C–C bond formation to give the arylated product and regenerate the Pd(0) catalyst. Since previous experiments established that the NH group of the NIXANTPHOS ligand is deprotonated under strongly basic conditions,[87] the authors proposed that intermediate **81** is in equilibrium with its tautomer **82**, and that the position of the equilibrium is determined by cation–π interactions. Experimental and computational results are consistent with cation–π interactions of the potassium salt favoring **82**, and consequently offer a rationale for the selective formation of the arylated furan **79**. Design and control of cation–π interactions thus provides a new and largely unexploited handle to achieve catalytic divergent C–H functionalizations.

Electronic preferences *vs.* C–H acidity

Formation of a carbon–metal bond is typically one of the intermediate steps in transition metal-catalyzed C–H functionalization schemes, and the outcome of this step often determines the regioselectivity of the overall transformation. Moreover, several processes are available for achieving the formation of the C–M bond, the most common being the direct oxidative addition of a low-valent metal into the C–H bond and assisted concerted metalation–deprotonation (CMD) mechanisms. Less direct processes are also encountered, including deprotonation of the C–H bond followed by transmetalation, electrophilic metalation of π-bonds (S_EAr-type), or carbometalation of π-bonds (Heck-type), the latter two being followed by the eventual loss of a proton. The ability to funnel reaction mechanism selectively along one or another of these metalation pathways has been exploited to achieve divergent C–H functionalization reactions.

Pd-Catalyzed C3-/C7-arylation of pyrazolopyrimidines. In 2015, Bedford *et al.* reported a divergent Pd-catalyzed C–H arylation of pyrazolo[1,5-*a*]pyrimidines **83** (Scheme 24).[88] In the presence of a phosphine-free Pd catalyst, the C–H_a bond at the most electron-rich 3-position is arylated, affording **84** with a regioselectivity indicative of an electrophilic palladation process. By contrast, a phosphine-ligated Pd catalyst promotes the direct arylation of the C–H_b bond at the most acidic 7-position to produce **85**, suggesting in this case the base-assisted CMD palladation mechanism.

Pd-Catalyzed intramolecular C2-/C3-arylation of furancarboxamides. The intramolecular arylation of furancarboxamides reported in 2016 by the Yin group offers another example where the choice of ligand and reaction conditions can favor one Pd C–H arylation mechanism over others, resulting in divergent



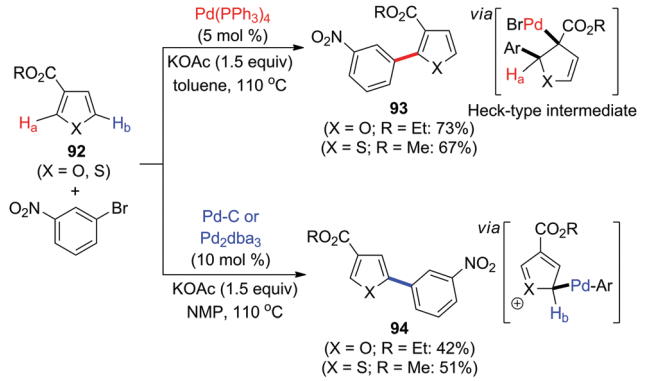
Scheme 24

Scheme 25

product selectivity (Scheme 25).[89] When the brominated furan-carboxamide **86** is reacted with a carbonate base in the presence of a Pd/PPh_3 catalyst, arylation occurs at the α-position to result in the formation of spirooxindole **87**. The observed regioselectivity is consistent either with an electrophilic palladation pathway or with a Heck-type carbopalladation following the initial oxidative addition into the Ar–Br bond. By contrast, when arylation is conducted with a Pd/P(*o*-$C_6H_4OMe)_3$ catalyst and pivalic acid, arylation occurs at the β-position to give the fused quinolone **88**. Selectivity for the latter product is instead consistent with a pivalate-assisted CMD palladation mechanism. The selectivity for either α- or β-arylation was preserved in the case of the higher homologue **89**, to selectively afford spirodihydroisoquinolinone **90** or the fused azepinone **91** (Scheme 25b)

Electrophilicity *vs.* carbometalation and C–H acidity

Pd-Catalyzed sp^2 C–H arylation of furans, thiophenes. In 2003, Sharp *et al.* reported the Pd-catalyzed regioselective arylation of 3-furoate and 3-thiophenecarboxylate esters **92** with aryl bromides (Scheme 26).[90] It is proposed that a nonpolar solvent and phosphine ligands stabilize the oxidatively formed

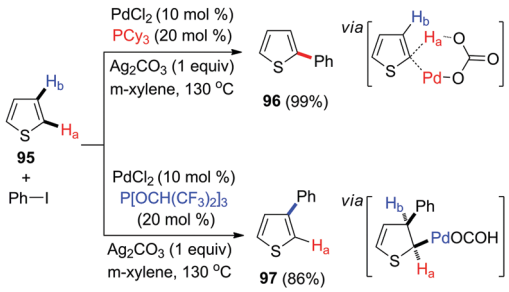


Scheme 26

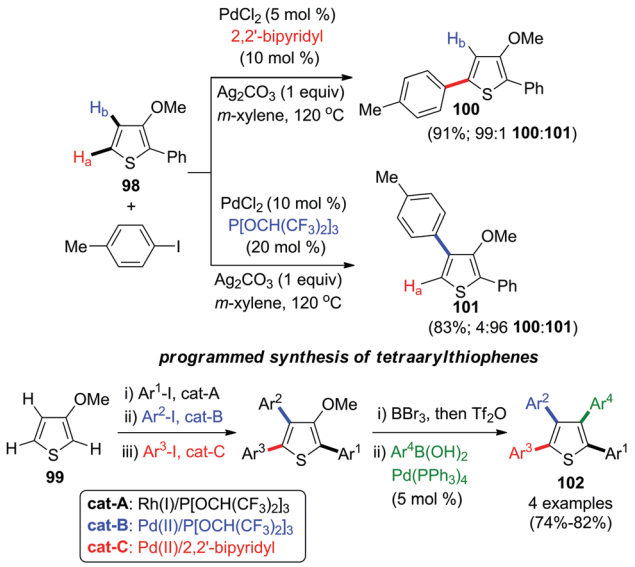
ArPd(II)X species, affording the Heck-type intermediate *en route* to the 2-arylated product **93** *via* β-hydride elimination. Conversely, in a polar solvent, the absence of stabilizing phosphine ligands promotes the ionization of the ArPd(II)X species to form an electrophilic cationic Pd(II) species. The latter reacts preferentially at the more electron-rich 5-position giving a cationic intermediate to afford the 5-arylated product **94** after deprotonation and reductive elimination.

Itami *et al.* reported that the Pd-catalyzed arylation of unsubstituted thiophene **95** with aryl iodides occurs at the 2-position affording 2-arylthiophenes such as **96** when the electron-rich phosphine PCy_3 is used as ligand (Scheme 27).[91] However, the selectivity is reversed with the electron-poor phosphite ligand $P[OCH(CF_3)_2]_3$, giving 3-arylthiophenes such as **97**. Computational studies suggest that C2-selectivity arises through a concerted metalation–deprotonation (CMD) process, while a Heck-type carbopalladation favors the C3-arylated product.[92] More recently, the Larrosa group demonstrated that C3-selective arylation of thiophenes (and benzothiophenes) with aryl iodides proceeds at room temperature in presence of a $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst and Ag_2CO_3 without ancillary ligands when the reaction is performed with HFIP as the solvent.[93] Based on KIE experiments, a Heck-type carbopalladation is once again implicated to rationalize the C3-regioselectivity.

The electronic and coordinating properties of 3-methoxythiophenes are exploited in the divergent C–H arylation of these heterocycles. 3-Methoxy-2-phenylthiophene **98**, which can itself be synthesized by a Rh-catalyzed C2-selective arylation of 3-methoxythiophene **99**,[94] is selectively arylated at the more acidic and



Scheme 27

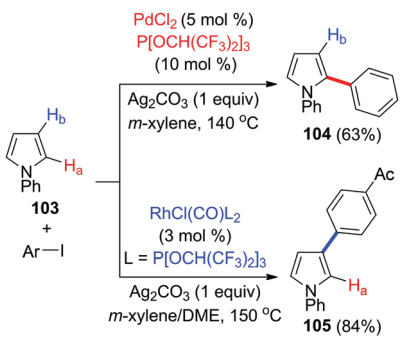


Scheme 28

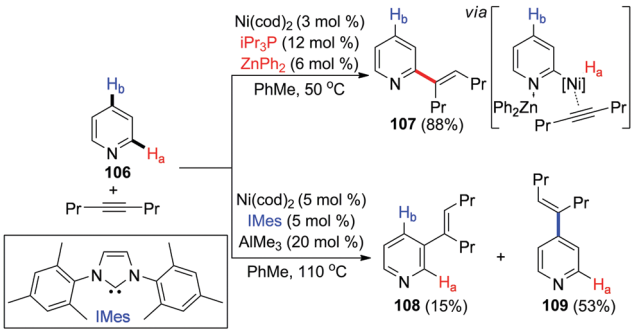
nucleophilic 5-position to give **100** in the presence of a catalytic system based on a Pd(II) precursor in the presence of 2,2′-bipyridyl as a ligand (Scheme 28).[95] By contrast, changing the ligand to the fluorinated phosphite $P[OCH(CF_3)_2]_3$ provides the 4-arylated regioisomer **101**. The latter is more consistent with a Heck-type carbopalladation mechanism while the former is more consistent with a CMD palladation. The possibility of equilibrating regioisomeric carbopalladation intermediates that convert into the final arylthiophene at different rates has also been suggested.[92] Combining these three regioselective C–H arylation protocols with a Suzuki–Miyaura cross-coupling after exchanging the methoxy group for a triflate ester allows for a programmed synthesis of tetraarylthiophenes **102**.

Electronic preferences *vs.* steric control

Catalyst-controlled α/β-arylation of pyrroles. In an extension of their work on the regioselective arylation of thiophenes, Itami, Yamaguchi, and co-workers developed divergent catalyst systems for the α- or β-arylation of *N*-substituted pyrroles (Scheme 29), and applied them in the synthesis of lamellarins C and I.[96] The Nagoya group identified that, under Pd catalysis, arylation of *N*-phenylpyrrole **103** with iodoarenes proceeds with



Scheme 29



Scheme 30

complete selectivity for the α-position, providing **104** in moderate yield. Conversely, arylation of **103** performed with an iodoarene under the catalysis of a highly electrophilic Rh complex provided high selectivity for the β-arylated product **105**. Although mechanistic experiments were not performed for the Pd system, its α-selectivity appears consistent with either an electrophilic or a CMD palladation process. In the case of Rh catalysis, the authors favor an electrophilic S_EAr-type C–H activation process that is highly sensitive to the steric influence of the pyrrole *N*-substituent to explain the observed β-selectivity.

Ni-Catalyzed C2-/C4-alkenylation of pyridines. Nakao, Hiyama, and co-workers reported a Ni-catalyzed alkenylation of pyridines where the inherent preference for C2 functionalization can be redirected with the judicious combination of a bulkier catalyst and a sterically demanding Lewis acid activator (Scheme 30). When pyridine **106** is reacted with 4-octyne in the presence of a catalytic amount of a Ni(0) precursor, triisopropylphosphine, and diphenylzinc as a Lewis acid activator, the *E*-alkenylated pyridine **107** is obtained as major product with small amounts of a C2-dienylated side-product.[97] It is proposed that Lewis acid activation *via* coordination to the pyridine nitrogen is essential to activate the heterocycle towards C–H functionalization by the Ni catalyst.[23] Following this initial report, the same team demonstrated that the use of the bulkier ligand IMes results in a steric clash with the N-coordinated Lewis acid $AlMe_3$, and make it impossible for the catalyst to approach the 2-position.[98] Under those conditions, alkenylation only occurs at the 3- and 4-positions (C3 : C4 = 15 : 53) to give the *E*-alkenylated pyridines **108** and **109**, respectively. The Ong group obtained comparable results using $AlMe_3$ and a different sterically hindered NHC ligand.[99] Finally, it should be noted that similar approaches have been successful in the C4-selective alkylation of pyridines with alkenes.[98,100]

5. Kinetic control *vs.* thermodynamic control of regioselectivity

Catalytic divergent C–H functionalization schemes are also possible when two or more intermediates on the reaction pathway can interconvert and lead to different regioisomers of the products. Control of regioselectivity is thus governed by the equilibrium between the intermediates, and the respective energy barriers for

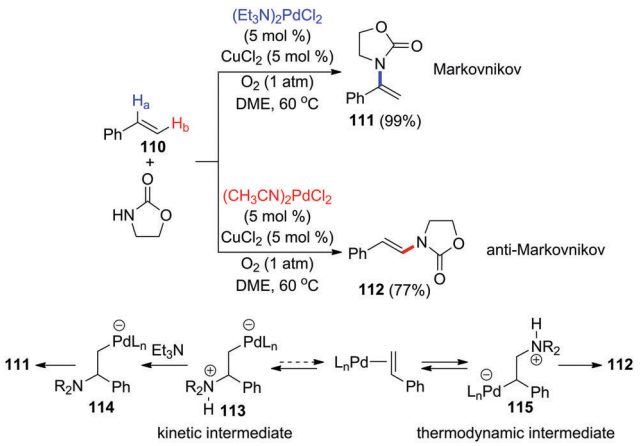
the sequences leading to the either regioisomeric product (Curtin–Hammett kinetics).

Pd-Catalyzed oxidative amination of alkenes

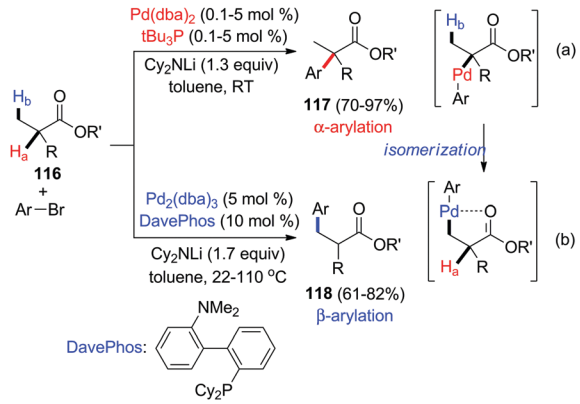
The catalytic oxidative amination of alkenes (aza-Wacker) is a useful method for the synthesis of enamines. Although its mechanism does not involve a C–H metalation step, it is nonetheless formally equivalent to the C–H functionalization of an alkene. Stahl *et al.* reported that regioselectivity in the Pd-catalyzed oxidative amination of styrene **110** with oxazolidinone could be controlled by the choice of a ligand at the Pd center (Scheme 31).[101] With a tertiary amine ligand, the Markovnikov adduct **111** is formed selectively, while the anti-Markovnikov adduct **112** is formed with a nitrile ligand. Mechanistic investigations revealed that the addition of a small amount of Et_3N, or other Brønsted bases, to the reaction mixture under nitrile-ligated conditions changes the selectivity. This is consistent with an irreversible deprotonation of the intermediate **113**, producing **114** *en route* to the kinetic product **111**. This event prevents equilibration with the intermediate **115** responsible for the formation of the thermodynamic product **112**.[102] Stahl *et al.* also reported catalyst-controlled regioselectivity in the synthesis of branched conjugated dienes *via* aerobic oxidative Heck reactions.[103]

Pd-Catalyzed α- and β-arylation of esters

The acidity of the α-proton of carbonyl compounds facilitates their functionalization using Pd catalysts.[104] For example, Hartwig *et al.* reported that, in the presence of the electron-rich bulky phosphine ligand tBu_3P, the ester enolate of **116** reacts with ArPd(II)Br to afford the α-arylated ester **117** *via* a C-bound Pd–enolate (Scheme 32a).[105,106] Building on these advances, Clot, Baudoin, and co-workers developed a ligand-controlled Pd-catalyzed β-arylation of esters using the aminophosphine ligand DavePhos to afford **118** (Scheme 32b).[107] Kinetic studies and DFT calculations revealed that β-arylation is kinetically favored for DavePhos or PCy_3, but not for tBu_3P, and that the rate-determining step of the catalysis with DavePhos is the Pd enolate–homoenolate isomerization sequence.[108]



Scheme 31



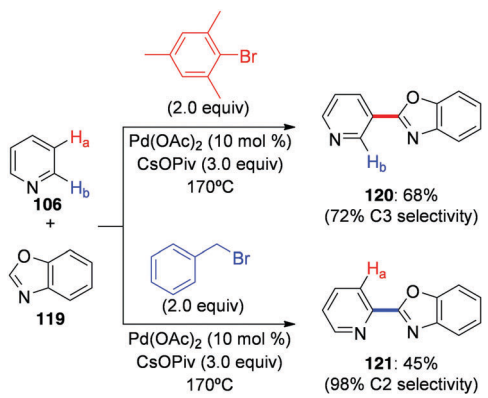
Scheme 32

6. Other modes of regioselectivity

In numerous cases, the development of effective divergent C–H functionalization reactions has proceeded faster than the acquisition of data to support mechanistic hypotheses with respect to the observed regioselectivity. In this regard, dehydrogenative (oxidative) C–H/C–H couplings are often less fully developed than the corresponding redox-neutral C–H/C–X couplings. Since the nature of the base that neutralizes the HX by-product is known to affect the regioselectivity of the latter schemes, it is not surprising that the choice of oxidizing agent in the former schemes affects regioselectivity.

Oxidant-controlled Pd-catalyzed cross-dehydrogenative divergent coupling of pyridine and benzoxazole

In 2016, the Itami group reported a Pd-catalyzed cross-dehydrogenative coupling (CDC) between pyridine **106** and benzoxazole **119** (Scheme 33).[109] In this transformation, an aryl or benzyl halide acts as the formal oxidizing agent. Most interestingly, it was found that the choice of halide has a profound impact on the regioselectivity of the reaction. In the presence of a bulky aryl bromide, such as bromomesitylene, the oxidative coupling is selective for the 3-position of pyridine (*i.e.* H_a) over the 2- or 4-positions to provide pyridyl benzoxazole **120**. Using benzyl



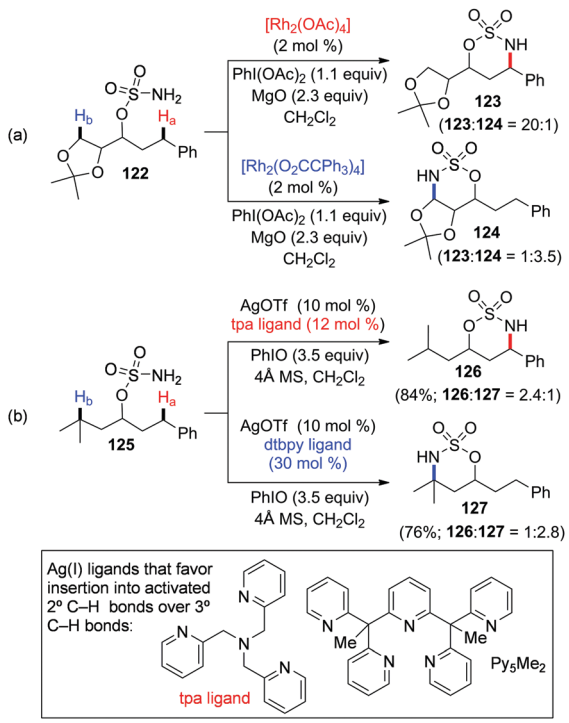
Scheme 33

bromide as the oxidizing agent in place of bromomesitylene leads to a reversal of the regioselectivity in favor of the 2-position of pyridine (*i.e.* H_b) to provide **121** instead. No rationale was provided to explain the reversal of regioselectivity, but control experiments rule out the involvement of *N*-benzylpyridinium salts or benzyl pivalate generated *in situ* in the C2-selective reaction.

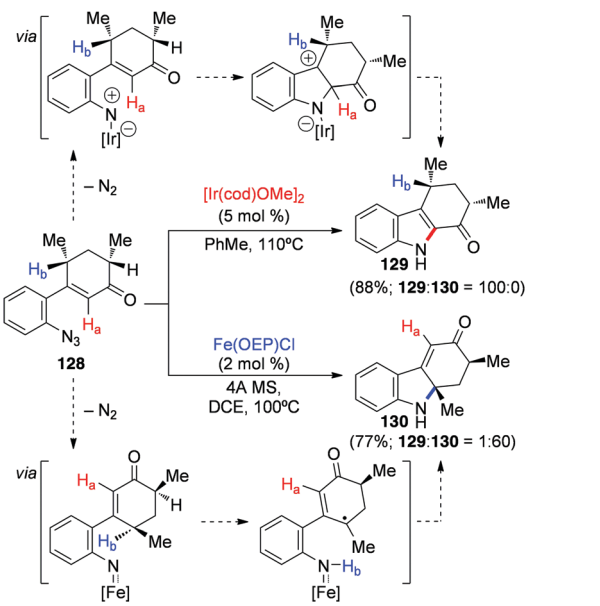
Ligand- and catalyst-controlled aminative sp^3 C–H insertions with metal nitrenoids

The high reactivity of nitrene intermediates can be tamed and controlled *via* the formation of nitrene metal complexes (metal nitrenoids). Depending on the electronic structure of the nitrene and the choice of metal and ligands, these intermediates will follow divergent reaction pathways (*e.g.* insertion into C=C π bond *vs.* insertion into C–H σ bonds) and reaction mechanisms (*e.g.* concerted electrophilic *vs.* rapid abstraction-rebound *vs.* longer-lived radical intermediates).[110] Control over these reaction pathways and mechanisms allows the design of catalytic divergent C–H amination reactions. The Du Bois group reported Rh(II)-catalyzed regioselective intramolecular aminations. In the presence of a $[Rh_2(OAc)_4]$ catalyst, the benzylic sp^3 C–H_a bond in **122** can be selectively aminated to give **123**, while a more sterically demanding catalyst such as $[Rh_2(O_2CCPh_3)_4]$ oxidatively functionalizes the ether C–H_b bond to produce **124** as a major product (Scheme 34a).[111] The sp^3 C–H insertion in such substrates is highly diastereoselective (>10:1) under $[Rh_2(OAc)_4]$ catalysis, but the diastereoselectivity is diminished with a $[Rh_2(O_2CCPh_3)_4]$ catalyst.[112] Ligand-controlled reaction outcomes in intramolecular C–H amination reactions have also been demonstrated for Ag(I) catalysts. The Schomaker group demonstrated that the choice of ligand can alter the reaction preference for tertiary sp^3 C–H bonds or activated benzylic, allylic and propargylic secondary sp^3 C–H bonds (Scheme 34b), by controlling the coordination geometry and steric environment about the Ag(I) center.[113] For instance, when sulfamate **125** is reacted with iodosobenzene in the presence of a Ag(I) catalyst coordinated with tris(2-pyridylmethyl)amine (tpa), C–H insertion occurs at the 2° benzylic position to provide **126** as the major isomer. By contrast, in the same reaction performed with 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as the ligand for sliver, the regioselectivity is reversed to predominantly give the 3° C–H insertion product **127** as the major isomer. The same group later identified 2,6-bis[1,1-bis(2-pyridyl)ethyl]pyridine (Py_5Me_2) as a ligand superior to tpa to favor nitrene insertion into activated 2° C–H bonds over 3° C–H bonds.[114] It is also worth mentioning that in the case of alkene substrates, the choice of the ligands within the coordination sphere of Ag results in a preference for either allylic C–H amination (sp^3 C–H insertions) or aziridination (C=C π-bond insertion) in both intramolecular and intermolecular reactions.[115]

In 2016, the Driver group reported a divergent synthesis of fused indoles derivatives from *ortho* styryl azides **128** that occurs through the intermediacy of metal nitrenoids (Scheme 35).[116] Upon reaction of **128** with an Ir(I) catalyst, the fused indole **129** that is formally the product of insertion of the nitrene into the sp^2 C–H_a bond is exclusively obtained in high yield. By contrast, when the same styryl azide **128** is reacted in the presence of an iron(III) octaethylporphyrin [Fe(OEP)Cl] catalyst, the selectivity is reversed in favor of a formal insertion of the nitrene into the allylic C–H_b bond, providing the 2*H*-indole **130** with high selectivity. When Rh(II) carboxylate catalysts are employed, variable mixtures of **129** and **130** are instead obtained. Mechanistic investigations have suggested that whereas **129** is obtained *via*



Scheme 34

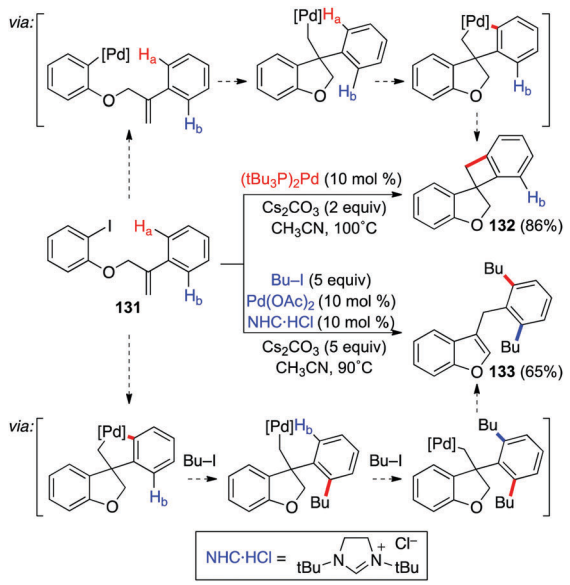


Scheme 35

a polar electrocyclic mechanism, **130** results from a hydrogen atom abstraction at the allylic position followed by radical recombination. These conclusions are further supported by the strong dependence of the regioselectivity of the metal nitrenoid formal C–H insertion on the ease of formation of the allylic radical intermediate.

Ligand-controlled Pd-catalyzed divergent alkylative cyclizations

Future advances in transition metal-catalyzed divergent C–H functionalization reactions need not be limited to the discrimination for one reactive C–H bond among many. More ambitious transformations will allow chemists to control more drastically divergent reaction pathways with an adjustment of catalysts, ligands, and reaction conditions. In an eloquent demonstration of this approach, Schoenebeck, Lautens, and co-workers demonstrated how Pd-mediated C–H alkylative cyclizations can be redirected to afford products with varied carbon skeletons (Scheme 36).[117] When aryl iodide **131** is reacted in presence of cesium carbonate base and a $(t\mathrm{Bu_3P})_2\mathrm{Pd}$ catalyst, oxidative addition is followed first by a cyclization *via* the carbopalladation of the alkene, then by an aryl C–H palladation to form a spiropalladacyclic intermediate, and finally by a sp^2–sp^3 C–C reductive elimination to afford **132**. The reaction pathway can be redirected by instead relying on a NHC-ligated Pd catalyst in the presence of an alkyl iodide to yield the *ortho*-alkylated 3-benzylbenzofuran **133**. Mechanistic and computational studies suggests that, under the latter condition, reductive elimination from the spiropalladacyclic intermediate is slow, allowing it to be intercepted by the alkyl iodide to achieve the *ortho*-alkylation of the aryl ring. Following the double *ortho*-alkylation, an interesting 1,2-migration is proposed *via* the β-aryl elimination of the sterically congested arene, followed by a re-insertion into the resulting exocyclic alkene. Finally, β-hydride elimination furnishes **133**.



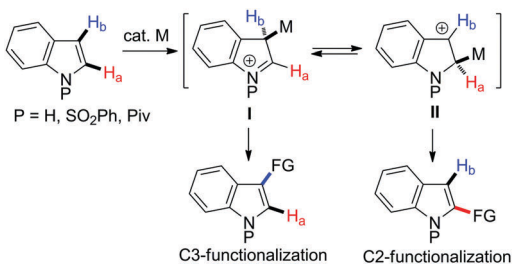
Scheme 36

7. Divergent catalytic C2–C7 indole and indoline C–H functionalizations

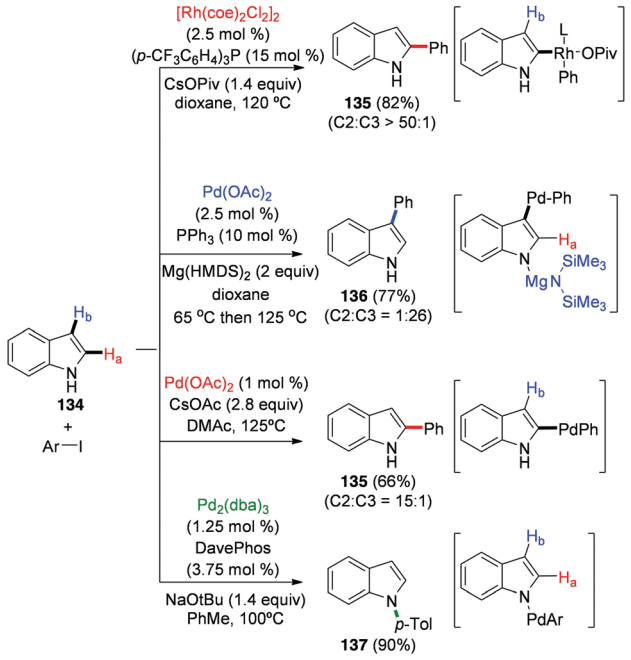
The ubiquity of the indole nucleus and of its C2–C3 saturated indoline congener in natural products and pharmaceuticals provides an impetus for the development of catalytic methods for their divergent C–H functionalization. Delivering a toolbox of reactions capable of generating substituted derivatives at any of the 2- to 7-positions thus constitutes a worthwhile goal. In this section, we present some examples of those efforts as a showcase for the different approaches to control regioselectivity that are discussed in the previous sections. The electron-rich indole nucleus is a particularly good π-nucleophile, with reactivity comparable to that of allyl stannanes, silyl enol ethers, or enamides.[118] Indoles react preferentially at the 3-position with traditional and organometallic electrophiles to result in electrophilic aromatic substitution products, which constitutes their innate reactivity pattern.[119] The appeal of C–H divergent functionalization of the indole nucleus is compounded by the lack of availability and/or affordability of halogenated indoles. Whereas 3-bromoindole is readily available by the direct electrophilic bromination of indole,[120] and 5-bromoindole *via* the electrophilic bromination of its bisulfite adduct,[121] other isomers must typically be obtained by a ring-synthesis of the indole nucleus starting from brominated arene precursors.[122,123] As a consequence, divergent C–H functionalization has become a highly attractive approach to selectively access substituted indoles.

Catalyst-controlled C2- and C3-arylation of indoles

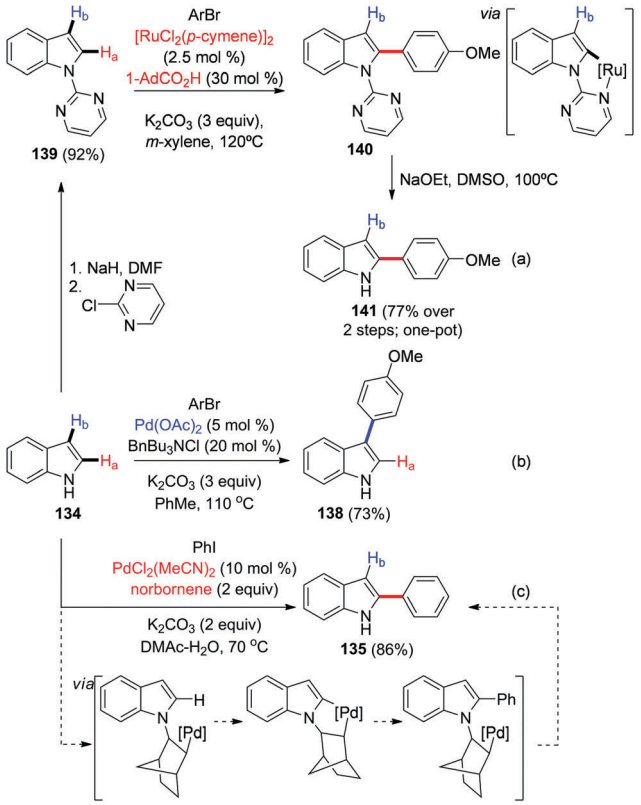
Several catalytic systems for the C–H arylation of indoles at the 2- or 3-positions have been developed.[124] A global mechanistic pathway has emerged in which an electrophilic transition metal catalyst π-coordinates the C2═C3 double bond.[125] Polarization of this bond by the adjacent nitrogen donor is postulated to facilitate, either kinetically or thermodynamically, an electrophilic metalation at the more nucleophilic 3-position. However, the C3-metalated intermediate **I** can, under certain reaction conditions, reversibly isomerize to the C2-metalated isomer **II** (Scheme 37). In several examples, a preference for C2 functionalization has been observed for Pd-catalysis, but regioselectivity is affected by the choice of a specific catalyst, ligands, and solvents. The following examples showcase the factors that influence the equilibrium to achieve divergent C–H functionalization from a common indole starting material.



Scheme 37



Scheme 38

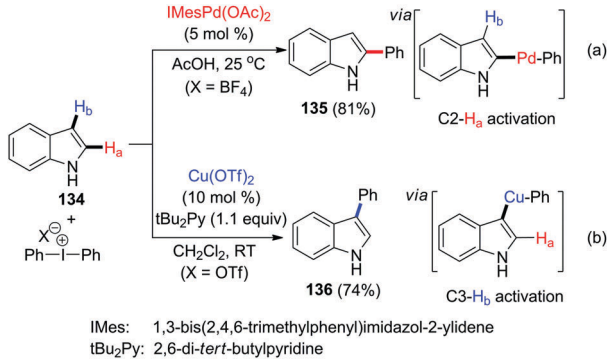


Scheme 39

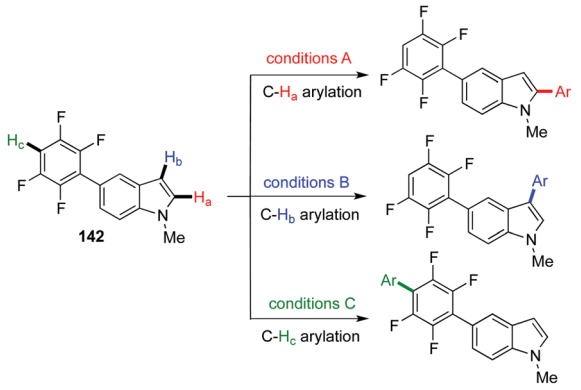
Sames and co-workers developed regioselective C2- and C3-arylation of NH-indoles **134** with iodobenzene in which selectivity is controlled by the choice of catalytic conditions (Scheme 38). Under Rh catalysis, the C2-metalated intermediate is assumed to be the most relevant intermediate since only the C2-phenylated indole **135** is obtained ($>50:1$).[126] By contrast the C3-phenylated **136** is formed predominantly (**135**/**136** = 1 : 26) under Pd catalysis with the sterically bulky $Mg(HMDS)_2$, under the postulated involvement of a C3-palladated indole as the key intermediate.[127] Pd catalysis appears especially capricious, as small changes in the reaction conditions revert to C2 phenylation.[128] Finally, it should be pointed out that the high regioselectivities obtained with either method are particularly notable in view of the reported Pd-catalyzed[129] (or Cu-catalyzed)[130] N1 arylation of **134** with iodoarenes to give **137** in the presence of stronger bases.

The C3-selective arylation of indole **134** with aryl bromides under Pd catalysis has also been reported (Scheme 39b) to give products such as **138**,[131] but C2 selectivity with aryl bromides is not as high as with aryl iodides. For example, under the Sames conditions (Scheme 38), the selectivity only reaches a 2 : 1 ratio of **135** to **136**.[128a] Metal coordinating *N*-substituents at the indole ring including acyls, carbamoyls, and pyridyls can affect the **I** ⇆ **II** equilibrium (Scheme 37) and act as DGs to favor C2 functionalization.[124] The *N*-pyrimidyl group is particularly useful in view of the ease of installation and cleavage, and the facile formation of cyclometalated intermediates.[132] The Ackermann group demonstrated in 2011 that under Ru catalysis and in the presence of a bulky carboxylic acid, *N*-pyrimidyl indole **139**, readily obtained from indole **134**, is selectively C–H arylated at the 2-position to give **140**. Subsequent deprotection of the *N*-pyrimidyl group can be carried out in a one-pot operation to afford the C2-arylated NH indole **141** (Scheme 39a).[133] Transient DGs have also been employed to direct the C–H functionalization of NH indoles at the 2-position. The Bach group showed that under Pd catalysis and in the presence of norbornene, the direct arylation of indole **134** with iodobenzene provides the C2-arylated product **135** (Scheme 39c).[134] Although the authors focused their mechanistic investigations on the C2-selective alkylation of indoles, the mechanism for the C2-selective arylation reaction under these conditions appears consistent with an initial aminopalladation of norbornene, which facilitates the formation of a cyclopalladated intermediate through C–H activation at the 2-position. Following the formation of the C2–Ar bond, β-elimination with extrusion of norbornene and subsequent protolysis provides **135.** Finally, arenediazonium salts have also been used as aryl halide surrogates in the Pd-catalyzed C2-selective arylation of indoles.[135]

The divergent electrophilic arylation of **134** with diaryliodonium salts is also achieved using either Pd or Cu catalysis. Sanford and co-workers developed a Pd-catalyzed C2-arylation of indoles that involves a Pd(II)/Pd(IV) cycle (Scheme 40a).[136] The C3 regiosiomer is obtained by Gaunt *et al.* by instead using a Cu(II) precatalyst in a transformation that (Scheme 40b), as observed in the *meta*-arylation of anilide (Scheme 15b),[47] involves a Cu(I)/Cu(III) catalytic cycle.[137,138] The most selective C3-arylation uses a diaryliodonium salt bearing a larger spectator 2,4,6-triisopropylphenyl (TRIP) group, [TRIP-I-Ar]OTf. Notably, *N*-methylindoles exhibit comparable regioselectivity in these transformations. Interestingly, a transition metal-free variant of



Scheme 40

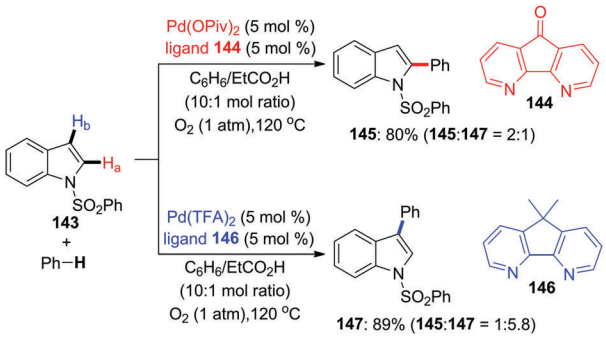


Conditions A: aryl iodide (2.0 equiv), $Pd(OAc)_2$ (5 mol %), 2-nitrobenzoic acid (1.5 equiv), Ag_2O (0.75 equiv) in DMF (0.5 M) at 45°C.

Conditions B: diaryliodonium triflate (1.3 equiv), $Cu(OTf)_2$ (10 mol %), 2,6-di-*tert*-butylpyridine (1.0 equiv) in DCM (0.1 M) at 50°C.

Conditions C: aryl bromide (1.0 equiv), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), PivOH (30 mol %), K_2CO_3 (2 equiv) in isopropyl acetate (1.0 M) at 80°C.

Scheme 41



Scheme 42

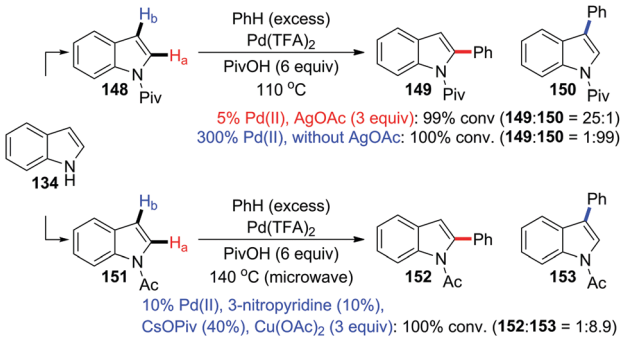
the C3-selective arylation with diaryliodonium salts has also been reported.[139] Although both Pd and Cu catalysts are thought to first metalate indole at the 3-position, a rapid C3-to-C2 migration is proposed in the case of Pd to account for the formation of 2-phenylindole. Here again, coordinating substituents at N1 can affect the regioselectivity of the reaction by shifting the **I** ⇆ **II** equilibrium (Scheme 37). In contrast to the C3-arylation of **134** with $[Ph_2I]OTf$ under Cu catalysis, *N*-acetylindole is selectively arylated at the 2-position (9 : 1 C2 : C3 at 60 °C) under comparable conditions. *N*-Arylation is not observed under the Gaunt protocol, although the Cu-catalyzed *N*-arylation of NH indoles with diaryliodonium salts has been reported.[140] Numerous other C2-selective arylations of indoles with organometallic reagents such as arylboron derivatives and arylsilanes have also been reported.[141]

Divergent sp^2 C–H functionalization of poly(hetero)arenes

The number of attainable regioisomers can be increased when other factors (*cf.* Section 4) are controlled to achieve functionalization at positions other than the indole 2- or 3-positions. To obtain the selective and predictable C–H bond functionalization of poly(hetero)aromatic compounds, the Fagnou group applied substrate-specific Pd-catalyzed orthogonal arylation protocols. For example, the tetrafluorophenylindole **142** is arylated under neutral to mildly basic conditions at the indole 2-position under Pd/RCOOH-catalysis and at the indole 3-position using Gaunt's Cu-catalysis.[137] Finally, under more basic conditions (K_2CO_3), deprotonation at the acidic tetrafluorophenyl C–H_c favors its selective arylation under Pd/phosphine catalysis (Scheme 41).[142] DFT-calculations of concerted metalation–deprotonation (CMD) pathways also accurately predict the relative reactivity of C–H bonds in electron-rich heteroarene substrates.

Pd-Catalyzed oxidative arylation of indoles

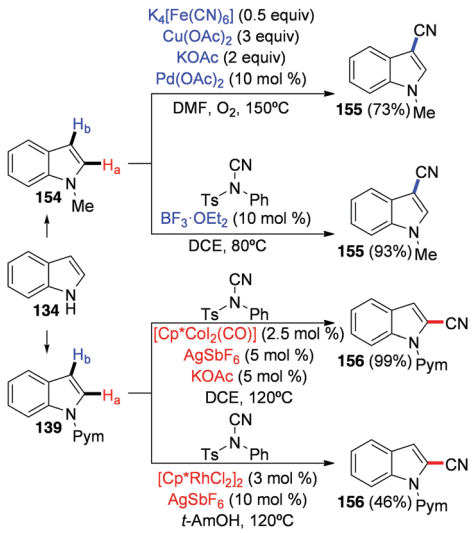
The Pd-catalyzed divergent arylation of *N*-acylated or sulfonylated indoles is observed simply by tuning the electronic properties of nearly geometrically identical ligands. Stahl *et al.* reported that C2- *versus* C3-selectivity in Pd-catalyzed oxidative coupling of *N*-sulfonyl indole **143** with benzene can be controlled by the electronics of a fused bipyridine ligand (Scheme 42).[143] When $Pd(OPiv)_2$ is used with the electron-poor diazafluorenone ligand **144**, the C2-phenylated indole **145** is formed as a major product with 2 : 1 regioselectivity. Conversely the use of a $Pd(TFA)_2$ precatalyst with the more electron-donating ligand **146** yields the C3-arylated indole **147** as the major product with a 1 : 5.8 ratio of **145** : **147**. The origins of this effect are yet to be elucidated, and may involve more than mere ligand electronics.[144] A related C2- or C3-selective oxidative phenylation of *N*-pivaloylated indole **148** has been previously reported by Fagnou *et al.* (Scheme 43).[145] In the presence of AgOAc as oxidant, the C2-phenylated indole **149** is formed as the major product with 25 : 1 regioselectivity, while C3-phenylated indole **150** is formed nearly exclusively in the absence of Ag(I), but with a 300 mol% loading of the Pd(II) precatalyst. To obtain a C3-phenylated indole in high yield and selectivity by this reaction without the need for such high loadings in Pd, it is necessary to replace the *N*-pivaloyl group in **148** by the *N*-acetyl substituent in **151**. The latter substrate can be oxidatively arylated with benzene in the presence of a Pd(II) precatalyst, pivalic acid, 3-nitropyridine, cesium pivalate and copper(II) acetate to afford a 1 : 8.9 mixture of **152** and **153**.[146,147]



Scheme 43

Catalyst-controlled C2- and C3-cyanation of indoles

Divergent C–H functionalization of indoles are far from being limited to arylation reactions. Both electrophilic and oxidative cyanation reactions have been employed to introduce a cyano group at either the 2- or 3-position of indoles. The choice of reagents, catalysts, and DGs installed at the 1-position controls the regioselectivity of the reaction (Scheme 44). In the presence of a Pd catalyst, a Cu(II) salt and molecular oxygen as the oxidizing agents, and potassium ferrocyanide as a source of cyanide anions, *N*-methylindole **154** is selectively transformed into the 3-cyanoindole **155**.[148] Electrophilic cyanations of the same substrate **154** with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid catalyst affords the same product **155** in good yields,[149] confirming the typical reactivity of indoles as C3 nucleophiles toward electrophilic reagents. Transition-metal catalysis redirects C3 cyanation with NCTS to the 2-position for indoles bearing coordinating substituents at the 1-position, such as with *N*-pyrimidylindole **139**. The laboratories of Ackermann and Glorius first independently reported that a Co catalyst carries out the directed C2-cyanation to afford 2-cyanoindole **156** as the sole regioisomer.[150] A related Rh catalytic system also affects this regioselective transformation.[151]



Scheme 44

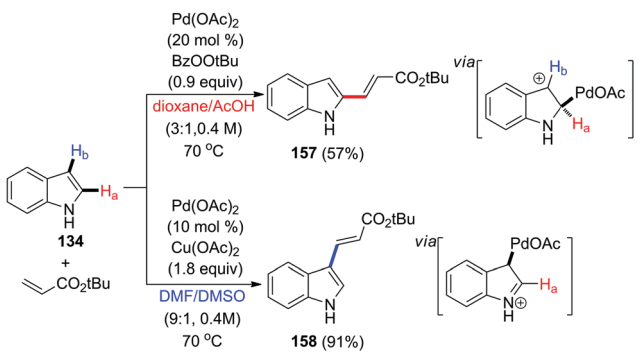
In the latter case, however, better yields are obtained for *N*-pyridylindoles than for *N*-pyrimidylindoles such as **139**.

Solvent-controlled Pd-catalyzed C2- and C3-alkenylation of indoles

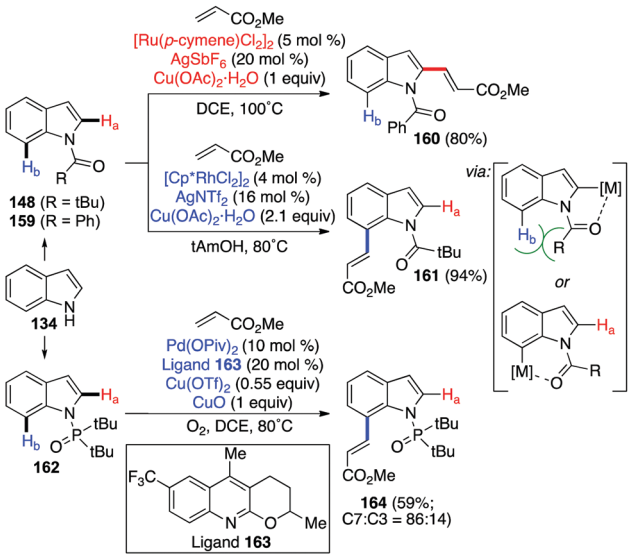
The Pd-catalyzed Fujiwara–Moritani-type (oxidative Heck) coupling of indoles devoid of coordinating substituents at N1 (*e.g.* NH-indole **134**) with acrylates has long been known to favor the formation of C3-alkenylated products because of the greater nucleophilicity of indoles at that position.[152] Nonetheless, several coordinating substituents at N1 redirect the regioselectivity of the transformation to favor the formation of C2-alkenylated indoles (*vide infra*).[153] However, in 2005 Gaunt *et al.* reported that the C2- and C3-regioselectivity of the Pd-catalyzed Fujiwara–Moritani-type (oxidative Heck) coupling of NH-indole **134** with acrylates can be controlled by the choice of a solvent system (Scheme 45).[154] In a carboxylic acid solvent, the C2-alkenylated product **157** is formed as the major product, while C3-alkenylated product **158** is formed nearly exclusively in strongly coordinating polar solvents. Gaunt *et al.* also reported that this Pd-catalyzed regioselective C2- and C3-oxidative alkenylation can also be extended to pyrroles having different *N*-protecting groups.[155]

Directed C2- and C7-alkenylation of indoles

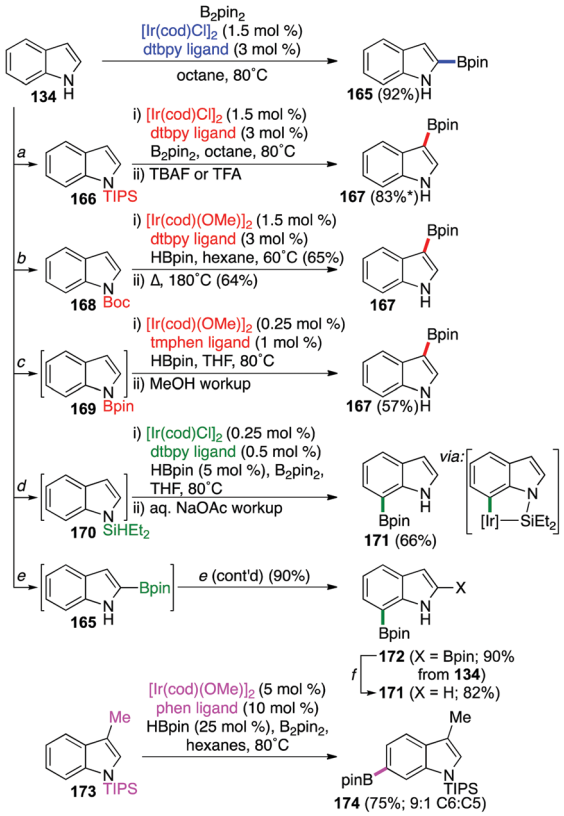
Beyond functionalization at the more commonly encountered 2- and 3-positions, the demand for synthetic methods to functionalize at will any position of the indole (or indoline) nucleus has spurred the development of transition metal-catalyzed C–H functionalization reactions at the less easily targeted 4- to 7-positions. The careful choice of a DG can favor reactivity at one of several possible reactive sites. Divergent protocols for the functionalization of indoles bearing a protecting group at the 1-position are among the most impressive in this regard.[156] As indicated above, the innate reactivity of indoles in oxidative Heck reactions favor alkenylation at the 3-position. The use of a coordinating group at the 1-position has been successful to redirect the regioselectivity of the alkenylation to the less nucleophilic 2-position.[153] The Prabhu group showed that acyl derivatives such as the *N*-benzoylindole **159** undergo selective C2 alkenylation with acrylate esters when treated with a Ru catalyst in the presence of silver and copper additives to provide **160** (Scheme 46).[157] However, with bulkier acyl groups such as the *N*-pivaloyl group



Scheme 45



Scheme 46



*Yield given for the borylation step only. (*a*) i) NaH; ii) TIPS-Cl; (*b*) Boc_2O, cat. DMAP; (*c*) HBpin, Et_3N; (*d*) Et_2SiH_2, $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol %), PhMe, RT; (*e*) HBpin, $[Ir(cod)(OMe)]_2$ (1 mol %), dtbpy (2 mol %), hexane, 60°C; (*f*) $Bi(OAc)_3$ (20 mol %); MeOH-THF, 80°C.

Scheme 47

of **148**, steric hindrance between the substituent at N1 and the C7 hydrogen disfavors metalation at C2. Instead, the acyl group flips over to favor metalation at C7. For instance, when **148** is treated with acrylate esters in the presence of a Rh catalyst and silver and copper additives, the C7-alkenylated derivative **161** is instead obtained.[158] The di-*tert*-butylphosphinyl group of **162**, introduced earlier as a directed metalating group in selective C7-lithiation of **162** with *n*-butyllithium,[159] can also direct the C7-selective oxidative alkenylation of indoles with acrylate esters in a Pd/ligand **163** catalytic system and in the presence of Cu(II) additives to give **164**.[160] The use of sterically hindered coordinating substituents at the 1-position of the indole nucleus to direct C–H functionalization the C7 has also been exploited in transformations beyond oxidative alkenylations, notably in Ir-catalyzed C7-sulfonamidations of **148** with sulfonyl azides.[161]

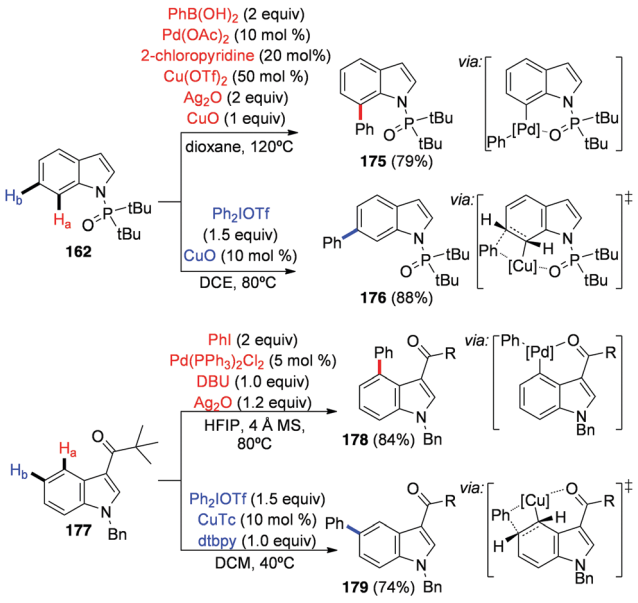
Divergent Ir-catalyzed C–H borylation of indoles

The Ir-catalyzed C–H borylation of arenes has been successfully exploited to achieve the divergent functionalization of indoles and other heterocycles.[1h,10] When the parent indole **134** is treated under the conditions developed by Miyaura, Ishiyama, Hartwig, and co-workers, borylation exclusively occurs at the 2-position to give the borylated indole **165** (Scheme 47).[162,163] Since the Ir-catalyzed borylation reaction is very sensitive to substrate sterics, the regioselectivity of the borylation reaction can be redirected to the away from C2 and towards the 3-position with the introduction of the bulky triisopropylsilyl (TIPS) protecting group at N1 in **166**.[164] Protodesilylation of the N1 protecting group then provided the C3-borylated indole **167**. The laboratories of Smith and Maleczka replicated the steric blocking of the more reactive 2- and 7-positions with the NBoc protecting group in **168**.[165] This second approach to C3-borylated indole **167** is advantageous in view of the lower cost of the Boc protecting group, and the ease of deprotection under neat thermolytic conditions. More recently, the same groups in collaboration with the Merck Research Laboratories reported that pinacolborane (HBpin) can be used not only as the borylation agent but also to install the NBpin protecting group at the 1-position to sterically block the 2- and 7-positions.[166] In this one-pot process, indole **134** is first treated with pinacolborane in the presence of triethylamine to afford indole **169**, which is then borylated with pinacolborane in the presence of an Ir catalyst and tetramethylphenanthroline (TMP) as the optimal ligand. Deprotection of the NBpin group occurs spontaneously upon a methanolic workup to provide the C3-borylated indole **167** in higher yield with this traceless protecting group than with the 2-step NBoc route. In 2010, the Hartwig group reported that a hydrosilane $SiEt_2H$ substituent, installed at the 1-position of indole **134** *via* a Ru-catalyzed dehydrogenative silylation reaction to result in **170**, acts as a DG to achieve regioselective borylation at C7.[167] The reaction is postulated to proceed through an insertion of the Ir catalyst into the Si–H bond of the silane group at N1 and the formation of an iridacyclic intermediate that directs the borylation reaction at C7. As for the NBpin group at N1, the N–Si bond of the resulting borylated **170** is readily hydrolysed upon aqueous workup and does not require an additional deprotection step to afford **171** as the ultimate product in satisfactory yields. Ir-Catalyzed borylation

of 2,3-disubstituted indoles occurs at the 7-position, as illustrated by the Gaunt group in their total synthesis of dictyodendrin B.[138] C7-Borylation also occurs for indoles bearing a sterically demanding group at C2, such as a Bpin substituent. Indeed, when indole **134** is borylated under the presence of an excess of the borylating agent (HBpin or B_2pin_2), the C2 borylated indole **165** further reacts selectively to afford the 2,7-diborylated indole **172** in excellent yields.[168,169] Following on earlier reports from the Movassaghi group, which exploit the greater sensitivity towards protodeborylation of the C2-Bpin group than the C7-Bpin group in 2,7-diborylated tryptophan and tryptamine derivatives,[170] Maligres, Smith, Maleczka, and co-workers optimized a $Bi(OAc)_3$ catalyzed protodeborylation of **172** at C2 that selectively affords the C7-borylated indole **171**.[171] No divergent protocols capable of achieving the selective borylation of **134** at the 4- to 6-positions have been reported. However, the Baran group identified Ir-catalyzed borylation conditions for 3-substituted indoles bearing the bulky TIPS group at N1, such as **173** and several tryptophan derivatives, that proceed with high selectivity for the 6-position over the equally sterically accessible 5-position.[172] For example, when indole **173** is reacted with B_2pin_2 in the presence of an Ir precatalyst, phenanthroline as the ligand and catalytic amounts of pinacolborane, the C6-borylated indole **174** is obtained in 75% yield with a 9 : 1 selectivity favoring the C6 isomer over the C5 isomer.

Directed C4-, C5-, C6- and C7-arylation of indoles

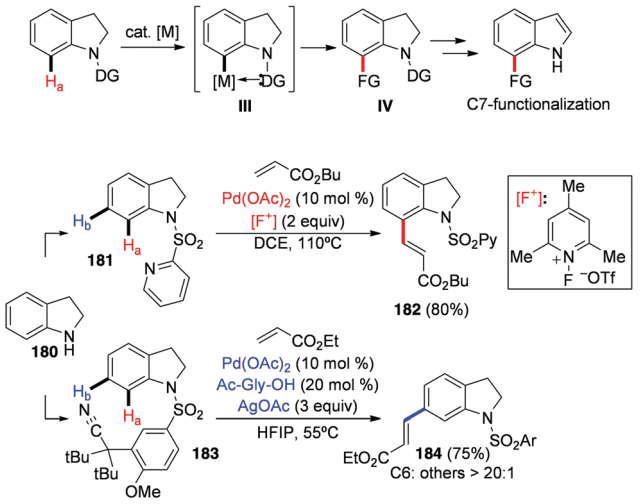
Regioselective C–H functionalization at the 6-position of indoles remains very rare.[173] In addition to the example above by the Baran group, a pair of regioselective reactions introduced by the Shi group can be exploited to affect the divergent arylation of indoles at either the 6- or the 7-position (Scheme 48, top).[160,174] When indole **162**, which for steric reasons orients its P=O bond toward the C7–H bond, is treated with phenylboronic acid in the presence of a Pd catalyst, 2-chloropyridine as a ligand, and Cu(II) and Ag(I) additives, the C7-phenylated indole **175** is isolated in good yield alongside only trace amounts ($\leq$4%) of the C3-phenylated isomer. The regioselectivity, as for the alkenylation of the same indole derivatives **162** (Scheme 46), is likely derived from a directed cyclopalladation at C7. By contrast, when indole **162** is reacted with the organometallic surrogate diphenyliodonium triflate in the presence of a Cu catalyst under conditions reminiscent of Gaunt's *meta*-selective arylation of anilides (Scheme 15),[47] the C6-phenylated indole **176** is instead obtained. Redirection of the regioselectivity is a consequence of the carbocupration pathway of the latter transformation, which when guided by the phosphinyl group at N1 results in an intermediate with the arene substituent at C6 and Cu at C7 prior to rearomatization.[48] The same approach was extended to the selective C4- or C5-arylation of indoles bearing a directing pivaloyl group at the 3-position (Scheme 48, bottom).[175] When *N*-benzylated 3-pivaolylindole **177** is treated in HFIP with iodobenzene in the presence of a Pd catalyst, DBU as base, and a Ag(I) additive, the C4-arylated indole **178** is obtained in 84% yield. By contrast, when the same pivaloylindole **177** is reacted in dichloromethane with diphenyliodonium triflate in the presence of a Cu catalyst, the regioselectivity is switched to provide the 5-arylated product **179**. In both cases, protolytic cleavage of the pivaloyl group was demonstrated with *p*-toluenesulfonic acid to reveal the parent 4- or 5-arylated *N*-benzylindole in excellent yields.



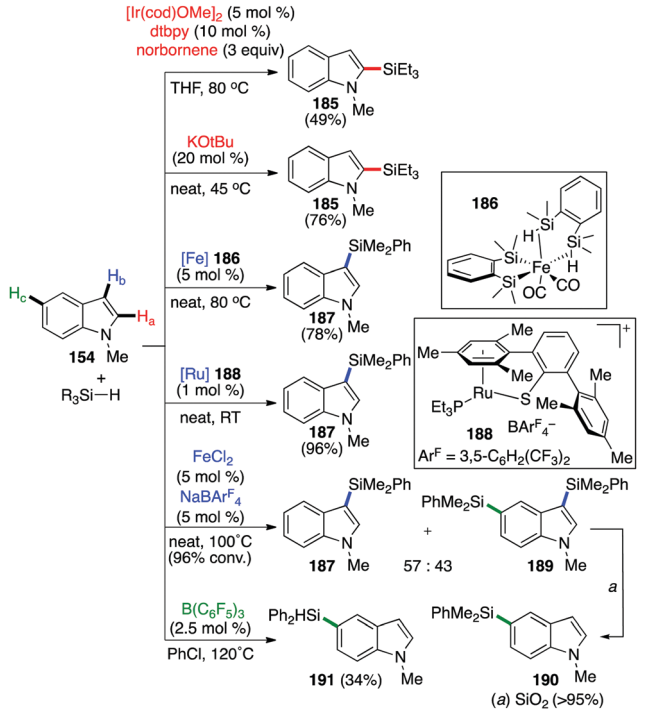
Scheme 48

Directed C6- and C7-alkenylation of indolines

The paucity of reliable C–H functionalization methods for the 6- or 7-positions of the indole nucleus, until recently (*e.g.* Scheme 48), provides the impetus for the development of alternate approaches. Indolines such as **180**, which lack the more reactive C2=C3 π-bond of indoles **134**, offer a practical solution in this regard. Their innate π-nucleophilicity in electrophilic aromatic substitution reactions favor functionalization at the 5-position, and DGs installed at N1 can favor cyclometalation at C7 to provide intermediates such as **III** on the way to 7-substituted indolines **IV**. If desired, cleavage of the DG and oxidative rearomatization, which can be affected by reagents such as DDQ or MnO_2, provide an indirect route to C7-functionalized indoles (Scheme 49, top). For instance, when *N*-(2-pyridyl)sulfonyl indoline **181** is reacted with acrylate esters in the presence of a Pd catalyst and a *N*-fluoropyridinium salt as the oxidizing agent, the C7-oxidative alkenylation product **182** is selectively obtained, presumably through the intermediacy of a complex such as **III** (Scheme 49, middle).[176] The electron-withdrawing sulfonyl group, which can be reductively cleaved with Zn/NH_4Cl, likely also limits undesired electrophilic C–H metalation and/or functionalization at the 5-position. Moreover, oxidative rearomatization to the C7-functionalized indole was demonstrated with DDQ. The same approach has been successfully applied with a variety of DGs at N1 in selective C–H alkenylation, arylation, alkylation, alkynylation, acylation, amination, amidation, and cyanation of indolines at the 7-position.[177] By employing a U-shaped *N*-arylsulfonate bearing a nitrile ligand, the laboratories of Movassaghi and Yu redirected the C–H alkenylation of



Scheme 49



Scheme 50

indolines to the more remote 6-position (Scheme 49, bottom).[178] Hence, when indoline **183** is treated with acrylate esters in the presence of a Pd catalyst, an *N*-acylamino acid ligand, and silver(I) acetate in HFIP solvent, the C6-alkenylated indoline **184** is obtained with high selectivity. The role of the sulfonyl-linked nitrile ligand appears to be similar to that found previously in *meta*-selective directed C–H functionalization, bringing the Pd center in closer proximity to the C–H bond at the 6-position (Scheme 11). Deprotection of the sulfonyl group can be achieved under reductive conditions with Mg/MeOH, although under these conditions the α,β-unsaturated esters are also hydrogenated. Deprotection is also achieved with aqueous base with concurrent saponification of the ester group. Selective C–H arylation and acetoxylation at C6 was also demonstrated for indolines related to **183**.[178,179]

Divergent C–H silylation of indoles

The properties and reactivity of the C–Si bond often parallel that of the C–B bond. The Hiyama cross-coupling, although less frequently encountered than its boron counterpart, can generally provide the same products as the Suzuki–Miyaura cross-coupling, and silane reagents share similar shelf stability with organoboron reagents. Moreover, the C–Si bonds are readily oxidized to the corresponding alcohols (Tamao–Fleming), halogenated under electrophilic conditions, and participate in other transition metal-catalyzed reactions ranging from conjugate additions to aminations. Consequently, significant research efforts have been aimed at the development of catalytic C–H silylation reactions with hydrosilanes or disilanes that parallel the success of C–H borylation reactions with boranes or diboron reagents.[180] These efforts have resulted in a synthetic toolbox that allows for the divergent C–H silylation of indoles at the 2-, 3- or 5-position (Scheme 50), in addition to NH silylation at the unprotected 1-position.[167,181] The Falck group reported in 2008 that indoles such as **134** or **154** are selectively silylated at the 2-position with hydrosilanes in the presence of a Ir/dtbpy catalytic system similar to that employed in the Ir-catalyzed borylation of indoles (Scheme 47), but that the use of THF solvent and norbornene is required to achieve satisfactory yields.[182] The latter alkene is believed to act as the stoichiometric dihydrogen acceptor in this transformation, and the indole nitrogen directs the regioselectivity. In this regard, *N*-methylindole **154** is not as efficiently silylated as the parent indole **134**, and the steric hindrance of *N*-tosylindole redirects the silylation to the 3-position. Similar results were reported for the Rh- and Ir-catalyzed silylation of NH indoles at the 2-position with hydrosilanes,[183] and at the 3-position for the Ir-catalyzed silylation of *N*-(triisopropylsilyl)-indole **166** with fluorodisilanes.[184] Interestingly, Stoltz, Grubbs, and co-workers later established that transition metal catalysts are not required for the C2 silylation of 1-substituted indoles with hydrosilanes. High yields and regioselectivity greater than 20 : 1 can be achieved in the mere presence of abundant and inexpensive potassium *tert*-butoxide as the catalyst.[185] Under neat conditions and with a 20 mol% loading of the base, the silylation of *N*-methylindole **154** can be achieved on a 100 g scale to afford **185** in 76% yield after simple filtration and distillation. The lack of product formation in control experiments with radical traps suggests that a radical mechanism may be operative in this C–H functionalization. Unlike group 9 catalysts, silylation of *N*-methylindole **154** with group 8 catalysts results in selective functionalization at the 3-position. For instance, reaction of **154** with dimethylphenylsilane in the presence of a catalytic amount of the Fe complex **186** under neat conditions gives the 3-silylindole **187**.[186] Silylation of **154** at the 3-position was also demonstrated by Ito and Nishiyama with a phebox iron dicarbonyl complex as the catalyst.[187] The Ru complex **188**, introduced by Oestreich, Ohki, Tatsumi, and co-workers, is a more active group 8 catalyst for the conversion of **154** into **187**.[188]

Under optimized conditions, full conversion to **187** is achieved with only 1 mol% loading of **188** within 20 minutes at room temperature, with perfect selectivity (>99 : 1 C3 : C2) and no solvent nor stoichiometric dihydrogen acceptor being required. The authors have put forward a catalytic cycle where a cooperative metal–ligand heterolytic oxidative addition of the hydrosilane across the Ru–S bond result in a Ru hydride and a R_3Si^+ cation that is loosely bound to the sulfur atom. The π-nucleophilic indole then attacks this silyl cation in an electrophilic aromatic substitution step, which provides a rationale for the excellent selectivity for the 3-position. Rearomatization releases a proton, which bonds to the basic sulfur atom. The catalytic cycle is completed by reductive elimination of H_2 across the HRu–SH bond to regenerate **188**. A more air-stable, albeit less reactive variant of the complex **188** bearing a NHC ligand in place of PEt_3 was later introduced.[189,190] The Oestreich group later reported in 2016 a much simpler protocol for the electrophilic Friedel–Crafts type silylation of electron rich arenes including indole **154** with hydrosilanes.[191,192] Under this new protocol, simple heating of the neat substrate and hydrosilane in the presence of catalytic amounts of $FeCl_2$ and $NaBAr^F{}_4$ is sufficient to achieve full conversion, bypassing the need for the synthesis of more sophisticated catalysts such as **186** or **188**. Silylation of indole **154** occurs at the 3-position, as expected for an aromatic electrophilic substitution mechanism, but also at the 5-position. The latter appears to be the result of a reversible hydrogenation of the C2=C3 bond of **154** and/or **187** under the reaction conditions. The resulting indolines are activated for S_EAr at the 5-position, which provides a rationale for the formation of **189**. Interestingly, protodesilylation at C3 occurs readily upon workup on silica gel, providing access to the C5-silylated isomer **190**. Access to the C5-silylated indole has also been reported by the Hou laboratory, which disclosed that **154** is regioselectively with Ph_2SiH_2 in the presence of a catalytic amount of the Lewis acid $B(C_6F_5)_3$ to give **191**.[193,194] The presence of the Si–H bond in **191** can facilitate subsequent transformations to silyl ethers and silanols that are more reactive in Hiyama cross-couplings than aryltrialkylsilanes. Most recently, Oestreich and co-workers demonstrated that the Friedel–Crafts-type silylation of **154** with hydrosilanes is also feasible to afford 3-silylated indoles such as **187** in the presence of a catalytic amount of the Brønsted acid $[H(OEt_2)_2]^+[BAr^F{}_4]^-$, whose role is to generate the silicon electrophile by protonation of the hydrosilane.[195]

8. Conclusions

As showcased for the indole nucleus in the previous section, recent advances in transition metal-catalyzed C–H bond functionalization have greatly impacted synthetic strategies, and a number of competing approaches for the control of the regioselectivity of those reactions have emerged. The synthetic practitioner can now use these methods to reliably access multiple regioisomers of a product more directly, rapidly, and efficiently than would have been thought possible a decade ago. In particular, the controlled selective activation of a single C–H bond among the multitude found in a substrate is not only of practical importance to obtain high yields and clean reaction profiles, but it also opens paths for divergent catalysis providing different products from a common starting material.

Notwithstanding the advances described in this review, ideal divergent C–H functionalization schemes where a single set of starting materials is selectively converted into regioisomeric products simply by changing the catalysts, ligands, additives, solvents, or reaction conditions remain quite rare. Often, additional steps may be required to install and later remove suitable DGs, or to convert intermediates into a desired set of regioisomeric products *via* protection/deprotection steps. Perfecting ideal divergent catalytic C–H functionalization methods that are both economical and practical in synthesis, and extending them to a broader realm of C–H substrates will be the objectives of researchers in this field for years to come. In particular, the development of catalytic divergent sp^3 C–H functionalization reactions is still far less mature than that of sp^2 C–H functionalization reactions. Finally, the expanding body of knowledge will soon allow the chemists to develop divergent C–H bond functionalization reactions that go far beyond the synthesis of regioisomers, and selectively provide a skeletally diversified array of products from the same readily available starting materials.

Acknowledgements

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