Unconventional Site-Selectivity in Palladium-Catalyzed Cross-Couplings of Dichloroheteroarenes under Ligand-Controlled and Ligand-Free Systems

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Abstract

Halides adjacent to nitrogen are conventionally more reactive in Pd-catalyzed cross-couplings of dihalogenated *N*-heteroarenes. However, a very sterically hindered *N*-heterocyclic carbene ligand is shown to promote room-temperature cross-coupling at C4 of 2,4-dichloropyridines with high selectivity (~10:1). This work represents the first highly-selective method with broad scope for C4-coupling of these substrates where selectivity is clearly under ligand-control. Under the optimized conditions, a broad scope of substituted 2,4-dichloropyridines and related compounds undergo cross-coupling to form C4—C$_{(sp2)}$ and C4—C$_{(sp3)}$ bonds using organoboron, -zinc, and -magnesium reagents. The synthetic utility of this method is highlighted in multistep syntheses that combine C4-selective cross-coupling with subsequent nucleophilic aromatic substitution reactions. The majority of the products herein (71%) have not been previously reported, emphasizing the ability of this methodology to open up underexplored chemical space. Remarkably, we find that ligand-free "Jeffery" conditions enhance the C4-selectivity of Suzuki coupling by an order of magnitude (>99:1). These ligand-free conditions enable the first C5-selective cross-couplings of 2,5-dichloropyridine and 2,5-dichloropyrimidine.
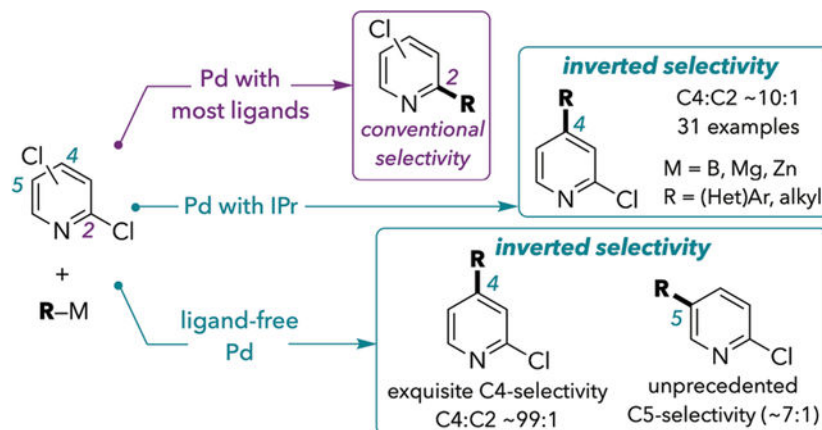
Graphical Abstract

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INTRODUCTION

Nitrogen-containing heterocycles are privileged scaffolds in discovery-oriented synthesis such as medicinal chemistry. Heteroaromatic cores can be elaborated through cross-coupling reactions, which are among the most widely used methods in organic synthesis.[1] Heteroarene starting materials containing multiple halogen leaving groups are practical building blocks since cross-coupling often occurs with predictable selectivity to give a product that retains one halide. Halides, especially chlorides, are valuable structural features of drug-like molecules. In fact, 15% of the unique small molecule drugs approved by the FDA from 1994 to 2012 are chlorinated.[2] For 6-membered nitrogen-containing heteroarenes, cross-coupling typically takes place at a C—X bond adjacent to nitrogen, if present.[3] It is generally very challenging to invert the conventional site preference to react at a C—X bond distal to nitrogen. As such, innate substrate biases leave significant chemical space underexplored by organic synthesis.

Like other nitrogen-containing heterocycles, 2,4-dichloropyridines nearly always undergo cross-coupling adjacent to nitrogen (at C2, example in Scheme 1A, left).[4,5,6,7] Houk and Merlic explained this selectivity based on a distortion-interaction model: the C2—Cl bond is weaker, and is therefore easier to distort into the transition state geometry.[8] C2 is also more positively charged due to its proximity to nitrogen, which may enhance attractive interactions with a reductant such as Pd(0). Preferential cross-coupling at C4 to leave a C2-chloride intact is possible if C4 is substituted by bromide or iodide, but heteroarenes containing mixed halogens are often much less accessible than dichlorinated substrates.

Dai, Chen, and coworkers provided the first evidence that 'innate' selectivity could be inverted by judicious ligand choice.[9] In the presence of the bulky monophosphine QPhos, 1 undergoes Suzuki-Miyaura cross-coupling preferentially at C4, albeit with modest selectivity and yield (Scheme 1A). In contrast, the diphosphine dppf promotes conventional

selectivity leading exclusively to the C2-coupled product. In 2019, we reported that the room-temperature Pd/SIPr-catalyzed cross-coupling of **2** gives exclusive reaction at the C4-triflate (Scheme 1B, right).[10] This result was surprising, not only because the C2 site of di(pseudo)halogenated pyridines is normally more reactive toward cross-coupling, but also because Pd/SIPr is usually *chemo*selective for chloride over triflate(Scheme 1B, left). Based on the anomolous selectivity for the reaction of **2** in Scheme 1B, we began exploring the use of the *N*-heterocyclic carbene (NHC) ligand SIPr and its unsaturated analog IPr for C4-selective cross-coupling of dichloropyridines. During the course of our investigations, Yang and coworkers reported the use of a Pd(PEPPSI)(IPr) catalyst for C4-selective Suzuki-Miyaura cross-coupling of 2,4-dichloropyridines.[11] A series of standard optimization reactions using **1** at 60–100 °C revealed that the Pd(PEPPSI)(IPr) catalyst provides C4-selectivity ranging from 2.5 : 1 to 10.4 : 1, varying with solvent and base. Intriguingly, a ten-fold improvement in selectivity was found upon switching to unusual conditions that employ KI, NaOAc, and PEG400, together with the addition of a second batch of Pd(PEPPSI)(IPr) and a second base (Na_2CO_3) after ~12 h (Scheme 1C).

Here, we report that the use of IPr under mild conditions (often room temperature) enables a broader scope of C4-selective cross-couplings of 2,4-dichloropyridines and related substrates (Scheme 1D, left). Control studies demonstrate that site-selectivity is ligand-controlled under the conditions that we report. However, we further disclose that ligand is *not* necessary to achieve high C4-selectivity under some high temperature conditions, including those previously reported by Yang et al. We find that ligand-free conditions analogous to those used in the Jeffery-Heck reaction lead to much higher C4-selectivity than can be achieved under ligand-control (~99:1 versus ~10:1 for reactions of **1**, Scheme 1D, right). These ligand-free conditions enable unprecedented C5-selectivity in the cross-coupling of 2,5-dichloropyridine and 2,5-dichloropyrimidine. At present, the ligand-free conditions are less general than the ligand-controlled system. Preliminary evidence suggests that the unprecedented selectivity in the absence of strongly coordinating ligands (e.g., phosphines or NHCs) may be a consequence of multinuclear Pd species.

RESULTS AND DISCUSSION

Initial Discovery of C4-Selective Suzuki Coupling.

The unexpected C4-OTf selectivity shown in Scheme 1B led us to apply our previously reported reaction conditions[10] to the Suzuki-Miyaura cross-coupling of 2,4-dichloropyridine (**1**). The Hazari precatalyst (η^3-1-*t*Bu-indenyl)Pd(SIPr)(Cl)[12] (**3a**) was used with KF as a base in THF at room temperature (Table 1, entry 1). Gratifyingly, these conditions afforded **1b** as the major product, resulting from reaction at C4. The crude ratio of **1a** : **1b** = 1 : 8 reflects much higher C4-selectivity than had been previously reported with QPhos (Scheme 1A), and is similar to the selectivity later reported by Yang during most of their optimization studies.[11] The yield of **1b** increased when K_2CO_3 was used as the base (entry 2), and selectivity and yield improved slightly upon switching to catalyst **3b** containing the unsaturated analogue IPr (entry 3). Similar results were obtained in benzene (entry 5), but the polar solvents DMF and propylene carbonate led to an erosion of selectivity (entries 6–7).[13] The steric bulk of IPr appears to be important for selectivity: when using the smaller

ligands SIMes and IMes, much more cross-coupling at C2 was observed (entries 9–10). Interestingly, the unsaturated ligand IMes is slightly more selective than its saturated analog, SIMes. This observation parallels the trend seen with IPr versus SIPr (compare entries 5 and 8). Use of a ligand whose sterics are intermediate between SIPr and SIMes (SIMix) affords intermediate selectivity (entry 11). Finally, the ligand IPent, which bears longer alkyl *ortho*-substituents, promotes overarylation leading to a mixture of products **1b** and **1c** (entry 12).[14] None of **1b** and only trace **1a** was detected when the ligand was omitted (entries 4 and 13), demonstrating the critical role of the NHC ligand in both the selectivity and reactivity of the catalyst under these conditions. The mechanistic origin of the observed ligand-controlled selectivity is the topic of further study in our group and will be reported in the near future. In brief, our mechanistic studies indicate that IPr favors oxidative addition at $12e^-$ Pd(0), whereas reaction at $14e^-$ Pd(0) is more prominent with other ligands.

Scope of the C4-Selective Suzuki Coupling.

With optimized conditions in hand (Table 1, entries 3 and 5), we next examined the scope of aryl boronic acids in the Suzuki coupling. Substrate **1** undergoes Pd/IPr-catalyzed cross-coupling with diverse arylboronic acids (Scheme 2), affording the C4-coupled products in moderate to good isolated yields. Boronic esters are also competent cross-coupling partners in the reaction to form **1b**. The conditions are tolerant of aldehyde, nitrile, and alkene functional groups on the boronic acid coupling partner (**4b-6b**). Using 4-chlorophenylboronic acid, the major product **8b** results from reaction of the 4-pyridyl chloride, leaving both the 2-pyridyl and the aryl chloride intact. A pyrazoleboronic acid reacts well (**10b**), but poor conversions were observed with other heteroarylboron reagents (see SI). This limitation may be addressed through the use of heteroarylzinc or magnesium reagents instead of boronic acids (*vide infra*).

The optimized conditions enable Suzuki-Miyaura coupling of 2,4-dichloropyridines with diverse substituents at the 3-, 5-, and 6-positions. Aldehyde, nitrile, and unprotected amines are well-tolerated, and no competing amination products were detected in the reactions of aminopyridines. Interestingly, the C4-selectivity is eroded when there is an amino substituent at the 3- or 6-position (**14b** and **18b**), but high selectivity is retained when the amino group is at the 5-position (**16b**). This observation suggests that the ability of substituents to coordinate to palladium might play a role in the observed site selectivity. A limitation of this method is the substrate with a 6-trifluoromethyl group (**25**). Whereas diarylation is seen in ~5%–20% yield for most of the other reactions in Scheme 2, the major product of the reaction of **25** corresponds to diarylation, despite the use of only 1 equivalent of arylboronic acid (see SI). In addition to dichloropyridines, the analogous 2,4-dichloroquinoline and 2,4-dichloro-1,8-naphthyridine substrates undergo C4-selective coupling (**19b** and **21b**). These conditions are also effective for cross-coupling at the conventionally disfavored C5-site of 3,5-dichloropyridazines (**22b-24b**).[9] Additional chloride substituents at less electrophilic sites are well-tolerated, including at the 5-position of pyridine and at the 8-position of quinoline (**17b** and **20b**). However, bromide substituents react more quickly than C4-chloride (**27–28**). 2,4-Dibromopyridine (**26**) does not display the same behavior as its dichloro analogue; **26** leads to both C4-arylated and diarylated compounds as major products. Finally, these conditions are not effective for cross-coupling

distal to nitrogen using substrates **29** or **30**. With these substrates, the major product results from reaction at C2—Cl, representing conventional selectivity.

C4-Selective Kumada and Negishi Couplings.

The Pd/IPr catalytic system is also effective for promoting C4-selective cross-coupling with organozinc and organomagnesium nucleophiles. Although the Suzuki coupling is mostly limited to arylboronic acids, Negishi and Kumada conditions enable installation of heteroaryl and alkyl groups in good yield (Scheme 3). For example, a 2-pyridyl group was introduced at the C4 position of **1** using the corresponding Grignard reagent (product **31b**); this group is notoriously challenging to install through Suzuki coupling methods.[15] Secondary and primary alkyl Grignard reagents were effective coupling partners (**32b** and **33b**), and C4-methylation and benzylation could be achieved using zinc reagents (**35b** and **36b**). Interestingly, the selectivity of these reactions appears to be influenced by the identity of the coupling partner. Products **31b** and **33b** were the only products observed by GCMS from their respective reactions, whereas the C2-coupled compounds were minor products in the other reactions. This phenomenon may reflect decomposition of some C2-coupled products, leading to artificially high C4:C2 ratios (see SI).

Application to Multi-Step Syntheses.

We envisioned that the C4-selective cross-coupling methods could be particularly useful for accessing pyridine motifs with a C—C bond at C4 and a C—heteroatom bond at C2 ("substitution pattern **B**", Scheme 4A). Nucleophilic aromatic substitution (S_NAr) reactions are a commonly used strategy for introducing heteroatom substituents onto pyridine. For 2,4-dihalopyridines, transition metal-free S_NAr reactions tend to proceed at C4.[16] Conversely, as discussed above, the conventional site for *cross-coupling* reactions of these substrates is C2. As such, sequential cross-coupling and S_NAr reactions are useful for generating products with substitution pattern **A** based on typical selectivity, independent of the order of these steps. However, the complementary pattern **B** is not generally accessible by conventional methods.

Three compounds with substitution pattern **B** were prepared by Pd/IPr-catalyzed C4-selective cross-coupling followed by S_NAr reactions. The use of thiolate and iodide nucleophiles for the S_NAr steps enabled synthesis of products **37** and **38** (Scheme 4B). We were also able to apply this strategy to a novel synthesis of the Bruton's tyrosine kinase inhibitor **40**. The previously reported synthesis of this compound required 5 synthetic steps providing an overall yield of 3%.[17] However, our 2-step synthesis enables access to **40** in 66% overall yield.

Role of Catalyst Speciation in C4-Selectivity.

We were intrigued by the exceptional ~99:1 selectivity achieved under Yang et al.'s unusual conditions, as our own experience suggested that this high selectivity was uncharacteristic of a Pd/IPr catalyst. We hypothesized that selectivity might not be under ligand-control under the final optimized conditions that were previously reported.

Upon conducting ligand-free control reactions, we found that IPr is not necessary for the C4-selectivity in the system reported by Yang et al. (Scheme 5B). The C4-coupled product is formed in excellent selectivity using $PdCl_2$ *in the absence of added ligands*. As such, the selectivity in Yang's high-temperature reaction is not controlled by IPr and its mechanistic origin is not the same as that of the room temperature Pd/IPr-catalyzed conditions that we report here. Yang et al. suggest that KI might initially react with **1** to form 2-chloro-4-iodopyridine, which then undergoes selective cross-coupling at C4—I. However, inspired by a recent report by Fairlamb,[18,19] we were intrigued by the possibility that the high C4-selectivity in the Yang system might be attributed to a change in catalyst speciation from mono- to multi-nuclearity. Thus, we turned to alternative cross-coupling conditions that have been well-established to promote formation of palladium nanoparticles by applying "Jeffery-Heck" conditions toward the Suzuki coupling of **1** (Table 2). These so-called "Jeffery" conditions are characterized by the use of simple palladium salts, inorganic bases, and tetraalkylammonium additives.[20,21]

Gratifyingly, ligand-free Jeffery-type conditions using $PdCl_2$, Na_2CO_3, and 3–5 equivalents of NBu_4Br were found to afford remarkable C4-selectivity for the Suzuki-Miyaura coupling of **1** (Table 2, entries 1–2, **1a : 1b** = 1 : >99 by GC analysis). Comparable selectivity but somewhat lower conversion was observed with $Pd(OAc)_2$ or Pd_2dba_3 (entries 3 and 4). Similar results were obtained using NBu_4Cl instead of the bromide salt (compare entries 1 and 5), indicating that selectivity cannot be explained by initial Cl/Br exchange at C4. The use of only 1 equivalent of NBu_4Br (entry 6), replacing the halide with a noncoordinating anion such as PF_6 (entry 7), or complete omission of the quaternary ammonium salt (entries 8–9) results in diminished selectivity and yield of **1b**, consistent with the known roles of both coordinating anions and non-coordinating cations on stabilizing nanoparticles.[22] Added water has a marginally detrimental effect on selectivity when using 3 equiv of NBu_4Br (entries 10–11), but the combination of H_2O (5 equiv) and NBu_4Br (5 equiv, entry 14) appeared to improve conversion for some of the reactions in Scheme 6. Finally, lower catalyst loading (entry 12) or lower temperature (entry 13) adversely affect selectivity and yields of **1b**.

The optimized Jeffery-type ligand-free conditions are general to coupling of **1** and **19** with boronic acids bearing both electron-donating and electron-withdrawing functional groups (Scheme 6). In all cases, C2- and diarylation products were absent or observed in only trace quantities. As such, product purification is more facile compared to the Pd/IPr conditions. Remarkably, 2,5-dichloropyridine and 2,5-dichloropyrimidine undergo preferential coupling at C5 to afford products **29b** and **30b**. *This selectivity is unprecedented*: all previously reported cross-couplings of these substrates with spectroscopically-supported structural assignments proceed through C2—Cl cleavage.[23,24,25] Yields are only modest with these substrates as well as with many substituted 2,4-dichloropyridines and related electrophiles. Current work in our group aims to uncover the mechanistic origin of the unique selectivity under ligand-free conditions. We anticipate that mechanistic insight will enable improvements to the reaction scope.

CONCLUSION

Ligand-controlled selectivity is demonstrated with a Pd/IPr catalytic system. This system is effective for C4-selective Suzuki, Kumada, and Negishi cross-couplings of a variety of substituted 2,4-dichloropyridines and related substrates. This methodology allows installation of aryl, heteroaryl, and alkyl groups at the C4 position of pyridine while retaining a chloride substituent at C2. If desired, the chloride can subsequently be replaced with a different heteroatom through an S_NAr reaction. This synthetic sequence comprising C4-selective cross-coupling followed by S_NAr provides products with a substitution pattern that can be challenging to access through more conventional methods. The mechanistic origin of ligand-controlled inversion of typical site-selectivity is the focus of an upcoming report.

Intriguingly, ligand-free "Jeffery" conditions are found to increase the C4-selectivity in a Suzuki coupling of 2,4-dichloropyridine by an order of magnitude. For the first time, C5-selective cross-coupling of 2,5-dichloropyridine and 2,5-dichloropyrimidine is achieved through the use of these ligand-free conditions. By analogy to the Jeffery-Heck reaction, it is likely that palladium nanoparticles are involved under these ligand-free conditions. Ongoing work in our group examines the mechanistic basis for this atypical selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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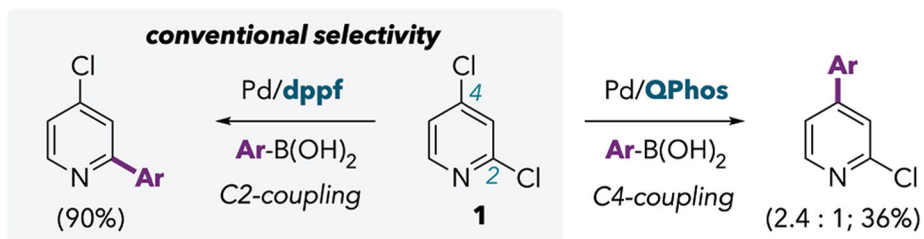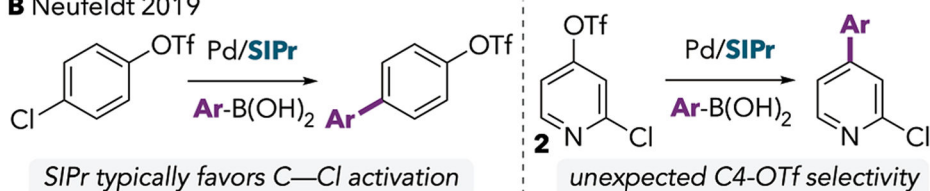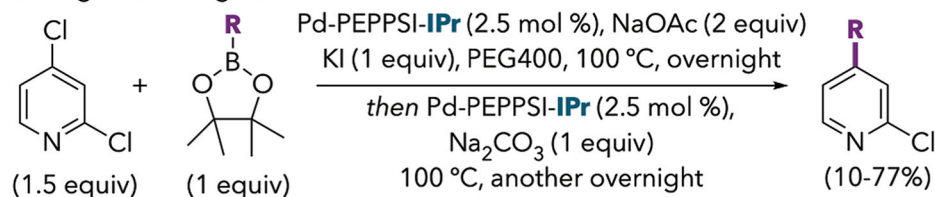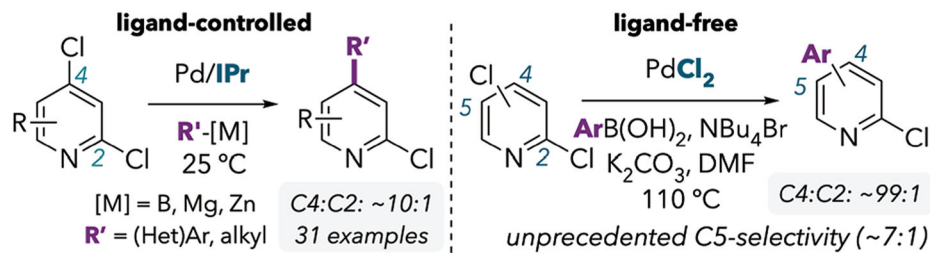
assignment of the products, see(a)Zheng L-L; Yin B; Tian X-C; Yuan M-Y; Li X-H; Gao F Pd/Cu bimetallic co-catalyzed direct 2-arylation of benzoxazole with aryl chloride. Tetrahedron Lett. 2019, 60, 151316;(b)Al-Khawaldeh I; Yasiri MJA; Aldred GG; Basmadjian C; Bordoni C; Harnor SJ; Heptinstall AB; Hobson SJ; Jennings CE; Khalifa S; Lebraud H; Martin MP; Miller DC; Shrives HJ; Souza JV; Stewart HL; Temple M; Thomas HD; Totobenazara J; Tucker JA; Tudhope SJ; Wang LZ; Bronowska AK; Cano C; Endicott JA; Golding BT; Hardcastle IR; Hickson I; Wedge SR; Willmore E; Noble MEM; Waring MJ An Alkynylpyrimidine-Based Covalent Inhibitor That Targets a Unique Cysteine in NF-κB-Inducing Kinase. J. Med. Chem 2021, 64, 10001–10018. [PubMed: 34212719]

A Dai, Chen 2013

conventional selectivity

A Dai, Chen 2013

B Neufeldt 2019

SIPr typically favors C—Cl activation   *unexpected C4-OTf selectivity*

C Yang, Liu, Huang 2020


D *this work*
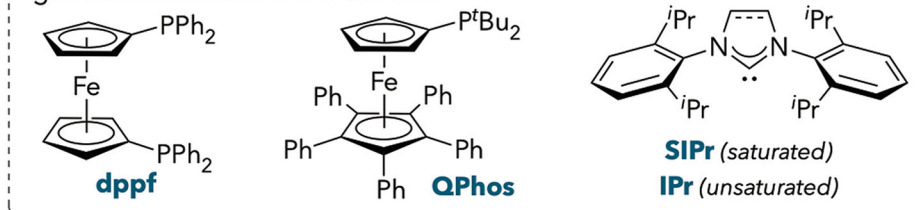
Scheme 1.
Ligand Effects on the Cross-Coupling Selectivity of 2,4-Dichloropyridines
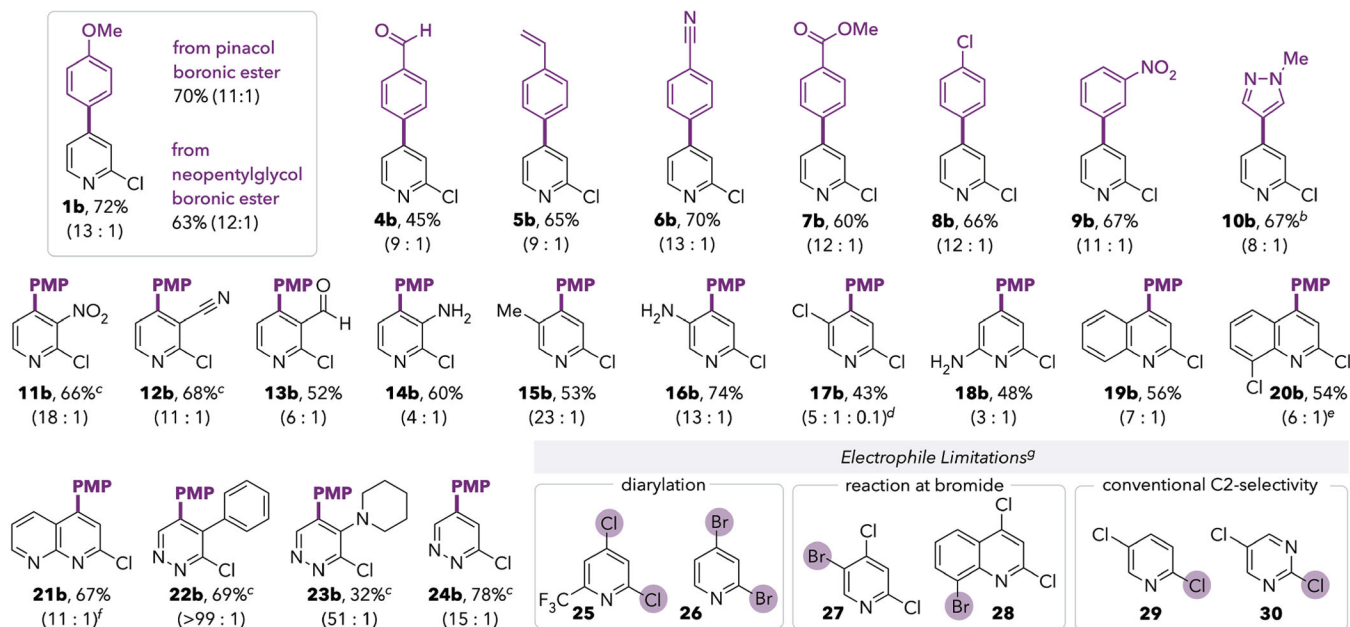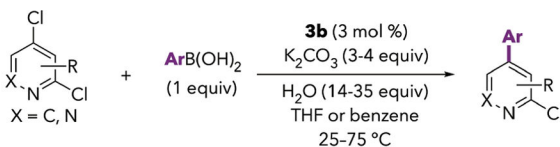
Scheme 2.

Scope of C4-Selective Suzuki-Miyaura Cross-Couplings Catalyzed by Pd/IPr[a]

[a]Isolated yields of products shown. Ratios are the crude ratio of C4:C2-coupled product prior to purification, based on GC signal integrations. ~5–20% diarylation was observed in all cases unless otherwise indicated (see SI for isolated yields when available). Reactions were conducted at room temperature unless otherwise indicated. [b]Reaction conducted at 75 °C. [c]Reaction conducted at 60 °C. [d]Ratio represents C4:C2:C5-coupled products. [e]No cross-coupling at C8 was detected. [f]3f (3 mol %) was used as the catalyst instead of 3b. [g]See SI for details.
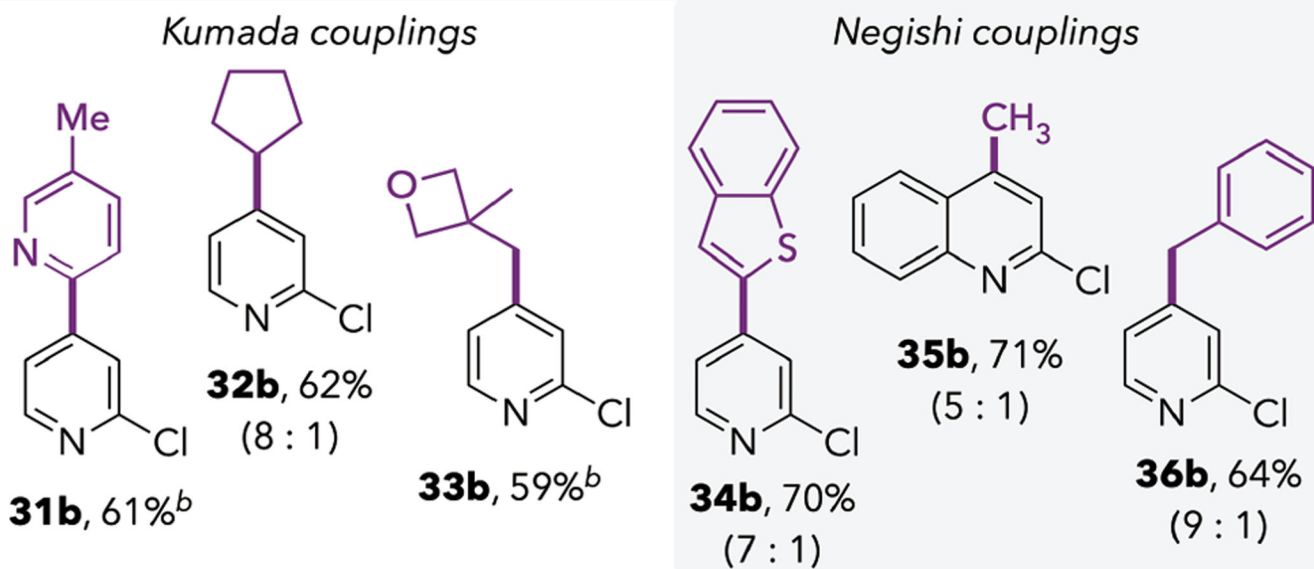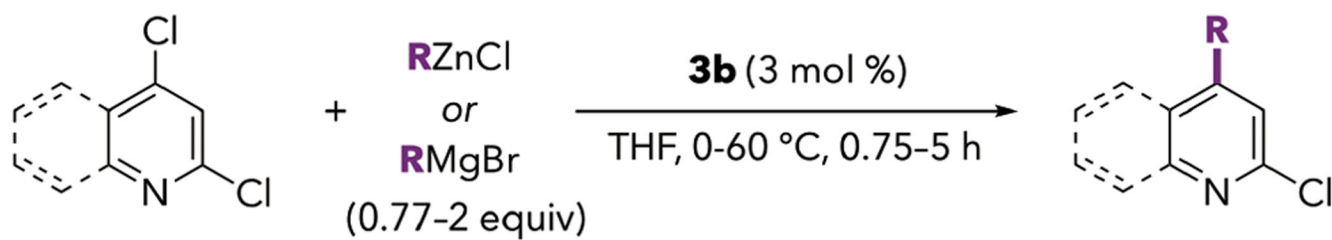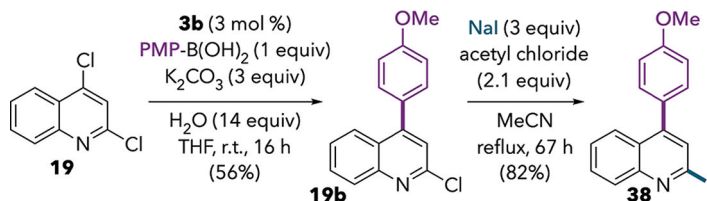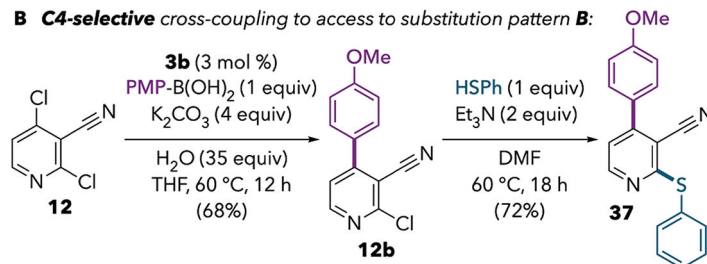
Scheme 3.

C4-Selective Negishi and Kumada Couplings of 2,4-Dichloropyridine and 2,4-Dichloroquinoline[a]

[a]Isolated yields of product shown. Ratios are the crude ratio of C4:C2-coupled product prior to purification, based on GC signal integrations. [b]Product shown was the only product observed.
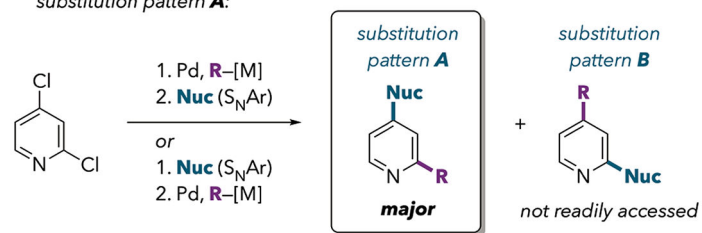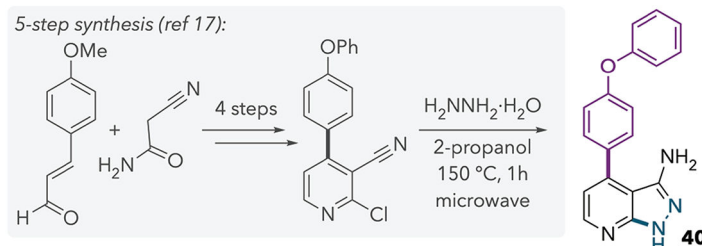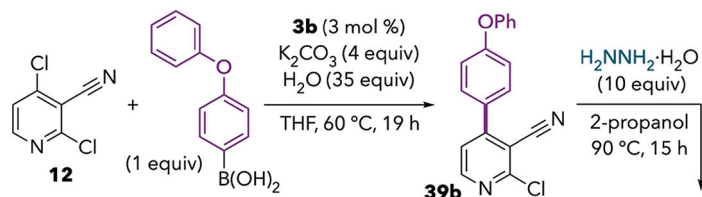
Scheme 4.
Sequential C4-Selective Cross-Coupling and S$_N$Ar Enable Access to a Challenging
Substitution Pattern

A Yang, Liu, Huang 2020

PEPPSI-**IPr** (2.5 mol %), NaOAc (2 equiv)
KI (1 equiv), PEG400, 100 °C, overnight

then PEPPSI-**IPr** (2.5 mol %),
Na₂CO₃ (1 equiv)
100 °C, another overnight

1b (65%)
(only product reported)
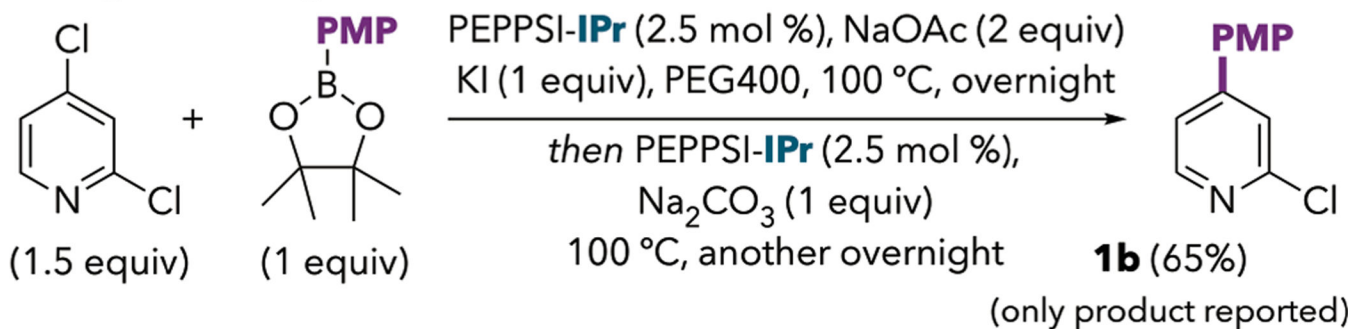
B control reaction (this work)

PdCl₂ (2.5 mol %), NaOAc (2 equiv)
KI (1 equiv), PEG400, 100 °C, overnight

then **PdCl₂** (2.5 mol %), Na₂CO₃ (1 equiv)
100 °C, another overnight

*ligand-free reaction gives same results:
selectivity is not ligand-controlled*

1b (60%)
>60:1
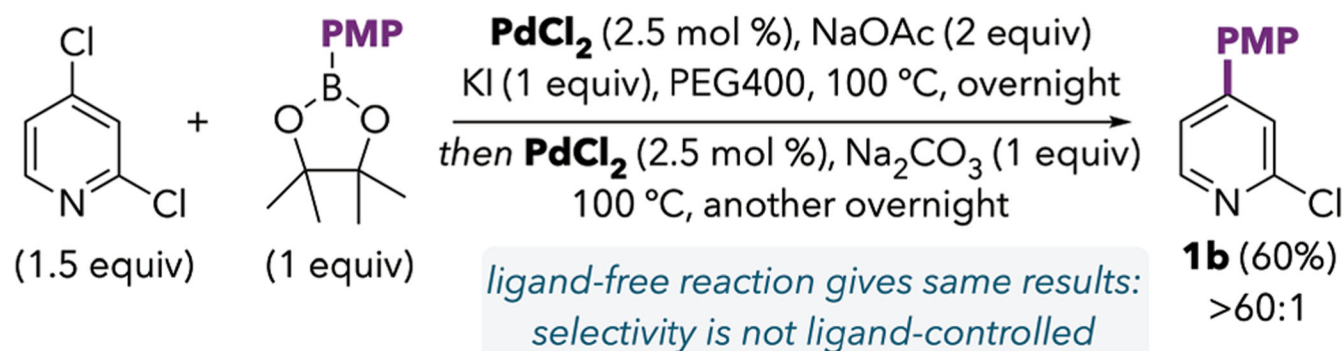
Scheme 5.
Control Reaction Based on Previously Reported C4-Selective Coupling Shows that
Selectivity is Ligand-Independent Under the Reported Conditions

A C4-selectivity

1b, 75% (92%)
(>99 : 1)

41b, 64%
(>99 : 1)

42b, 62% (75%)
(>99 : 1)

43b, 65%
(53 : 1)

44b, 49%
(>99 : 1)

B C5-selectivity

29, Y = CH
30, Y = N

(1.1 equiv)

Y = CH, **29b**, 20% (28%), (7.9 : 1)
Y = N, **30b**, 18% (27%), (4.8 : 1)
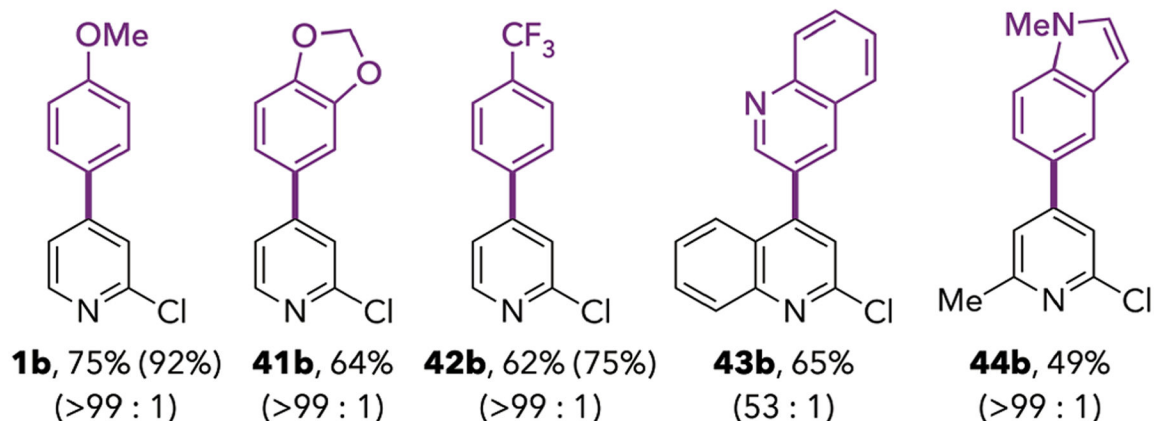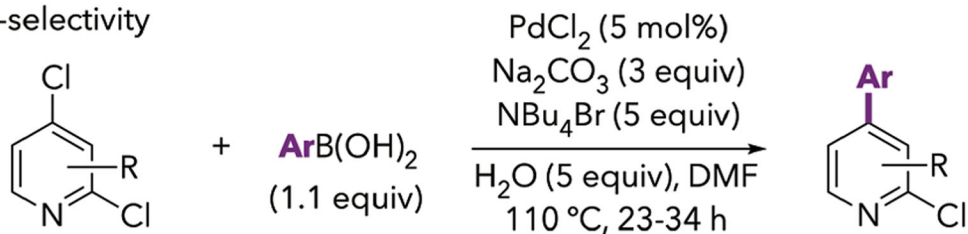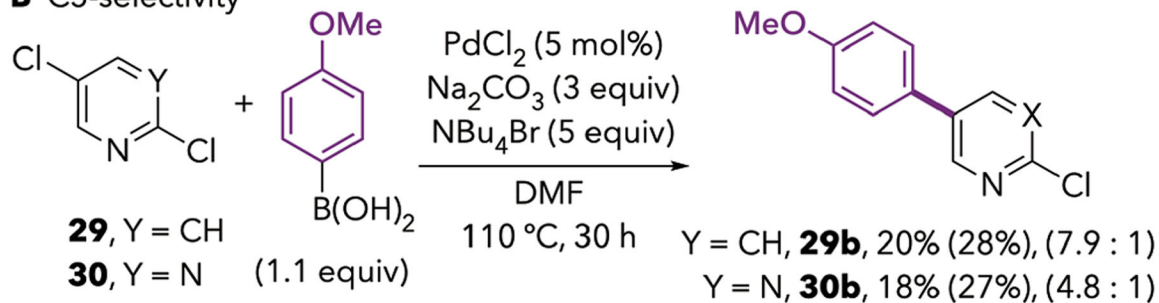
Scheme 6.
Scope of C4-Selective Suzuki-Miyaura Cross-Couplings Under Ligand-Free Catalysis[a]
[a]Isolated yields are reported. Yields in parentheses are the calibrated GC yields of the indicated product prior to purification. Ratios are the crude ratio of C4:C2- or C5:C2-coupled products prior to purification, based on GC signal integrations.

Table 1.

Optimization of the Pd/NHC-Catalyzed C4-Selective Suzuki-Miyaura Coupling[a]
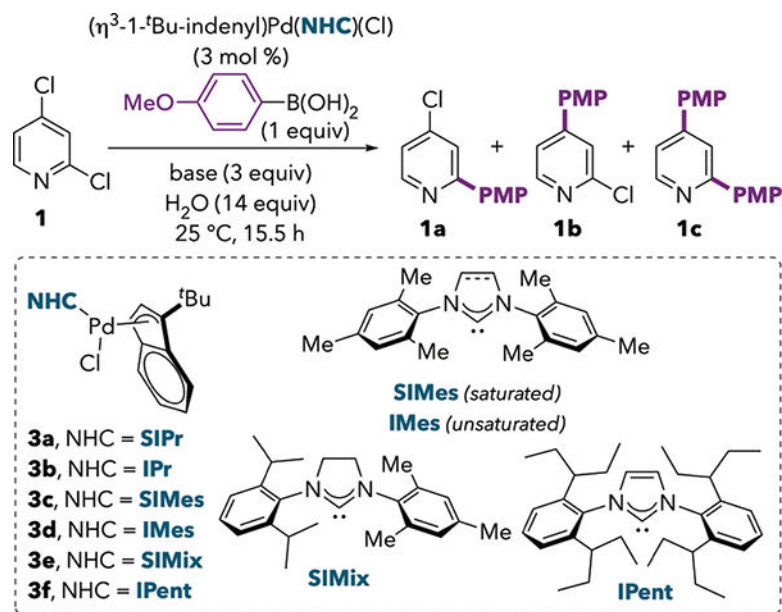
entry	NHC	solvent	1a (%)	1b (%)	1c (%)	1a : 1b
1[b]	SIPr	THF	5	39	5	1 : 8
2	SIPr	THF	7	66	10	1 : 9
3	IPr	THF	7	69	8	1 : 10
4[c]	--	THF	1	<1	0	--
5	IPr	C_6H_6	8	70	6	1 : 9
6	IPr	DMF	8	47	15	1 : 6
7	IPr	PC[d]	9	45	17	1 : 5
8	SIPr	C_6H_6	9	64	8	1 : 7
9	SIMes	C_6H_6	24	35	3	1 : 1.5
10	IMes	C_6H_6	23	40	3	1 : 1.7
11	SIMix	C_6H_6	8	34	2	1 : 4
12	IPent	C_6H_6	1	34	23	1 : 34
13[e]	--	C_6H_6	2	0	0	--

[a] GC yields calibrated against undecane as the internal standard. Average of two trials. PMP = *para*-methoxyphenyl.

[b] KF was used instead of K_2CO_3.

[c] No NHC ligand; Pd source was $PdCl_2$ (3 mol %).

[d] PC = propylene carbonate.

[e] No NHC ligand; Pd source was $(\eta^3$-1-^tBu-indenyl)$_2(\mu$-Cl)$_2Pd_2$ (1.5 mol %).

Table 2.

Optimization of the Ligand-Free C4-Selective Suzuki Coupling[a]
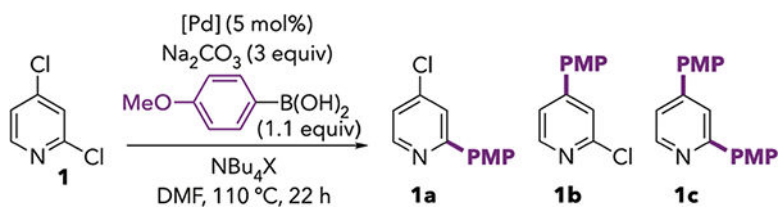
entry	[Pd]	NBu$_4$X (equiv)	1a (%)	1b (%)	1c (%)	1a : 1b (%)
1	PdCl$_2$	Br (3)	0.5	81	0.4	1 : >99
2	PdCl$_2$	Br (5)	0.5	84	0.4	1 : >99
3	Pd(OAc)$_2$	Br (3)	0.7	73	0.4	1 : >99
4	Pd$_2$dba$_3$	Br (3)	0.5	57	0.2	1 : >99
5	PdCl$_2$	Cl (3)	1.1	72	0.5	1 : 65
6	PdCl$_2$	Br (1)	1.2	69	0.7	1 : 58
7	PdCl$_2$	PF$_6$ (3)	3.0	48	3.1	1 : 16
8	PdCl$_2$	--	3.5	56	3.1	1 : 16
9[b]	PdCl$_2$	--	2.1	69	1.6	1 : 33
10[c]	PdCl$_2$	Br (3)	0.9	79	0.6	1 : 88
11[d]	PdCl$_2$	Br (3)	1.1	83	0.7	1 : 75
12[e]	PdCl$_2$	Br (3)	0.8	45	0.5	1 : 56
13[f]	PdCl$_2$	Br (3)	0.3	9	0.5	1 : 29
14[c]	PdCl$_2$	Br (5)	0.8	85	0.5	1 : >99

[a]GC yields calibrated against undecane as the internal standard. Average of two trials.

[b]With KBr (3 equiv).

[c]With H$_2$O (5 equiv).

[d]With H$_2$O (10 equiv).

[e]With 1 mol % of PdCl$_2$.

[f]Reaction run at 25 °C.