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The Road Less Traveled: Unconventional Site Selectivity in Palladium-Catalyzed Cross-Couplings of Dihalogenated *N*-Heteroarenes

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Abstract

The vast majority (≥90%) of literature reports agree on the regiochemical outcomes of Pd-catalyzed cross-coupling reactions for most classes of dihalogenated *N*-heteroarenes. Despite a well-established mechanistic rationale for typical selectivity, several examples reveal that changes to the catalyst can switch site selectivity, leading to the unconventional product. In this Perspective, we survey these unusual cases in which divergent selectivity is controlled by ligands or catalyst speciation. In some cases, the mechanistic origin of inverted selectivity has been established, but in others the mechanism remains unknown. This Perspective concludes with a discussion of remaining challenges and opportunities for the field of site-selective cross-coupling. These include developing a better understanding of oxidative addition mechanisms, understanding the role of catalyst speciation on selectivity, establishing an explanation for the influence of ring substituents on regiochemical outcome, inverting selectivity for some “stubborn” classes of substrates, and minimizing unwanted over-reaction of di- and polyhalogenated substrates.

Graphical Abstract

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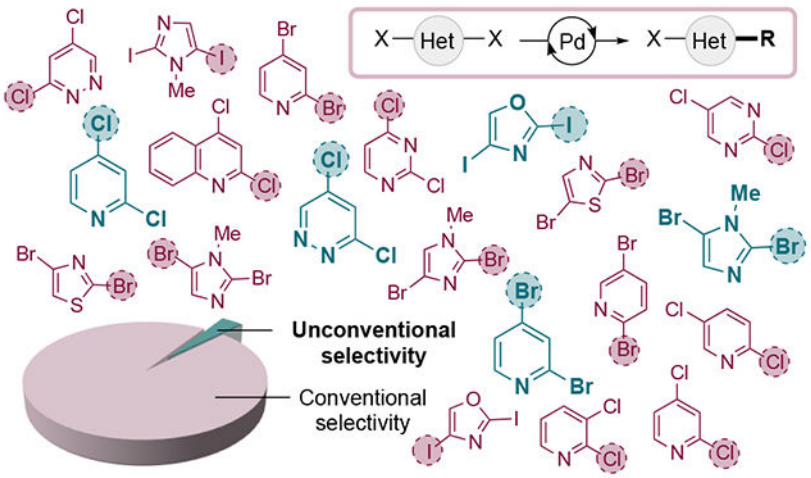
Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.



Keywords

cross-coupling; site selectivity; oxidative addition; heterocycles; mechanism

INTRODUCTION

Overview.

The challenge of regiocontrol is central to functionalizing heteroarenes, particularly in the context of ring substitution reactions including C—H functionalization, electrophilic aromatic substitution, nucleophilic aromatic substitution (S_NAr), and—relevant to this Perspective—cross-coupling. For heteroaromatic substrates bearing two or more halides, Pd-catalyzed cross-coupling reactions tend to proceed selectively, with a bias for reaction at sites adjacent to a heteroatom (Table 1).[1] This reactivity bias often enables straightforward synthesis of a single regioisomer. However, accessing target molecules with substitution patterns that are disfavored by cross-coupling is more challenging. A substrate-controlled approach to achieving unusual substitution patterns involves the use of substrates bearing mixed (nonidentical) halides. In this scenario, cross-coupling often takes place at the heavier halide even when there is a lighter halide at a privileged position α to a heteroatom. However, greater synthetic effort is required to prepare heteroarenes with mixed dihalides compared to identical dihalides, which translates into increased cost. Alternatively, unconventional site selectivity can be achieved through the use of catalyst-controlled approaches. Although the topic of catalyst-controlled site selectivity[2] is at the forefront of other research areas, such as C—H functionalization,[3] relatively little is known about the relationship between catalyst structure and cross-coupling site selectivity.[4] This Perspective surveys the handful of known examples in which unconventional or divergent site selectivity is achieved by changing the catalyst structure (e.g., through changing the ligand). In some cases, the mechanistic basis for the switch in selectivity is known, although others remain unexplained. Developing a better understanding of these reactions could lead to improved versatility of cross-coupling chemistry.

For the purposes of this Perspective, we define ‘conventional’ (or ‘typical’) selectivity as the regiochemical outcome that is reported in the large majority of literature examples for a given substrate class, to date. However, it has recently become clear that ligand choice, among other factors, can significantly affect selectivity (*vide infra*). As such, our perception of what is ‘typical’ is heavily influenced by a historical bias toward the use of certain ligands, especially PPh_3 and the related bisphosphine dppf (Table 1). As methods for achieving divergent selectivity become better established, the line between conventional and unconventional regioselectivity may eventually blur.

Multiple excellent reviews already provide a comprehensive picture of conventional selectivity.[1] The focus of this Perspective is the minority of cases in which the regiochemical outcome deviates from the norm, some of which are more recent than existing reviews. These deviations are rare. A SciFinder search suggests that, for many substrate classes, only 1-8% of cross-coupling reactions provide atypical selectivity (Table 1).[5] Furthermore, in many of these reports, the putative exceptional selectivity is not discussed nor is it supported by structural characterization. In other cases, the exceptions catalogued by SciFinder may reflect minor rather than major products. As such, the number of actual exceptions to conventional selectivity is likely lower than shown in Table 1. In this Perspective, we largely limit our discussion to *unsubstituted* dihaloheteroarenes. Substituents can lead to directing effects (see Outlook section), [6,7,8] but here we focus on cases in which unconventional site selectivity is achieved through changes to the catalyst rather than changes to the substrate.

Origin of Conventional Site-Selectivity.

In the vast majority of reports, a C—X bond α to a heteroatom, if present, is favored to undergo cross-coupling. Handy correlated conventional selectivity with positional electrophilicity as inferred from the ^{1}H NMR spectrum of the parent heteroarene.[9] The most deshielded proton of the parent heteroarene (α to one or more heteroatoms) usually corresponds to the most reactive site of the analogous halogenated substrate. The correlation is not perfect, however. For example, the most reactive site of 2,4-dichloropyrimidine (**9**) is C4, but the most deshielded proton of pyrimidine is attached to C2.[10] Through a series of computational studies, Houk and Merlic later showed that selectivity is often inversely correlated with C—X bond dissociation energy (BDE); that is, the most reactive C—X bond is usually the weakest one (distortion-controlled selectivity).[11] For example, the C4—X bond of **9** is weaker than C2—X (Figure 1). However, exceptions to the bond strength trend were noted when (1) the weaker C—X bond is on a carbocycle (**16**); (2) the two C—X bonds have identical or very similar BDEs (**17**); and (3) on a substituted ring in which the two halides are α to two different heteroatoms (**18**). In these cases, selectivity was better explained by a stronger attractive interaction between Pd and the more reactive site of the substrate (interaction-controlled selectivity). This attractive interaction is influenced by frontier molecular orbital distribution. For example, Houk’s DFT calculations indicate a stronger interaction between Pd and C2 of **16**, which can be explained by the much larger LUMO coefficient at C2 compared to C5.

Recent work by Leitch et al. contributes to a more complete picture of conventional selectivity.[12] Based on experimental results using $Pd(PCy_3)_2$, Leitch developed a model to

predict substrate reactivity toward oxidative addition based on several molecular descriptors. This model revealed that C—X bond strength, on its own, is a poor predictor of the rate of oxidative addition. Instead, the electrostatic potential (ESP) at the *ipso* carbon was determined to be the most important descriptor in this model, followed by the ESP at the more negative *ortho* atom. The model was demonstrated to accurately predict conventional selectivity for a wide range of dihalogenated heterocycles.

Despite the importance of Houk's and Leitch's work, these models do not directly suggest an explanation for the reported *exceptions* to conventional selectivity, wherein changes to reaction conditions lead to the atypical product. However, for Houk's distortion/interaction model, transition structures were optimized in the gas phase with a simple Pd-bisphosphine model $Pd(PH_3)_2$.[11a] For Leitch's molecular descriptor model, parameterization was based on results using $Pd(PCy_3)_2$ in a single solvent (THF).[12] It is known that the calculated mechanism for oxidative addition can change with palladium's coordination number, with ligand identity, and with the use of solvation models.[13,14,15] Thus it is reasonable to conclude that, in the exceptional situations where unconventional selectivity is observed, the transition states for C—X cleavage look significantly different from those that were the basis for Houk's and Leitch's models.

LIGAND-CONTROLLED SELECTIVITY

6-Membered Heterocycles.

Six-membered nitrogen heterocycles (azines) are ubiquitous in metabolites,[16] therapeutics,[17] agrochemicals,[18] and functional materials.[19] From metalation and S_NAr to catalytic C—H functionalization by transition metals, regioselective elaborations of 6-membered nitrogen-containing heteroarenes have been the subject of extensive investigation. In discovery chemistry settings, dihalogenated azines are among the mainstay building blocks for the construction of di- or polysubstituted nitrogen heterocycles via iterative cross-coupling or other substitution methods.[1]

In the context of cross-coupling, the regioselectivity outcomes with dihalogenated 6-membered *N*-heteroarenes—especially dihalopyridine derivatives—are now the most studied and best understood. As discussed above, for dihalogenated pyridines, pyridazines, and quinolines, halides α to nitrogen are conventionally more reactive than distal halides. Because of the polarity of the C—N bond of pyridine, C2 has more positive charge than the more distal carbons, making it more reactive toward Pd(0). Furthermore, α C—X bonds are weaker than other C—X bonds due to nitrogen's lone pair, which is in the same plane as C—X.

However, a few recent reports describe deviations from the conventional reactivity patterns when using sterically hindered ligands. In 2013, Dai, Chen, and coworkers demonstrated the first clear example of ligand-controlled inversion of site-selectivity.[20] Although dppf, a popular bidentate phosphine ligand, exclusively promotes coupling of 3,5-dichloropyridazine at the expected C3-site, the bulky monophosphine QPhos promotes reaction at the unconventional C5-site (C5:C3 = 20:1, Scheme 1, top). Under the optimized conditions, a broad scope of aryl, alkenyl, and heteroaryl boron nucleophiles were

selectively coupled at C5 of 3,5-dichloropyridazines. Additionally, QPhos was shown to mediate unconventional C4-arylation of 2,4-dichloropyridine, albeit with modest selectivity and yield (Scheme 1, bottom). Although a rationale for the unusual behavior of QPhos was not discussed at the time, the structural differences between QPhos and dppf provide a hint that palladium's ligation state could be a deciding factor in the regiochemical outcome. Hartwig had previously established that, in the presence of QPhos, Pd is monoligated during oxidative addition of chloro- and bromoarenes,[21,22] whereas Pd would almost certainly be bisligated when supported by the diphosphine dppf. Interestingly, RuPhos (2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl) was noted to promote diarylation of 3,5-dichloropyridazine despite a 1:1 ratio of the coupling partners.

Recently, hindered *N*-heterocyclic carbene (NHC) ligands have emerged as ligands that promote Pd-catalyzed cross-coupling at a distal site of dihaloazines. In 2019, Willans, Hardie, et al. reported that cyclotriveratrylene-tethered trinuclear Pd(II)-NHC complexes mediate Suzuki coupling at the 4-position of 2,4-dibromopyridine (**2**, C4:C2 = 6.5-10.7 : 1, Scheme 2), albeit with significant overarylation (**2c**).[23] Additionally, these ligands promote a greater proportion of C5-arylation at 2,5-dibromopyridine (**3**, C5:C2 = 1 : 1.3-1.6) compared to PPh_3 (C5:C2 = 1 : 14). The origin of selectivity was not determined in this report, although the authors suggested that it is unlikely to result from cooperative multinuclear catalysis.

In 2020, Yang et al. reported a C4-selective Suzuki-Miyaura coupling of 2,4-dichloropyridine (**1**) under Pd-catalyzed conditions in the presence of the hindered NHC ligand IPr.[24] Throughout most of the authors' optimization efforts (Scheme 3), Pd-PEPPSI-IPr was found to afford the C4-arylated product **1b** with site-selectivity ranging from 2.5:1 to 10.4:1, depending on reaction solvent and base. Notably, the hindered ligands P^tBu_3 and $PAd_2(n\text{-Bu})$ effected modest selectivity for the C4-site in a dioxane/H_2O mixture. In this solvent system, RuPhos and IPr gave the largest proportion of unwanted diarylated product, although switching to PEG400 decreased diarylation with IPr. Remarkably, a drastic improvement in C4-selectivity (to ~99:1) was observed upon changing the reaction conditions to include KI and NaOAc (not shown in Scheme 3). However, it was recently found through ligand-free control reactions that selectivity under these latter conditions does not require IPr; as such, these results are discussed in the Speciation-Controlled Selectivity section below.

Recently, we further explored the role of ligand sterics on the site-selectivity of Suzuki couplings of 2,4-dichloropyridine derivatives.[15,25] In agreement with earlier reports, a systematic analysis of ligand trends revealed a clear correlation between increased steric congestion around the metal center and increased selectivity for the distal C—Cl site (Scheme 4A). The highest selectivity for reaction at the distal position was achieved with bulky NHC ligands. However, there is a trade-off that accompanies NHC ligand size: the proportion of diarylated product increases concurrently with the C4:C2 ratio of monoarylated products. This unwanted reactivity is especially notable with the ligand IPent. As such, IPr offers the best compromise between high C4:C2 selectivity and low diarylation:monoarylation, thus maximizing the yield of the C4-monoarylated product. Under our optimized room-temperature conditions, no reaction is observed in the absence of

IPr. A detailed scope investigation showed that Pd catalysis with IPr is general to Suzuki, Kumada, and Negishi cross-coupling at the distal site of diverse 2,4-dichloropyridines and -quinolines as well as 3,5-dichloropyridazines (Scheme 4B). This methodology allows installation of diverse sp^2 and sp^3-carbon substituents at a distal site while retaining a chloride α to nitrogen.

Taken together, the reports described so far in this section demonstrate an unmistakable relationship between ligand sterics and unconventional site-selectivity for 2,4-dihalopyridines and pyridazines. We recently proposed that this correlation can be explained by the tendency of larger ligands to promote low-coordinate (i.e., 12 e^-) PdL during the selectivity-determining oxidative addition step.[15] Less hindered ligands, especially those that are better π-acceptors, favor 14 e^- PdL_2 during the oxidative addition step. DFT calculations with a model system comprising PhCl and $Pd(PMe_3)_n$ (n = 1 or 2) suggest that 12 e^- and 14 e^- palladium may be biased toward different mechanisms for oxidative addition (Figure 2, top). Monoligated $Pd(PMe_3)$ prefers to react through a classic, 3-centered concerted mechanism in which Pd interacts with both chloride and the *ipso* carbon of the substrate. In contrast, bisligated $Pd(PMe_3)_2$ prefers a displacement-type mechanism in which Pd interacts with both the *ipso* and the *ortho* carbons, but does not interact directly with chloride. A displacement-type mechanism for oxidative addition has been proposed in several previous instances, and is also referred to as an S_NAr-like mechanism[14,26] or a dissociative process.[13] Our analysis of frontier molecular orbitals suggests that the distinct mechanisms arise from differences in orbital symmetries when comparing the HOMOs of mono- vs. bis-ligated Pd. PdL has a σ-type HOMO, whereas the HOMO of PdL_2 has π-type symmetry once it is bent into the geometry required for forming the pre-oxidative addition π complex with the substrate (Figure 2, bottom). The HOMO σ-symmetry of PdL enables palladium to donate into a single ring atom of PhCl (a single lobe of the substrate's LUMO), consistent with the 3-centered concerted mechanism. On the other hand, the HOMO π-symmetry of PdL_2 enables palladium to donate into two ring atoms, consistent with the displacement mechanism.

For the substrate 2,4-dichloropyridine (**1**), the percent contribution to the LUMO is substantially greater at the C4 site (26% vs 8%, Figure 3A), which predicts more favorable orbital overlap between Pd and substrate at this site if Pd can only interact with a single ring atom, as is the case for monoligated PdL (e.g., L = IPr). Indeed, Pd/IPr-catalyzed cross-couplings of other dihaloheteroarenes also reveal a correlation between selectivity for a distal site and a relatively larger LUMO coefficient at that site (Figure 3B). In contrast to PdL, because PdL_2 can interact with two ring atoms, the LUMO coefficient at individual carbon atoms is less important. Instead, conventional selectivity for oxidative addition of the C2—Cl bond at PdL_2 is determined by other factors such as C—Cl bond strength and the polarity of the C2—N bond.

Consistent with this reasoning, calculated transition structures for the reaction of 12 e^- Pd(IPr) with 2,4-dichloropyridine suggest that the lowest energy pathway for reaction at either C2 or C4 involves a 3-centered concerted transition state (Figure 4, top). Reaction at C4 is predicted to be favored by 1.7 kcal/mol, which shows good agreement with experiment. In contrast, oxidative addition involving bisligated Pd(IPr)(**1**) is predicted to

proceed through a displacement-type mechanism at either site, with reaction at C2 favored by this mechanism. However, the structures involving Pd(IPr)(**1**) are markedly higher in energy than those involving Pd(IPr), and thus unlikely to be experimentally relevant. Similar observations are made with Pd(P^tBu_3) and Pd(P^tBu_3)(**1**), although Pd(P^tBu_3) is less C4-selective than Pd(IPr), likely due to the weaker σ-donicity of phosphines compared to NHC ligands (Figure 4, middle). On the other hand, parallel calculations using the less hindered ligand IMes predict that a displacement mechanism for reaction at C2 via Pd(IMes)(**1**) is energetically competitive with the concerted mechanism for reaction at C4 via monoligated Pd(IMes) (Figure 4, bottom). This prediction is consistent with the poor selectivity observed experimentally with IMes, and with the observation that selectivity skews toward the C2-coupled product when the Pd/IMes-catalyzed reactions employ higher concentrations of **1**.[15]

In summary, it appears that the ligand-controlled examples of unconventional site-selectivity in cross-couplings of dihalogenated azines can largely be explained by the ability of bulky ligands to promote 12 e^- Pd. Although more traditional 14 e^- Pd prefers to react α to nitrogen via a displacement mechanism involving a Pd•••N interaction, 12 e^- Pd cannot benefit from this interaction because its HOMO symmetry precludes such a mechanism. Instead, 12 e^- Pd reacts through a concerted mechanism at the site with a significantly larger LUMO coefficient, which can be a site distal to nitrogen. A similar mechanistic phenomenon may be at play in related systems wherein ligands control the *chemo*selectivity of cross-coupling of bromochloroazines. Sigman and Tan reported that several bulky ligands favor amination at the C5—Br of 5-bromo-2-chloropyridine (Scheme 5A).[27] However, most bidentate phosphines, in particular **20**, promote reaction at C2—Cl. In the Suzuki coupling of **21**, Ashcroft and Fussell found that several bulky monophosphines including QPhos favor reaction at Cl, while **22** (as well as PPh_3 and dppf) gave more reaction at Br (Scheme 5B).[28] These observations are consistent with the hypothesis that bisligated Pd reacts α to nitrogen via a displacement mechanism, whereas monoligated Pd—which doesn't benefit from a Pd•••N interaction during a 3-centered transition state—instead reacts with the weaker C—Br bond.

5-Membered Heterocycles.

Compared to 6-membered heteroarenes, relatively few cross-couplings of 5-membered heteroarenes have been reported (for examples, see Table 1). This might be explained by the more electron-rich character of 5-membered arenes, making them less reactive electrophiles. Because of the small number of publications on this topic and the diversity of 5-membered heteroarenes, it is difficult to define 'conventional' selectivity for these substrates. Handy's NMR-based model predicts that the C2-site of oxazoles, thiazoles, and imidazoles should be the most reactive based on a more downfield chemical shift for the corresponding hydrogen in the ^1H NMR spectra of the parent compounds (Figure 5, top). Houk's computations show that a C2—X bond of these substrates is weaker than a C4—X or C5—X bond, suggesting that the C2 site may be more reactive on the basis of distortion energies.[11b] The C2 carbon of oxazole, thiazole, and *N*-methylimidazole also has a more positive electrostatic potential than the other ring carbons,[29] which might predict greater reactivity at this site based on the selectivity principles described by Leitch et al.[12] Nevertheless, a literature survey suggests that selectivity for these substrate classes is not necessarily predictable by

established models. In particular, systematic studies by Strotman, Chobanian, and coworkers on 2,4- and 2,5-dihaloimidazoles, -oxazoles, and -thiazoles revealed that selectivity with some of these substrates depends on the phosphine ligand and/or the reaction solvent, as discussed below (Figure 5, bottom).[30]

The C2-site of **10** is expected to be more reactive based on Handy's model, C—I bond dissociation energies, and electrostatic potentials at C2 vs. C4. However, a preliminary ligand screen carried out by Strotman et al. resulted in *C4*-selective Suzuki coupling when using ligands such as PPh_3, dppf, XPhos (**23)**, and Xantphos (**22**) in THF (Scheme 6A). Among these, **22** promotes the highest C4-selectivity (13:1) as well as high selectivity for the monoarylated product over the diarylated product (~7:1). In contrast, P^tBu_3 enables inverted selectivity in THF, modestly favoring reaction at C2 by about 2:1. Because hindered ligands are known to promote low-coordinate PdL, one could speculate that this selectivity switch relates to palladium's ligation state during oxidative addition, similar to other examples discussed above in the context of 6-membered heteroarenes. However, a subsequent exhaustive ligand screen of ~200 achiral phosphines led Strotman *et al.* to identify 1,3,5-triaza-7-phosphaadamantane (**26**) as a ligand which promotes high selectivity for the C2-site in acetonitrile (~13:1). With its very small cone angle of 102°, even smaller than that of PMe_3 (116°),[31] **26** has little in common with the bulky ligand P^tBu_3. Furthermore, the bidentate phosphine **25** also slightly favors reaction at C2 in THF. These results seem to suggest against a hypothesis that low-coordinate PdL is responsible for C2-selectivity with this substrate. Importantly, the use of MeCN as solvent is critical to obtaining high C2-selectivity in the reaction of **10** using **26**. In THF, the reaction catalyzed by Pd/**26** is unselective (1:1). The selectivity with other ligands in MeCN was not reported.

Based on the anomalous selectivity effected by **26** in the reaction of **10**, Strotman compared **26** to other ligands for Suzuki couplings of several additional classes of substrates. Once again, **26** was unique in its ability to promote cross-coupling at the C2-site of **12** and **13** (Scheme 6B). Other ligands led to a mixture of products that were biased toward reaction at C5. The higher reactivity of C5—X with most ligands is contrary to the predicted reactivity with Handy or Houk's model: the ^{1}H NMR chemical shifts of imidazole and *N*-methylimidazole, [32] and the relative BDEs of C2—Cl and C5—Cl for chloroimidazoles,[11b] predict that C2—X should be the most reactive (Figure 5, top). Interestingly, other reports in the literature—employing either $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$—suggest that C2 is the preferred reaction site for 2,5-dibromoimidazoles. [33] However, none of these reports include detailed regiochemical characterization, whereas Strotman et al. substantiated the regiochemical assignments of their observed products with NOE experiments.

Despite the observed ligand-dependent divergent selectivity using 2,5-dihaloimidazoles and 2,4-diiodooxazole, Strotman et al. found that other dihalogenated 5-membered heteroarenes are not sensitive to ligand effects. 2,4- and 2,5-Dibromothiazoles (**14** and **15**) and 2,4-dibromoimidazole (**11**) were found to undergo C2-selective Suzuki coupling with all of the ~200 ligands screened by Strotman. The mechanistic origin of the ligand-controlled divergent selectivity with some 5-membered heteroarenes—and not with others—has not yet been reported.

SPECIATION-CONTROLLED SELECTIVITY

Thus far, this Perspective has highlighted examples in which atypical site selectivity is achieved due to unique steric or electronic properties of an ancillary phosphine or NHC ligand. However, very recent reports suggest that changes in catalyst speciation (i.e., from mono- to multinuclear) can have an equal or even more powerful influence on site selectivity compared to changes to the ligand environment at mononuclear Pd. Catalyst speciation can be complicated, and in many circumstances it is reasonable to expect a mixture of homogeneous, heterogeneous, and soluble nanoparticle species.[34] In particular, higher reaction temperatures can promote the conversion from mono- to multinuclearity, and some additives (e.g., tetralkylammonium halides or -hydroxides) can stabilize nanoparticles by preventing their aggregation into higher-order species.[35]

The conversion of mononuclear catalytic species into higher-order ones can sometimes translate into fundamental changes in the mechanism of cross-coupling. For example, Li and coworkers reported that the trinuclear Pd_3X cluster **27** may catalyze Suzuki cross-coupling through a mechanism in which transmetallation occurs first (Scheme 7).[36] The resulting species Pd_3Ar (**28**) then reacts further with the aryl halide electrophile via a σ-bond metathesis mechanism, furnishing the cross-coupled product and regenerating Pd_3X. This mechanism stands in contrast to the classic Suzuki reaction in that the two coupling partners enter the catalytic cycle in the reverse order, and there are no traditional redox steps (oxidative addition or reductive elimination). The likelihood of divergent mechanisms for multi- vs. mononuclear Pd is consistent with recent reports of divergent site selectivity for cross-couplings of dihaloheteroarenes catalyzed by multi- vs. mononuclear Pd, as discussed below.

2,4-Dibromopyridine.

Fairlamb et al. demonstrated that the regiochemical outcome of Suzuki and Kumada couplings of 2,4-dibromopyridine can be dependent on the ratio of PPh_3:Pd. Conventional C2-selectivity is observed with PPh_3:$Pd(OAc)_2$ ratios ≥3:1 (Scheme 8A).[37] In contrast, atypical C4-selectivity is seen with PPh_3:$Pd(OAc)_2$ ratios ≤2.5:1 or when using the preformed trimer $[Pd_3(\mu\text{-}Cl)(\mu\text{-}PPh_2)_2(PPh_3)_3]Cl$, providing product **2b** with up to 13:1 selectivity. The inclusion of tetraalkylammonium bromide or hydroxide salts was necessary to achieve high yield and selectivity for the C4-product, hinting toward the involvement of Pd nanoparticles (PdNPs) under conditions with low PPh_3:Pd ratios. Indeed, Fairlamb's group had previously shown that the combination of PPh_3 and $Pd(OAc)_2$ in a 2:1 ratio can lead to the *in situ* generation of Pd_3X clusters (Scheme 8B),[38] and related clusters were shown to be intermediates *en route* to nanoparticle formation.[39] As such, the evidence suggests that multinuclear Pd (likely PdNPs) is responsible for the atypical C4-selectivity at low PPh_3:Pd ratios. The mechanistic rationale for the unusual site preference of PdNPs is currently unknown, but Fairlamb suggests that one possible explanation could involve a switch in mechanism similar to that reported by Li (*vide supra*).

Dichloropyridines, quinolines, and pyrimidines.

In 2022, we reported that ligand-free “Jeffery” conditions facilitate exquisitely selective C4-coupling in the Pd-catalyzed Suzuki reactions of 2,4-dichloropyridine (>99:1) and 2,4-dichloroquinoline (53:1, Scheme 9). Remarkably, these conditions also favor reaction at the C5 position of 2,5-dichloropyridine (**6**) and 2,5-dichloropyrimidine (**8**). Preferential reaction at C5 of these substrates, with spectroscopically substantiated regiochemical assignments, had not been previously reported. Prior evidence supports the formation of nanoparticles under such Jeffery conditions involving a simple palladium salt ($PdCl_2$) in the presence of a tetralkylammonium halide.[35a,40] As such, it is likely that the unusual site-selectivity in this system is due to PdNPs, similar to the observations made by Fairlamb using 2,4-dibromopyridine. A direct comparison between the Jeffery conditions and Pd/IPr conditions for the Suzuki coupling of 2,4-dichloropyridine **1** indicates that speciation-control has the potential to be much more powerful than ligand-control. Whereas the Pd/IPr catalytic system typically provides ~10:1 selectivity, the ligand-free conditions lead to an order-of-magnitude improvement in selectivity (~99:1).

The remarkable improvement in selectivity under ligand-free conditions compared to Pd/IPr conditions led us to re-examine a previous report by Yang et al. As discussed above, Yang had shown that a PEPPSI-IPr catalytic system gives ~10:1 selectivity for the C4-position during Suzuki cross-coupling of 2,4-dichloropyridine under fairly routine reaction conditions.[24] However, they described a surprising jump in C4-selectivity upon modifying their high-temperature reaction conditions to include KI, along with two bases (NaOAc and Na_2CO_3) added at different times and a higher catalyst loading (Scheme 10A). These conditions are effective for achieving ~99:1 C4-selectivity for Suzuki coupling of a wide range of substituted dichloropyridines. Although the catalyst used by Yang was Pd-PEPPSI-IPr, the exquisite selectivity under their unusual reaction conditions resembles the selectivity that we observe under ligand-free conditions. As such, we investigated this system more closely with a ligand-free control experiment using $PdCl_2$ instead of Pd-PEPPSI-IPr (Scheme 10B). Indeed, the high selectivity was maintained in the absence of IPr, indicating that selectivity under Yang’s optimized conditions is not ligand-controlled. Rather, higher-order Pd species may be responsible for the observed unconventional selectivity.

OUTLOOK

As described above, unconventional or divergent site-selectivity has been established for a few classes of *N*-heteroarenes. Nevertheless, catalyst-controlled site-selective cross-couplings remain largely unexplored. Machine-learning algorithms for predicting selectivity are likely to be biased toward conventional selectivity patterns, promoted especially by dppf and PPh_3, due to the prevalence of these ligands in literature.[41] As such, the development of new methods may rely on improving our mechanistic understanding of selectivity. In particular, we consider the mechanistic picture to be lacking with respect to (1) the significance of two possible mechanisms for oxidative addition (concerted vs. displacement) and the relationship between the preferred mechanism and ligand/substrate identity, (2) the role of catalyst speciation, specifically in cases where multinuclear catalysts promote unconventional site selectivity, and (3) the influence of ring substituents on

the regiochemical outcome of cross-coupling reactions. Filling in these mechanistic gaps may lay the groundwork for overcoming additional challenges that face the field of site-selective cross-coupling, including inverting selectivity for some “stubborn” classes of substrates and minimizing unwanted over-reaction of di- and polyhalogenated substrates (e.g., avoiding diarylation). Here we summarize our perspective on these current challenges and opportunities.

Mechanism of Oxidative Addition.

Although oxidative addition of aryl halides at Pd(0) is traditionally thought of as proceeding through a 3-centered concerted mechanism, the existence of a second mechanistic possibility has been well-established. In particular, oxidative addition can also proceed through a pathway that has been termed “S_NAr-like”, “dissociative”, or “displacement” (Scheme 11A).[13,14,15,26,42] In this pathway, C—X cleavage does not involve interaction between Pd and X in the transition state; instead, Pd interacts with the *ipso* carbon and an *ortho* atom of the ring while X dissociates as an anion. Several computational studies have indicated that use of a solvation model is necessary to locate displacement-type transition structures, and that this pathway is more favorable in polar solvents or an externally applied electric field.[13,14,43] Calculations by Maseras et al. show that the preferred mechanism for the reaction between PhBr and PdL_n depends on the ligand identity and the value of n (1 or 2).[14] Palladium’s coordination number during oxidative addition can be influenced by ligand sterics[44] or even by substrate concentration.[45] In our own work, we found that the preferred mechanism for oxidative addition is intimately related to the divergent site selectivity observed in Pd-catalyzed couplings of 2,4-dichloropyridines using bulky ligands versus smaller or bidentate ligands.[15] Developing a better understanding of the circumstances under which these mechanisms (or other mechanisms) are relevant for other classes of dihaloheteroarenes may shed light on strategies for controlling site selectivity in less-explored substrate classes.

Catalyst Speciation.

As discussed above, the relevance of catalyst speciation (mono- vs. multinuclear) on site selectivity was discovered by Fairlamb in the context of couplings of 2,4-dibromopyridine.[37] Our group later provided evidence that multinuclear Pd also gives unique selectivity in reactions of 2,4-dichloropyridine, as well as 2,5-dichloropyridine and -pyrimidine.[25] Remarkably, it appears that multinuclear palladium has the potential to give much higher selectivities than systems in which selectivity is ligand-controlled. Despite the robust evidence for multinuclear speciation, especially in Fairlamb’s system, there is currently no explanation for *why* multinuclear Pd prefers to react at the distal site (Scheme 11B). Developing a deeper understanding of the mechanism of C—X cleavage at multinuclear Pd is expected to catalyze the development of new selective coupling methods which complement those involving mononuclear catalysis. Much is already known about the size and shape of PdNPs in Suzuki cross-coupling reactions.[46] At this time, however, the effect of these properties on site selectivity is unknown. Exploiting the current knowledge base about PdNP size and shape might enable the active sites for selective catalysis to be determined.

Ring Substituents.

For dihalogenated heteroarenes, the effect of substituent sterics and electronics on the site-selectivity of cross-coupling has largely been a matter of empirical study. In a few reports, there is evidence to support the coordination of a substituent (most often carboxylates) to Pd, directing oxidative addition to take place at an adjacent site.[6] However, other substituent effects cannot be explained by this phenomenon. In 2011, Khoje and Gundersen summarized the effects of six distinct substituents located at the C3-position of 2,4-dichloropyridine in Pd-catalyzed Stille couplings (Scheme 11C).[7] Consistent with its established conventional selectivity, Pd/PPh_3 effects C2-arylation in nearly every example. However, when the C3-substituent is a nitro group, arylation occurs almost exclusively at C4. There is currently no published rationale for this phenomenon, yet anomalous examples such as this one provide an opportunity to identify new mechanistic features which could complement our current understanding of selectivity.

“Stubborn” Substrate Classes.

For the majority of di- and polyhalogenated *N*-heteroarenes, strategies for inverting conventional site selectivity remain undeveloped or underdeveloped (examples in Scheme 11D). For many heteroaryl substrate classes, little selectivity information has been established due to poor reactivity. These substrates include substituted pyrazoles and fused 5,6-heterocycles such as benzimidazoles and indoles.[1g,47] For other substrates, existing literature seems to indicate that selectivity always follows a particular pattern. For instance, Strotman’s extensive ligand screening for the Suzuki couplings of 2,4- and 2,5-dibromothiazoles (**14** and **15**) and a 2,4-dibromoimidazole (**11**) resulted in C2-selective cross-coupling in all cases, leaving no option to access the opposite regioisomer through cross-coupling.[30] As an another example, 2,4-dichloropyrimidines present a particular challenge. These substrates generally react preferentially at C4 (both in cross-couplings and in S_NAr reactions), but a method to cross-couple selectively at C2 would be quite desirable due to the prevalence of the resulting motifs in bioactive compounds. However, it is difficult to envision a robust foothold for biasing reactivity toward C2, since multiple factors seem to favor reaction at C4. The C4—Cl bond is weaker, and the C4 carbon has a much larger LUMO coefficient. Thus, a method to successfully achieve C2-selective coupling may require a fundamentally different strategy than those that have been previously reported for other substrates.

Diarylation.

Undesired “overarylation” is common in cross-coupling reactions of dihaloheteroarenes when using bulky NHC or biarylphosphine ligands, despite a 1:1 ratio of substrate to nucleophile.[20,23a,24,25] This trend is consistent with literature reports involving halogenated aromatic carbocycles. For example, Larosa et al. found that IPent enables efficient “exhaustive arylation” of various dihalogenated arenes despite a deficit of nucleophile.[48] Further, Hein et al. have reported that both IPr and RuPhos are effective di- or polyamination catalysts for regioselective elaborations of tetrabromospirobifluorenes.[49] When a monofunctionalized product is desired, competitive overarylation detracts from the yield, in part because diarylated products can be challenging to separate from

monofunctionalized product. Furthermore, the accumulation of diarylated product in a reaction mixture can complicate an evaluation of site-selectivity if either monoarylated isomer undergoes a second arylation more rapidly than the other. Formation of diarylated product can thus artificially inflate or deflate the observed ratio of monoarylated products. In the context of Pd-catalyzed cross-couplings of dihalo(hetero)arenes, the mechanism of diarylation may mirror that of catalytic chain growth polymerizations in which oxidative addition of a nascent monoarylated product takes place more rapidly than dissociation of the catalyst from product at the end of a catalytic cycle. This mechanism is referred to as a chain-walking mechanism.[50] Kapdi et al. reported that several sulfonated alkylimidazolium ligands markedly disfavor diarylation of 2,6-dibromopyridine compared to IMes, PPh_3, and other ligands under Pd-catalyzed SMC conditions (Scheme 11E), hinting that ligand bifunctionality may play a role in assisting the dissociation step.[23] Further mechanistic study into the relationship between over-functionalization and ligand environment could guide catalyst design to minimize unwanted overfunctionalization.

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50. (a)Kiriy A; Senkovskyy V; Sommer M Kumada Catalyst-Transfer Polycondensation: Mechanism, Opportunities, and Challenges. Macromol. Rapid Commun 2011, 32, 1503–1517. [PubMed: 21800394] (b)Bryan ZJ; McNeil AJ Conjugated polymer synthesis via catalyst-transfer polycondensation (CTP): mechanism, scope, and applications. Macromolecules 2013, 46, 8395–8405.(c)Bryan ZJ; McNeil AJ Evidence for a Preferential Intramolecular Oxidative Addition in Ni-Catalyzed Cross-Coupling Reactions and their Impact on Chain-Growth Polymerizations. Chem. Sci 2013, 4, 1620–1624.

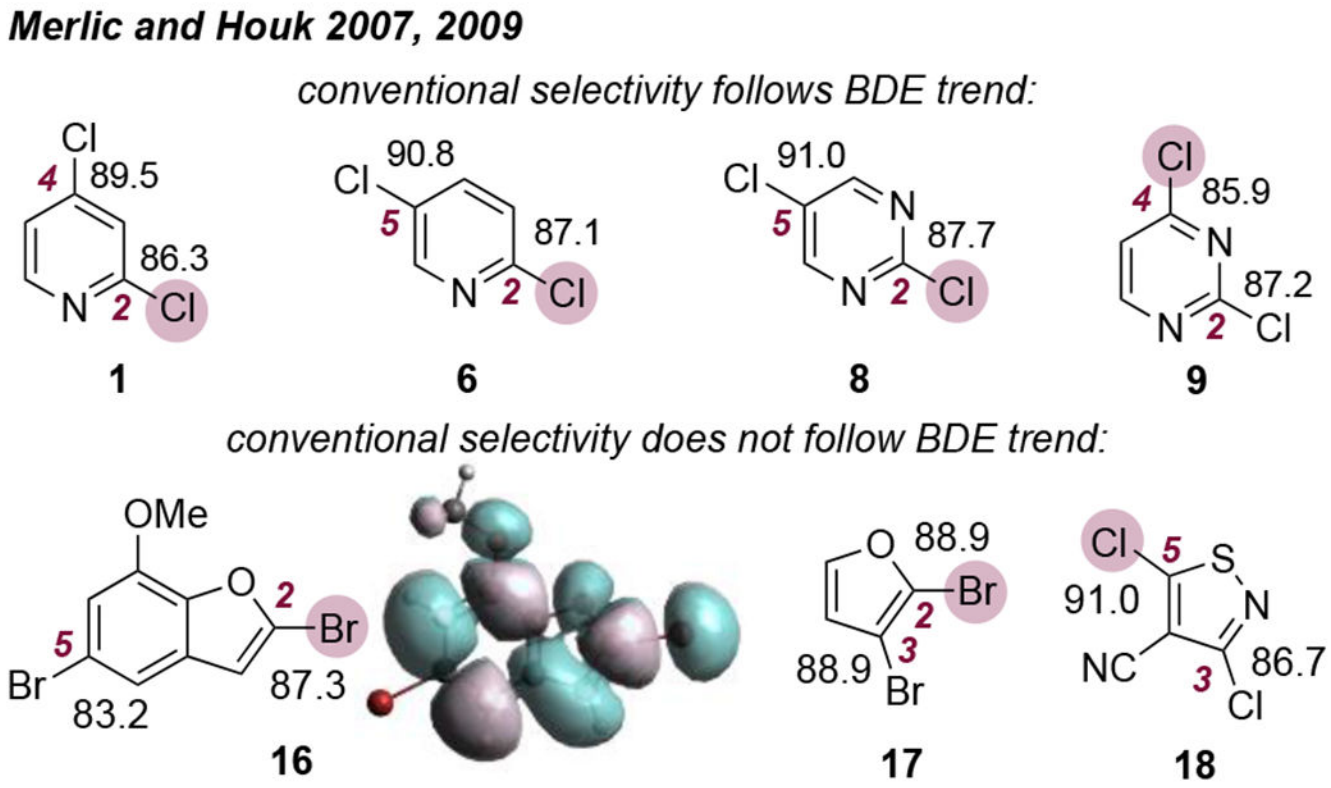


Figure 1.

Bond dissociation energies (BDEs) for selected dihalogenated substrates. BDEs calculated with B3LYP/6-31G(d). The highlighted halide corresponds to the conventional site of reactivity.[11]

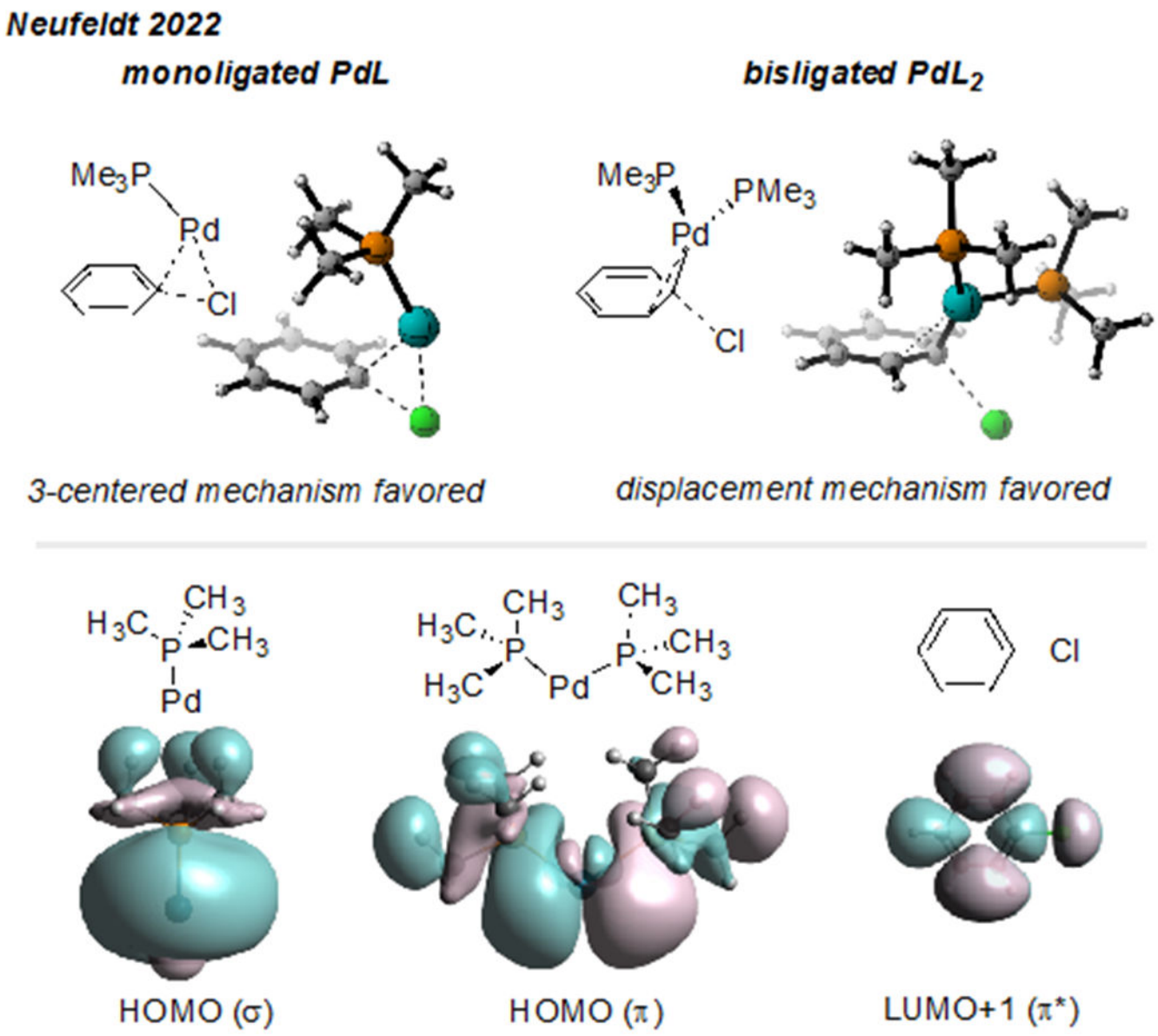


Figure 2.
PdL and PdL_2 can favor different mechanisms for oxidative addition due to differences in orbital symmetry.[15]

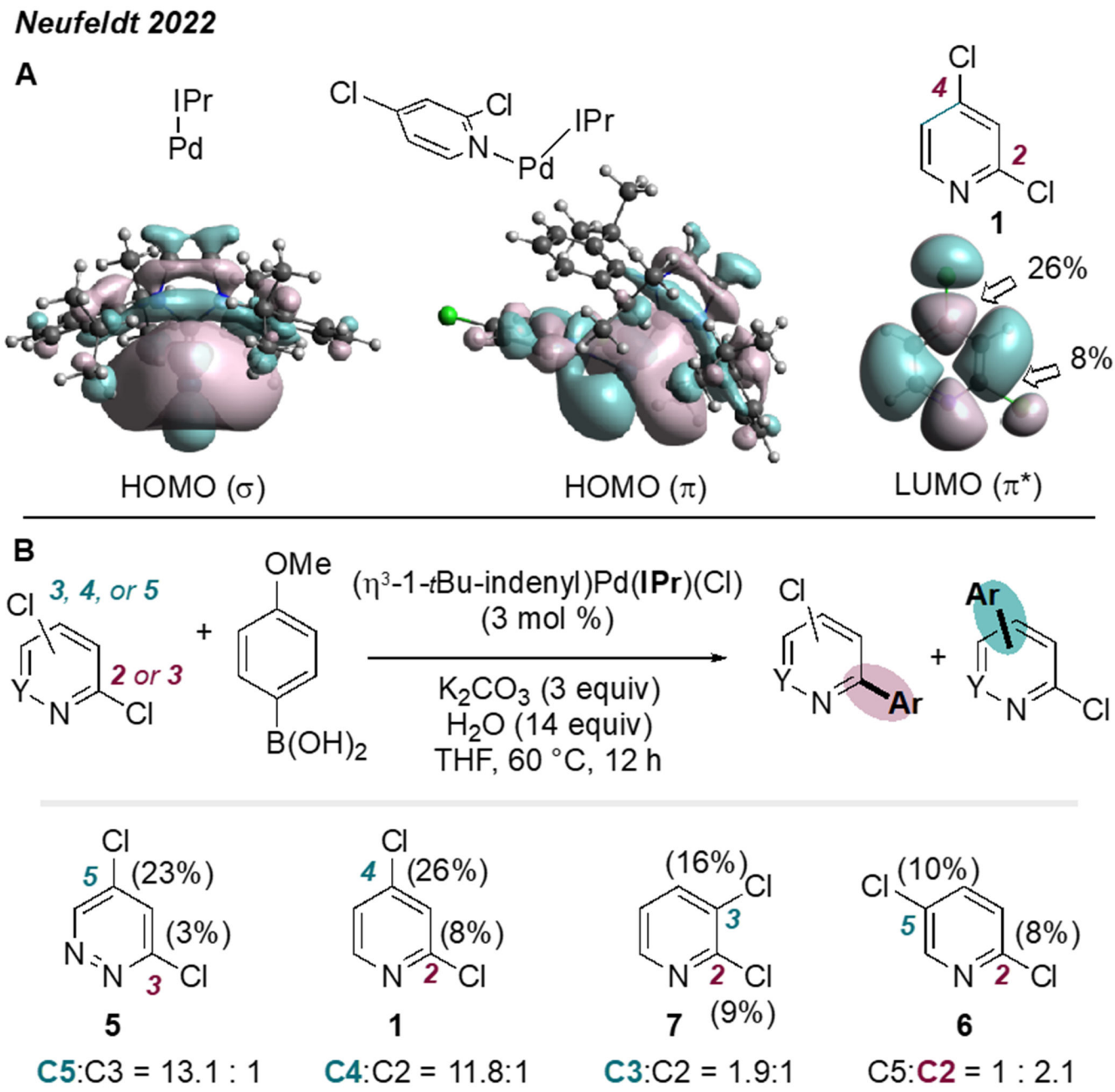


Figure 3.

(A) Frontier molecular orbitals of 12 e^- Pd(IPr), bent 14 e^- Pd(IPr)(**1**), and 2,4-dichloropyridine **(1)**. (B) The distal-selectivity of Pd/IPr-catalyzed Suzuki-coupling correlates with the difference in LUMO coefficients between the two sites (% contribution to LUMO is indicated in parentheses).[15]

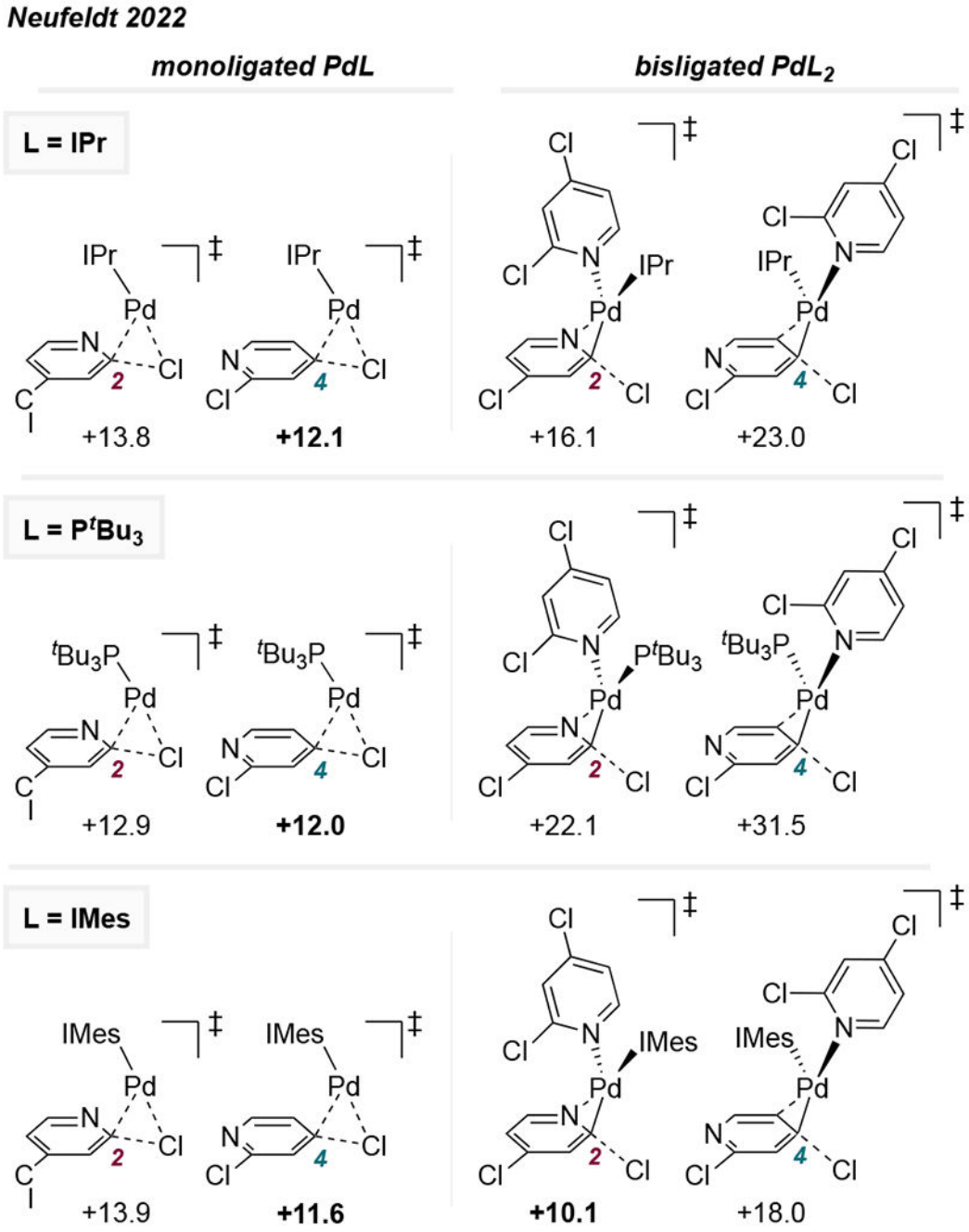


Figure 4.

Mono- and bisligated transition structures for oxidative addition of 2,4-dichloropyridine at Pd(IPr), Pd(P^tBu_3), and Pd(IMes). Free energies in kcal/mol relative to the lowest-energy preceding π-complex.[15]

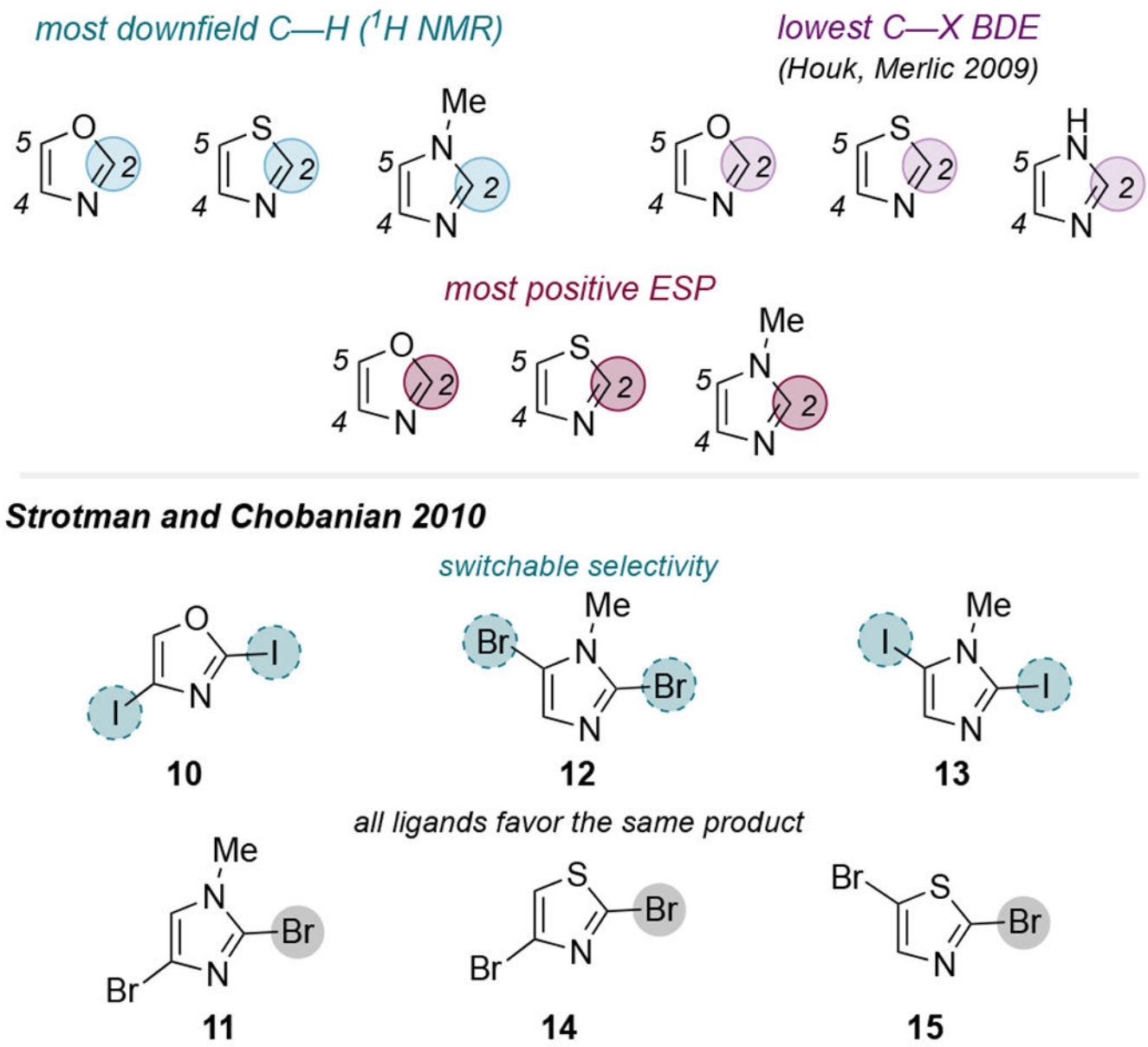
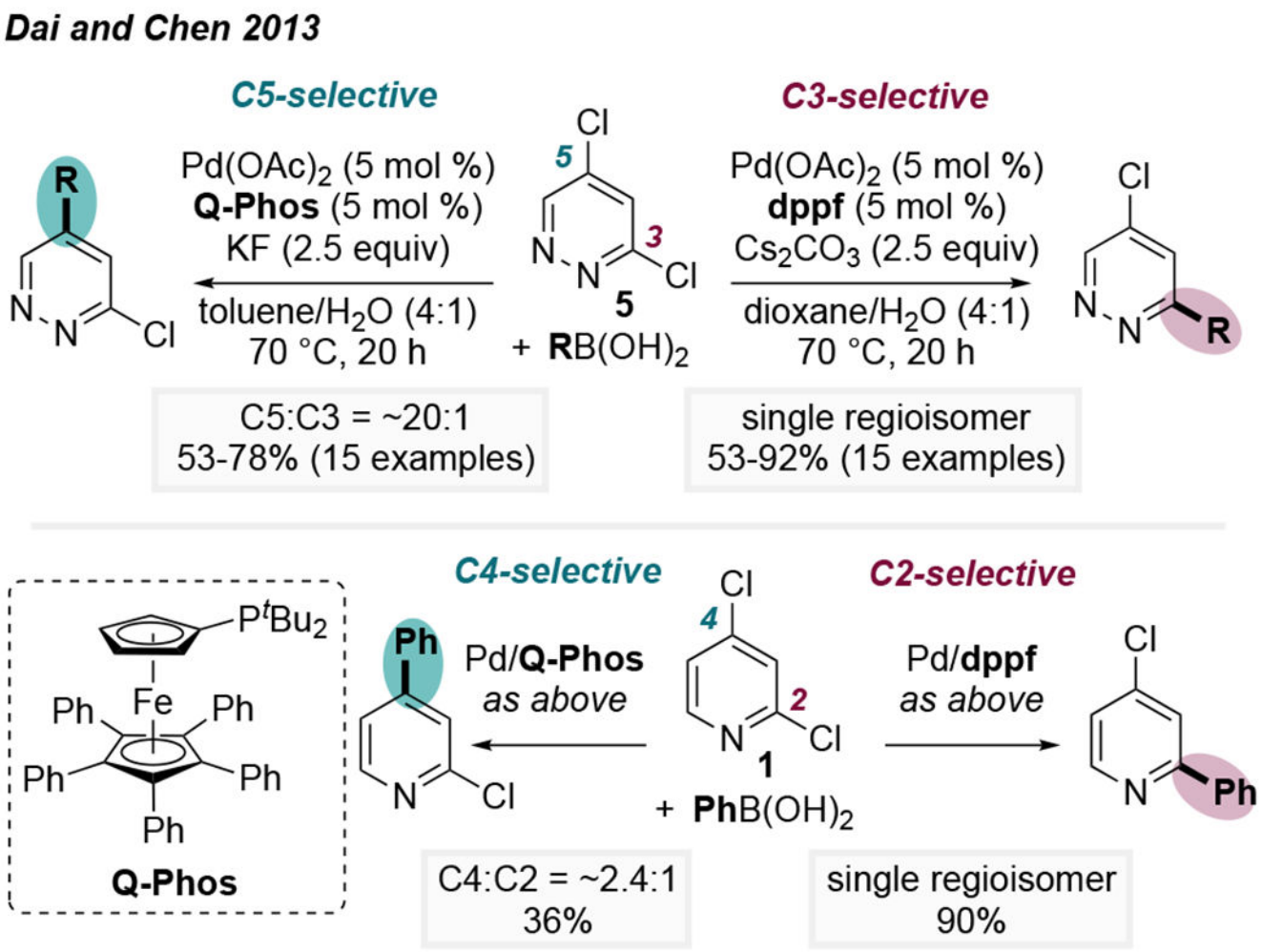


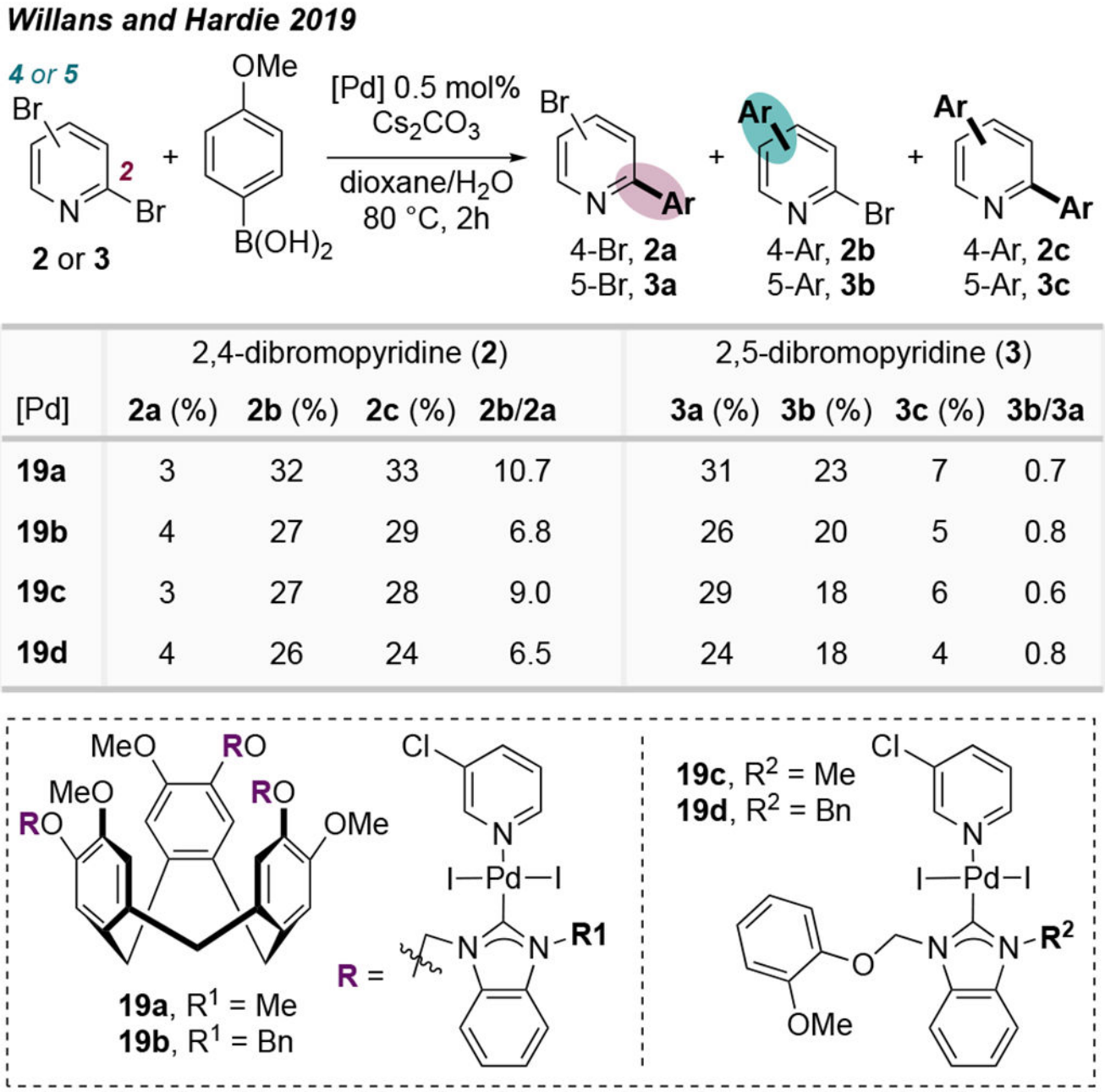
Figure 5.

(Top) Highlighted positions represent the expected site of highest reactivity for 5-membered heteroarenes based on Handy's NMR model,[9] Houk and Merlic's BDE calculations,[11b] and electrostatic potentials at carbon,[29] which are related to Leitch's model.[12] (Bottom) Summary of the actual selectivity behavior for the substrates studied by Strotman and Chobanian.[30]



Scheme 1.

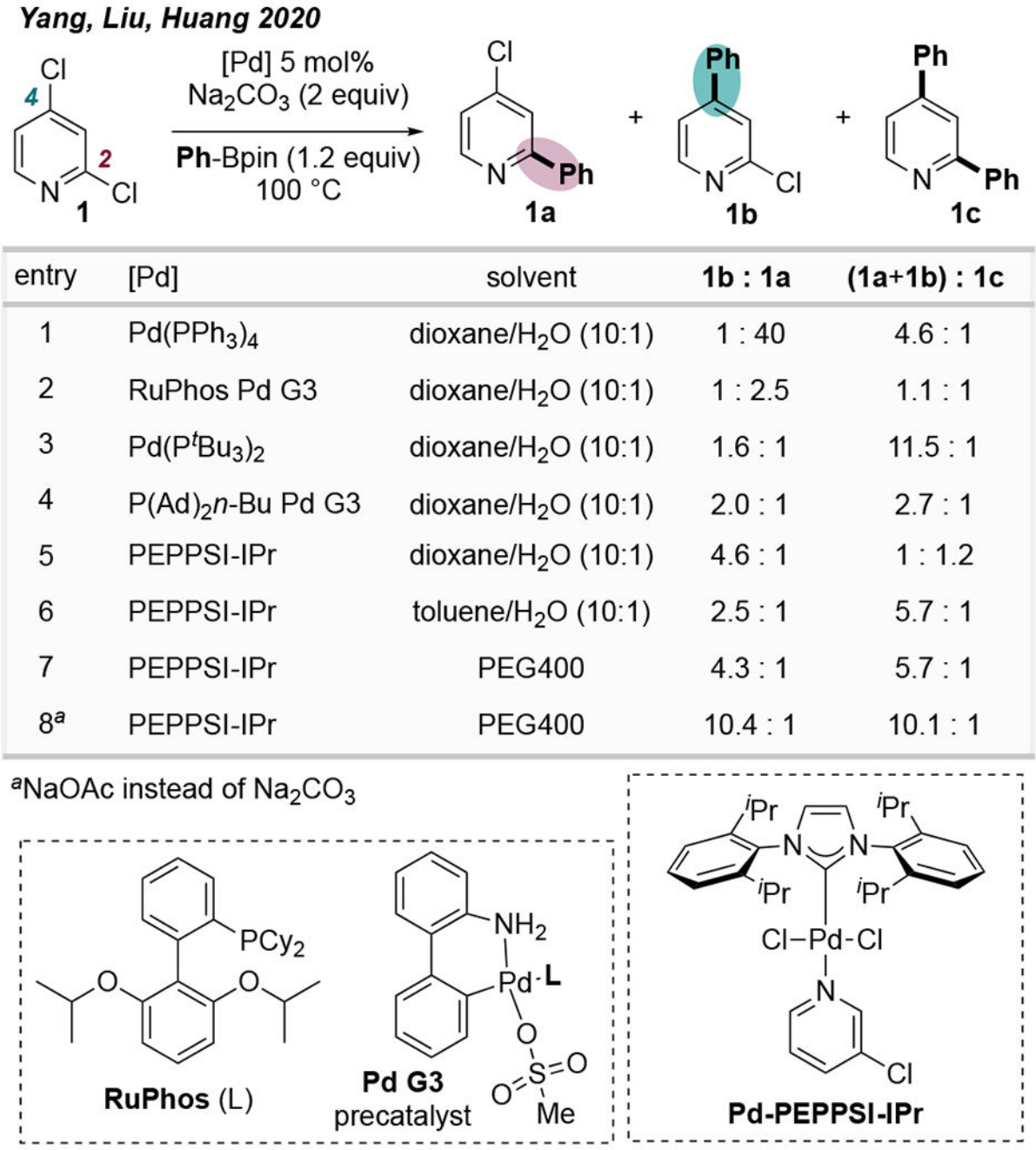
First Examples of Ligand-Controlled Inversion of Conventional Selectivity for 3,5-Dichloropyridazine and 2,4-Dichloropyridine[20]



	2,4-dibromopyridine (**2**)				2,5-dibromopyridine (**3**)			
[Pd]	**2a** (%)	**2b** (%)	**2c** (%)	**2b/2a**	**3a** (%)	**3b** (%)	**3c** (%)	**3b/3a**
19a	3	32	33	10.7	31	23	7	0.7
19b	4	27	29	6.8	26	20	5	0.8
19c	3	27	28	9.0	29	18	6	0.6
19d	4	26	24	6.5	24	18	4	0.8

Scheme 2.

Ligand-Controlled Inversion of Conventional Selectivity for 2,4-Dibromopyridine and Erosion of Conventional Selectivity for 2,5-Dibromopyridine[23a]

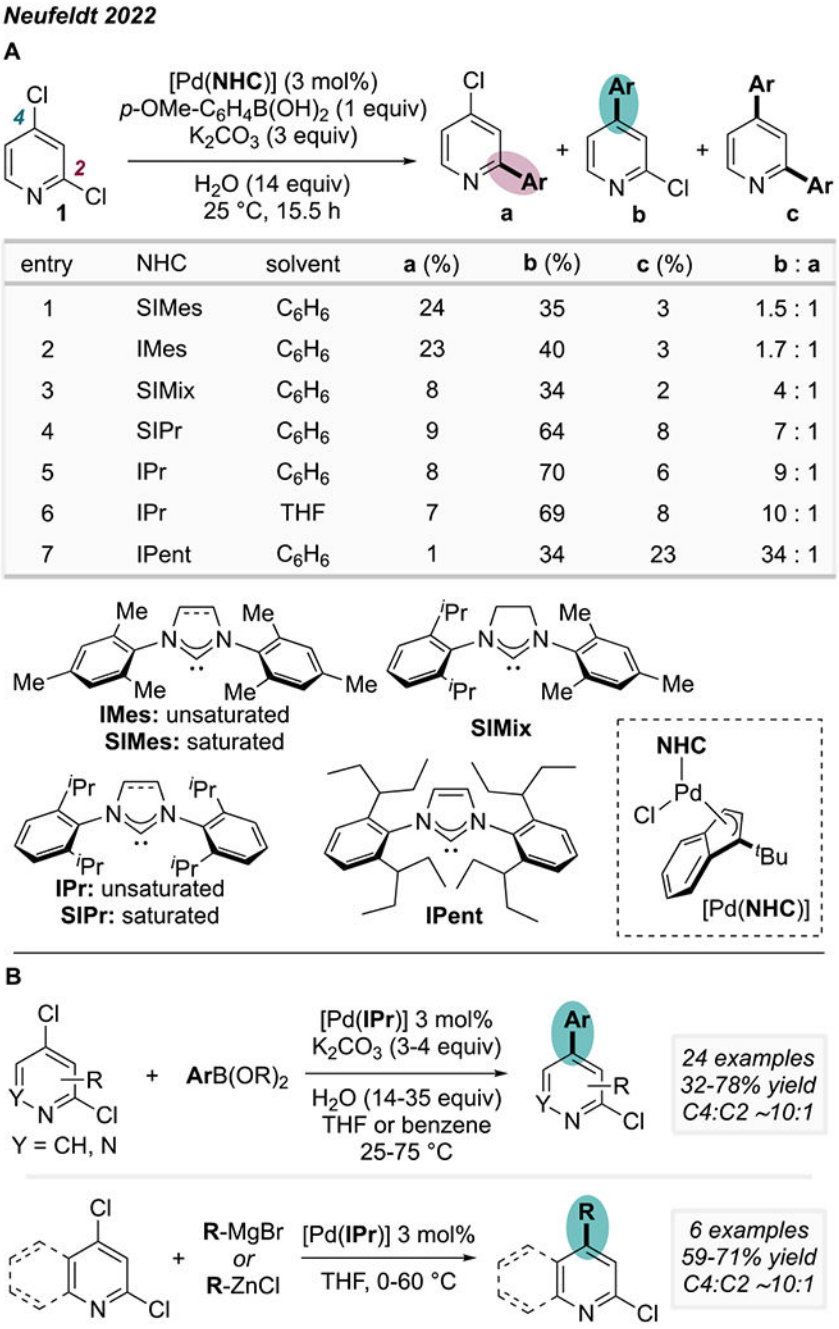


entry	[Pd]	solvent	1b : 1a	(1a+1b) : 1c
1	$Pd(PPh_3)_4$	dioxane/H_2O (10:1)	1 : 40	4.6 : 1
2	RuPhos Pd G3	dioxane/H_2O (10:1)	1 : 2.5	1.1 : 1
3	$Pd(P^tBu_3)_2$	dioxane/H_2O (10:1)	1.6 : 1	11.5 : 1
4	$P(Ad)_2n$-Bu Pd G3	dioxane/H_2O (10:1)	2.0 : 1	2.7 : 1
5	PEPPSI-IPr	dioxane/H_2O (10:1)	4.6 : 1	1 : 1.2
6	PEPPSI-IPr	toluene/H_2O (10:1)	2.5 : 1	5.7 : 1
7	PEPPSI-IPr	PEG400	4.3 : 1	5.7 : 1
8[a]	PEPPSI-IPr	PEG400	10.4 : 1	10.1 : 1

[a]NaOAc instead of Na_2CO_3

Scheme 3.

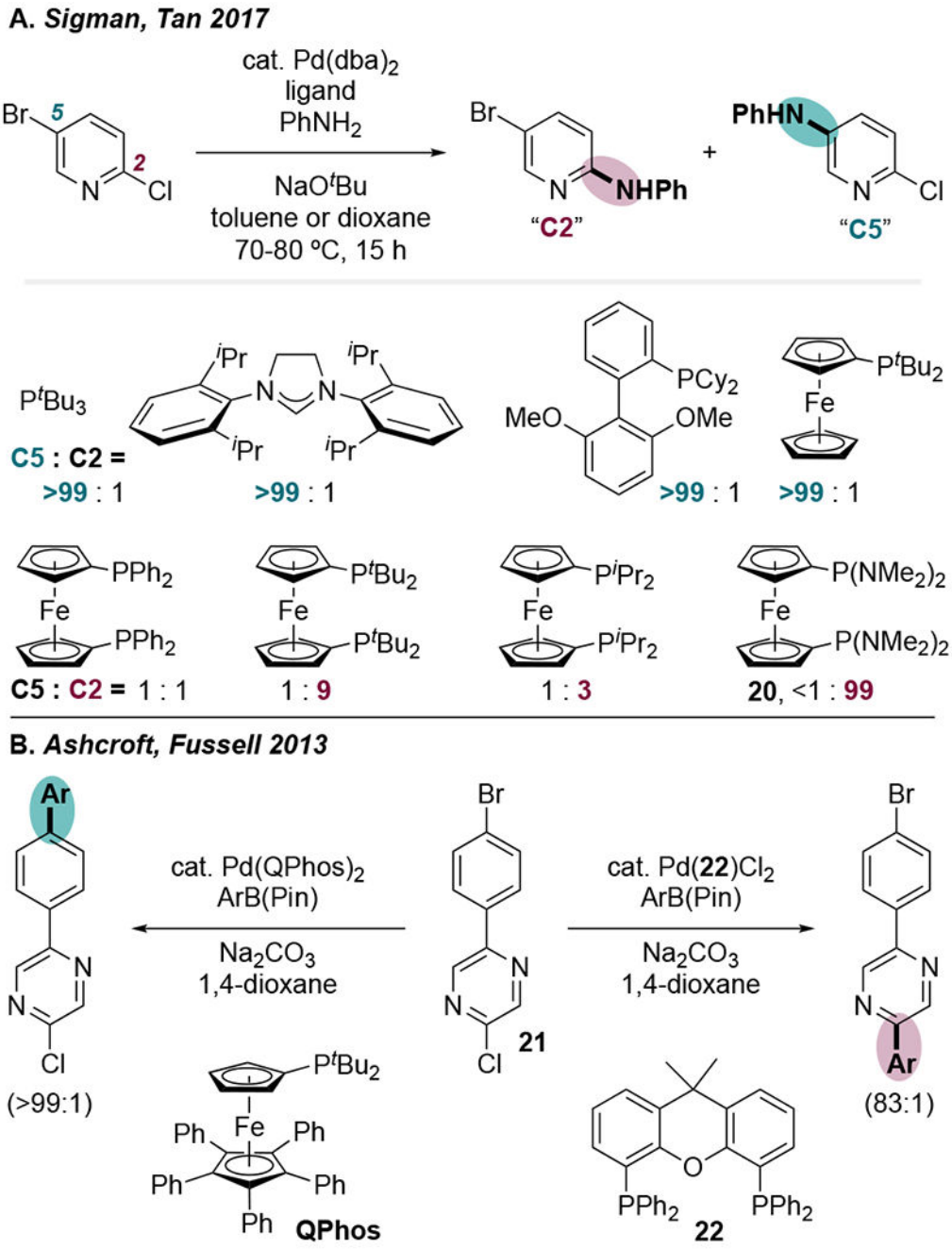
Salient Optimization Data from Yang et al. Showing that IPr Promotes C4-Selective Cross-Coupling of 2,4-Dichloropyridine[24]



entry	NHC	solvent	a (%)	b (%)	c (%)	b : a
1	SIMes	C_6H_6	24	35	3	1.5 : 1
2	IMes	C_6H_6	23	40	3	1.7 : 1
3	SIMix	C_6H_6	8	34	2	4 : 1
4	SIPr	C_6H_6	9	64	8	7 : 1
5	IPr	C_6H_6	8	70	6	9 : 1
6	IPr	THF	7	69	8	10 : 1
7	IPent	C_6H_6	1	34	23	34 : 1

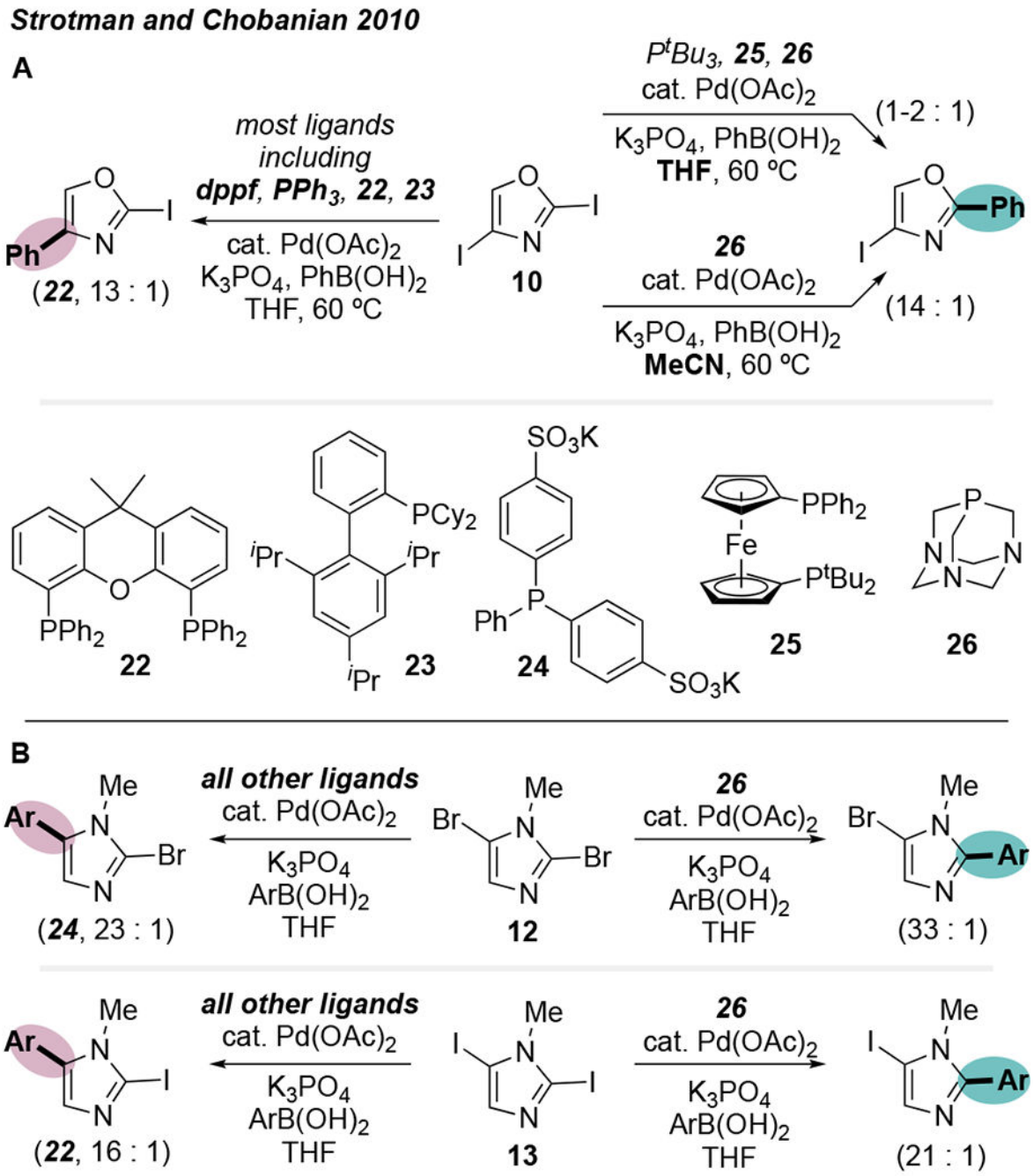
Scheme 4.

(A) C4-Selectivity with **1** Correlates with Ligand Sterics; (B) IPr Enables C4-Selective Suzuki, Kumada, and Negishi Coupling of Dichloroazines.[25]



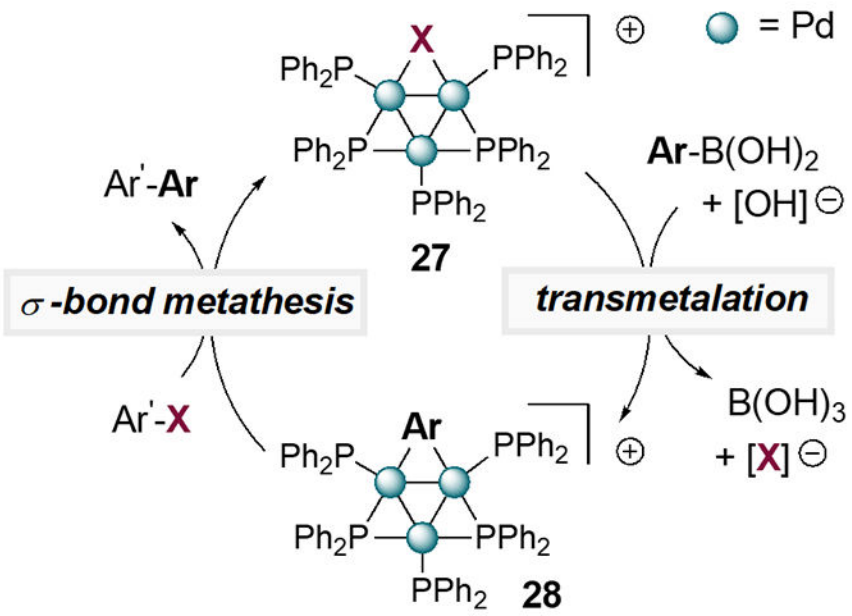
Scheme 5.

Ligand-Switchable Chemoselectivity Between Cl and Br on 6-Membered Heteroarenes Reported by (A) Sigman, Tan, et al.[27] and (B) Ashcroft, Fussell, and Wilford.[28]



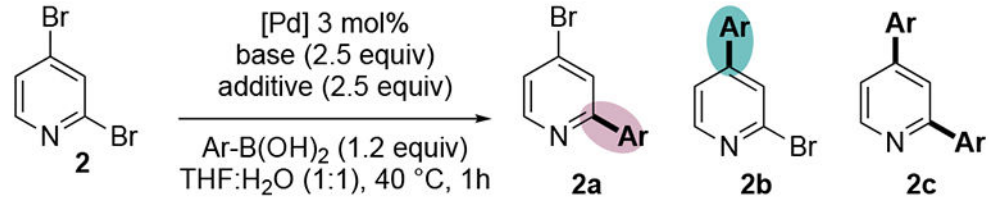
Scheme 6.

Ligand-Switchable Site Selectivity for 5-Membered Heteroarene Substrates: (A) 2,4-Diiodooxazole and (b) 2,5-Dihaloimidazoles.[30]



Scheme 7.
Proposed Catalytic Cycle for Pd_3X-Catalyzed Suzuki Cross-Coupling.[36]

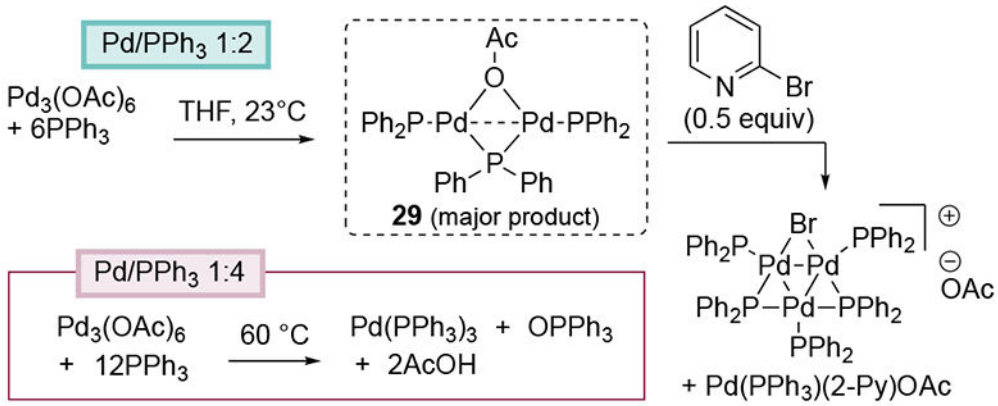
A *Fairlamb 2021*



entry	[Pd]	base	additive	**2a** (%)	**2b** (%)	**2c** (%)
1[a]	$Pd(OAc)_2$/ $1PPh_3$	*n*-Bu_4NOH	none	6	79	9
2[a]	$Pd(OAc)_2$/ $2PPh_3$	*n*-Bu_4NOH	none	10	64	7
3[a]	$Pd(OAc)_2$/ $3PPh_3$	*n*-Bu_4NOH	none	10	8	<1
4[a]	$Pd(OAc)_2$/ $4PPh_3$	*n*-Bu_4NOH	none	10	5	<1
5[b]	**29**	*n*-Bu_4NOH	none	15	69	16
6[b]		KOH	none	38	38	24
7[b]		KOH	*n*-Bu_4NBr	9	82	10
8[b]		KOH	*n*-Oct_4NBr	7	90	3

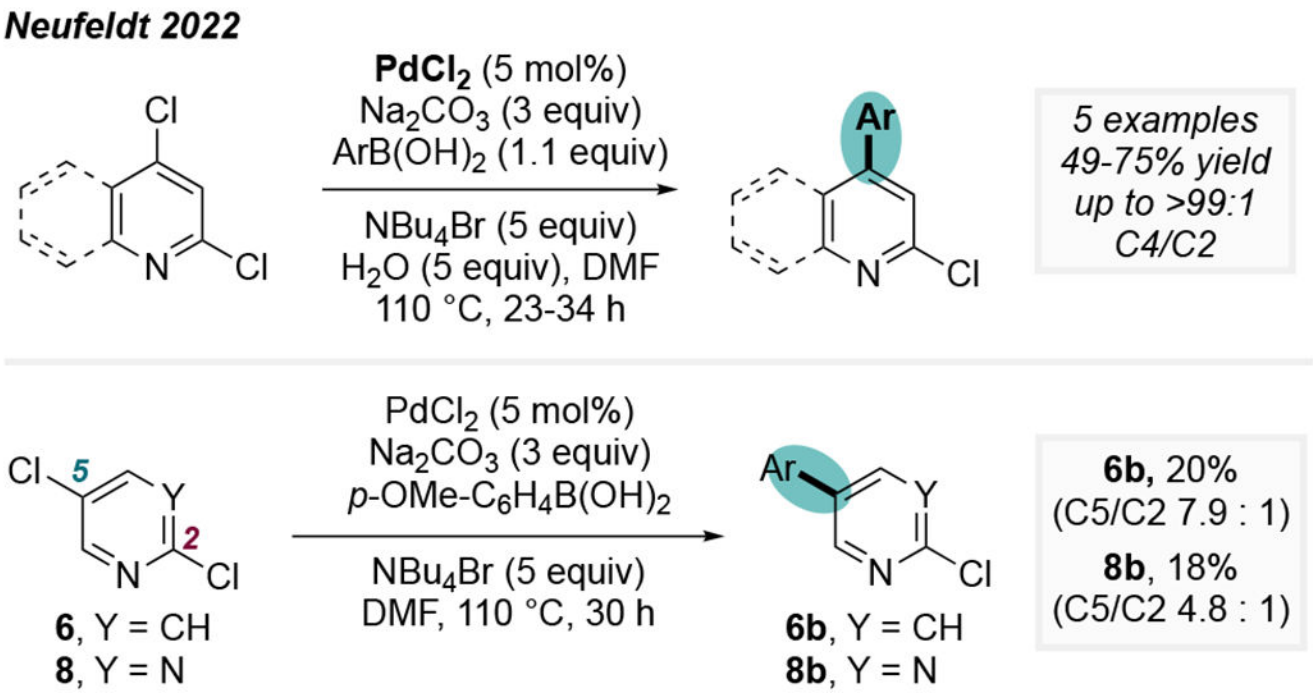
[a]Yields estimated from Figure 1 of reference 37. Ar = p-CF_3-C_6H_4. [b]Ar = *p*-OMe-C_6H_4

B *Fairlamb 2019*



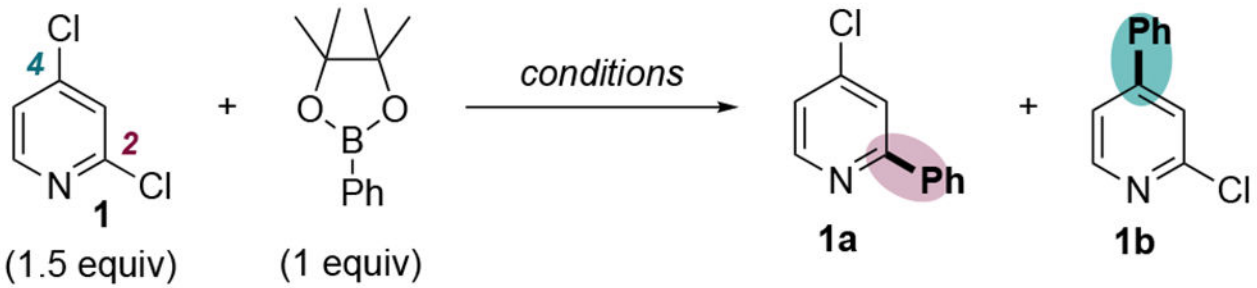
Scheme 8.

(A) Changes in Speciation can Modulate Site-Selectivity; (B) Modified Pd:PPh_3 Ratios Change Catalyst Speciation.[37,38]



Scheme 9.
Ligand-free ‘Jeffery’ conditions give unconventional selectivity.[25]

A *Yang, Liu, Huang 2020*

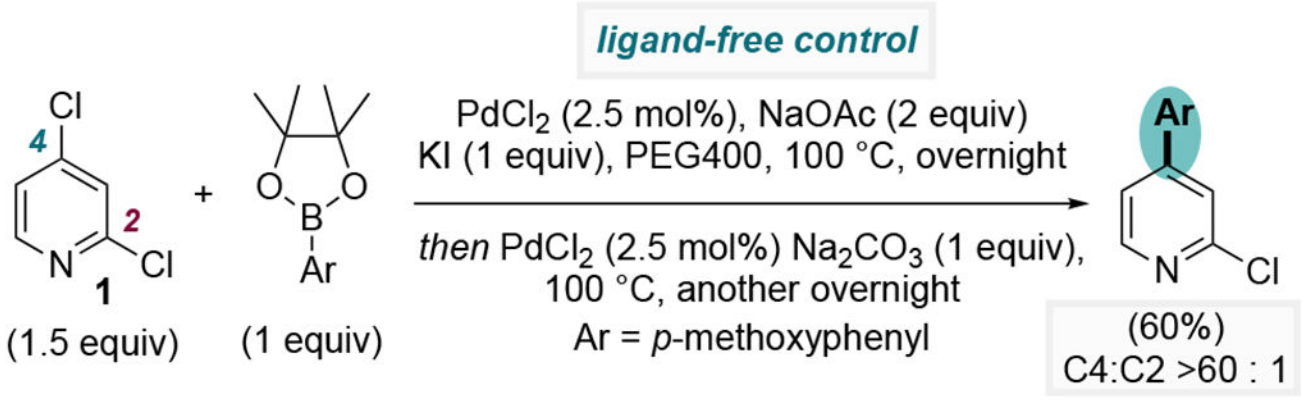


conditions	**1b** : **1a**	**1b** (isolated yield, %)
A	7 : 1	55%
B	**99 : 1**	76%

Conditions A: Pd-PEPPSI-IPr (5 mol %), Na_2CO_3 (2 equiv), KI (1 equiv), PEG400, 100 °C

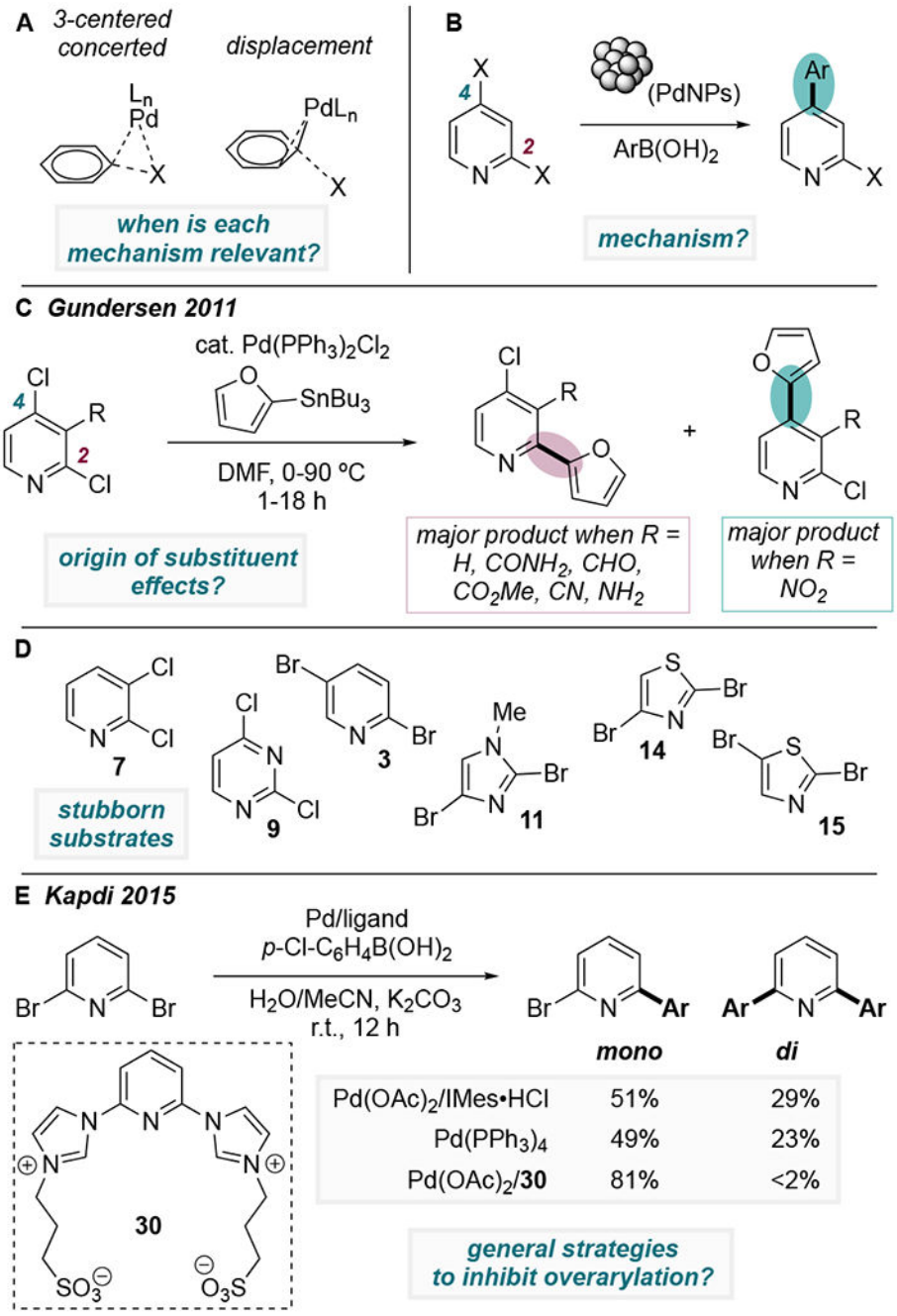
Conditions B:
Pd-PEPPSI-IPr (2.5 mol %), NaOAc (2 equiv), KI (1 equiv), PEG400, 100 °C, overnight
then
Pd-PEPPSI-IPr (2.5 mol %), Na_2CO_3 (1 equiv), 100 °C, another overnight

B *Neufeldt 2022*



Scheme 10.

(A) Modified Reaction Conditions Give Unusually High Selectivity with Pd/IPr.[24] (B) Control Reaction in the Absence of IPr Shows that Selectivity is Not Ligand-Controlled Under These Conditions.[25]

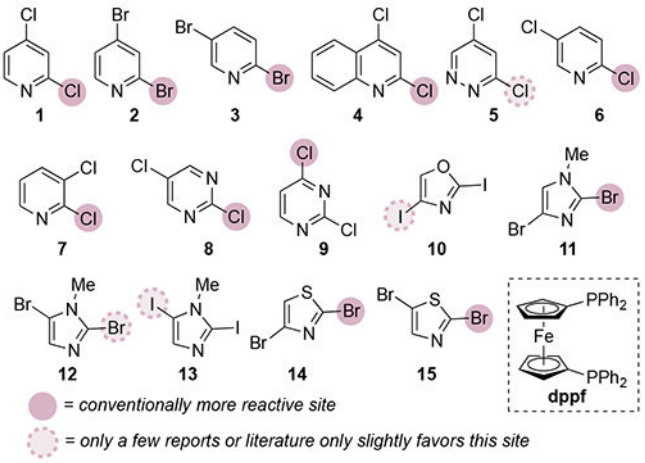


Scheme 11.

Challenges and Opportunities: (A) Understanding Significance of Different Mechanisms for Oxidative Addition, (B) Mechanistic Origin of Selectivity with Multinuclear Pd, (C) Substituent Effects on Selectivity, (D) Inverting Selectivity with “Stubborn” Substrates, (E) Minimizing Unwanted Difunctionalization.

Table 1.

Conventional Site Selectivity for Substrates Discussed in this Perspective.



Substrate	Total Examples[a]	Percentage of Examples with Conventional Selectivity (%)[b]	Percentage of Examples with PPh_3 or dppf (%)[c]
1	186	81	43
2	143	92	81
3	822	97	77
4	77	94	52
5	68	(56)	50
6	164	93	49
7	223	99	52
8	162	88	36
9	1284	99	92
10	23	(57)	22
11	15	100	40
12	11	(55)	36
13	1	(100)	0
14	59	100	78
15	222	100	66

[a] Total number of examples of Pd-catalyzed cross-coupling to form a C—C or C—N bond, according to a SciFinder search.[5]

[b] Percentage of examples for which the major product is indicated to result from coupling at the highlighted position. Values in parentheses indicate that the literature is near-evenly divided in describing selectivity or the number of examples is too small to evaluate.

[c] Percentage of examples for which PPh_3 or dppf were included in the reaction conditions.