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Ligand-Dependent Site-Selective Suzuki Cross-Coupling of 3,5-Dichloropyridazines

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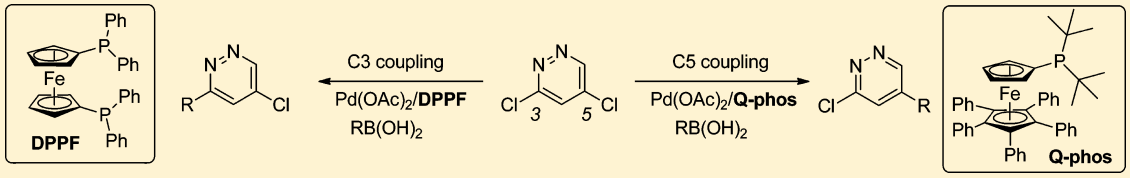
Supporting Information



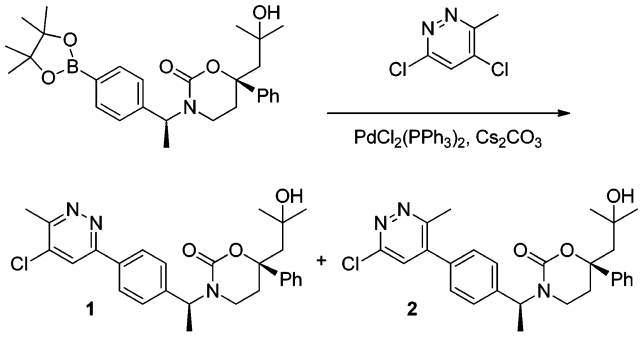
ABSTRACT: General methods for the highly site-selective Suzuki monocoupling of 3,5-dichloropyridazines have been discovered. By changing the ligand employed, the preferred coupling site can be switched from the 3-position to the 5-position, typically considered the less reactive C−X bond. These conditions are applicable to the coupling of a wide variety of aryl-, heteroaryl-, and vinylboronic acids with high selectivities, thus enabling the rapid construction of diverse arrays of diarylpyradazines in a modular fashion.

INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions of polyhalogenated heteroarenes have been investigated extensively and employed as key steps in the synthesis of important biological targets or their direct precursors.[1] For substrates bearing different halogens, chemoselective cross-couplings have been accomplished by taking advantage of reactivity disparities between the halogens.[2] However, with polyhalogenated heteroarenes bearing identical halogens, selectivity is hard to achieve. For example, in the synthesis of 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor, a mixture of compounds **1** and **2** was obtained with no control of regioselectivity (Scheme 1).[3] Thus, in the presence of identical halogens, steric effects, electronic effects, and the presence of directing groups in the reactants are all important factors in the determination of the final site-selectivity.[4] Recently, Strotman and Chobanian reported catalyst-controlled regioselective Suzuki couplings at both positions of dihaloimidazoles and dihalooxazoles.[5]

We have been interested in the synthesis of pyridazine derivatives that could be utilized in our drug discovery program. Ideally, we want to identify catalyst systems capable of selective substitution of C3 and C5 positions, which will give us the flexibility for SAR studies (Figure 1). Selectivity of the palladium-catalyzed cross-coupling reactions of heteroarenes bearing multiple identical halogens is mainly determined by the relative ease of oxidative addition. Based on the recent work by Houk and Merlic, the C−Cl bond α to nitrogen of pyridazine requires less energy to break (bond dissociation enthalpy, BDE,

Scheme 1. Synthesis of 11β-HSD1 Inhibitor 3



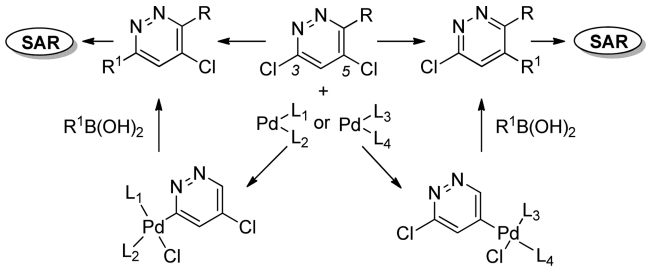


Figure 1. Ligand-dependent site-selective Suzuki cross-couplings.

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Figure 2),[6a] suggesting that the order of reactivity for 3,5-dichloropyridazine is C3 > C5. In other words, it is more challenging to develop a catalyst system to effect selective C5 coupling than C3 coupling. In addition, consideration must be given to avoid bis-coupling products, further complicating the development of highly selective catalyst system.

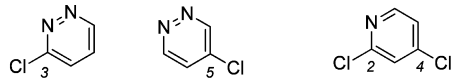


Figure 2. C−Cl BDEs (kcal/mol) of monochloropyridazines and 2,4-dichloropyridine using G3B3 (bold) and B3LYP (in parentheses) calculations.[6a]

RESULTS AND DISCUSSION

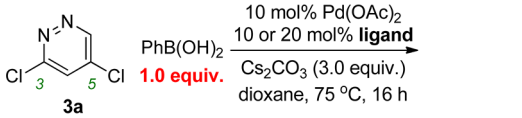
Our initial study focused on examining the ligand effect for the coupling of 3,5-dichloropyridazine (**3a**) and phenylboronic acid (1 equiv). Reactions were conducted with 10 mol % of $Pd(OAc)_2$, 10 (bidentate) or 20 (monodentate) mol % of ligand, and 3 equiv of Cs_2CO_3. Not surprisingly, a mixture of monocoupling products (**4a** and **5a**) and bis-coupling product (**6**) were observed from these reactions. As summarized in Table 1, the ligands exert profound effect on the chemoselectivity of the coupling, a phenomenon that has not been reported before. It was observed that, in general, electron-deficient bidentate ligands prefer coupling at C3 over C5 (Table 1, entries 1, 2, and 4−7) and DPPF gave the highest selectivity.[7] However, the selectivity could be reversed by using electron-rich monodentate ligands (Table 1, entries 8−14), with Q-Phos giving the highest selectivity in this position.[8] It is interesting to note that the electron-rich bidentate ligand DTBPF (Table 1, entry 15) has opposite selectivity as compared to DPPF (Table1, entry 1). This indicates that steric effect of the ligand play a role on the selectivity. We found it particularly surprising that Buchwald's biaryl-based monophosphines predominantly give the bis-coupling product (**6**), even when only 1 equiv of phenylboronic acid was used (Table 1, entries 16−20).[9] Results of the reaction conditions using RuPhos in entry 16 of Table 1 were confirmed on a 1 mmol scale, and **6** was isolated in 76% yield.

With these two complementary ligands (DPPF for C3-coupling and Q-Phos for C5-coupling) in hand, further optimization was perfomed to improve the selectivity and isolated yields. For C3-coupling, in the presence of DPPF, more thorough screens of bases, solvents, catalyst loadings and reaction temperatures were performed. Moreover, for the final conditions, we targeted more practical and glovebox-free conditions. After significant investigation, we established that performing the reaction with 5 mol % of $Pd(OAc)_2$, 5 mol % of DPPF, 2.5 equiv of Cs_2CO_3, in dioxane and water (4:1 ratio) at 70 °C for 20 h afforded the C3-coupled product in the highest yields.

We evaluated the scope of the C3-coupling of 3,5-dichloropyridazines (**3**) with various boronic acids under the optimized conditions, and the results are summarized in Table 2. The scope of the reaction with respect to the aryl boronic acids is broad. For example, electron-neutral (Table 2, entries 1, 2, 3, and 8), electron-rich (Table 2, entries 5, 11, and 12), and electron-poor (Table 2, entries 4, 6, and 7) phenylboronic acids all afford the 3-substituted pyridazines in good yields. Ortho-substituted phenylboronic acids seem to have better selectivity and give higher yields (Table 2, entries 3, 5, and 6) than meta- or para-substituted phenylboronic acids. Besides substituted phenylboronic acids, 5-indolylboronic acid (entry 13) and alkenyl pinacol boronate ester (entry 9) are also suitable under these conditions. We also tested several other electrophiles. The reactions between 4,6-dichloro-3-methylpyridazine (**3b**) and aryl boronic acids formed the desired products in good yields (Table 2, entries 10−13). Lower yields were obtained when a more electron-rich substrate, 4,6-dichloro-3-methoxypyridazine (**3c**), was used (Table 2, entries 14 and 15).

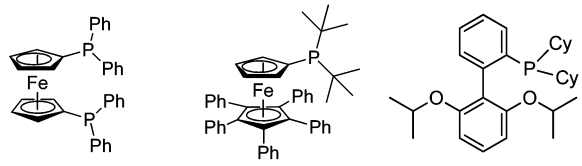
Having accomplished mono C3-couplings of **3**, we then turned our attention to optimize the C5-coupling. The optimization process of C5-coupling was very similar to the C3-coupling although it was more sensitive to the solvent and base efffects. We also determined that a 1:1 ratio of Pd:Q-Phos generated results similar to those with a 1:2 ratio. Additional experimentation with the combination of $Pd(OAc)_2$ and Q-

Table 1. Effects of Ligand on Phenylation of 3,5-Dichloropyridazine[a]



3a **4a** **5a** **6**

entry	ligand[b]	4a[d]	5a[d]	6[d]
1	**DPPF**	**82**	**0**	**18**
2	XantPhos	69	12	19
3	PPh_3[c]	76	0	24
4	DIPPF	61	18	21
5	DPPP	67	21	12
6	DPEPhos	44	35	21
7	(R)-BINAP	44	42	14
8	**Q-Phos**	**4**	**80**	**16**
9	CataCXium A	15	69	16
10	$^tBu_3P$[c]	8	71	21
11	AmPhos	10	79	11
12	AmgenPhos[c]	10	67	23
13	$(o\text{-Tol})_3P$	28	60	12
14	PCy_3[c]	35	38	27
15	DTBPF	16	54	30
16	**RuPhos**[e]	**17**	**4**	**79**
17	S-Phos[e]	21	12	67
18	DavePhos[e]	14	16	70
19	X-Phos[e]	10	15	75
20	BrettPhos	33	19	48



DPPF **Q-Phos** **RuPhos**

[a]All reactions were set up in a glovebox with 10 μmol scale. Ligand/Pd ratios of 2:1 for monodentate ligands and 1:1 for bidentate ligands. [b]Structures of all ligands are available in the Supporting Information. [c]Second-generation biphenyl precatalyst was used. [d]All of the numbers are normalized ratios of integrated peak areas VS internal standard. [e]**3a** was not consumed completely.

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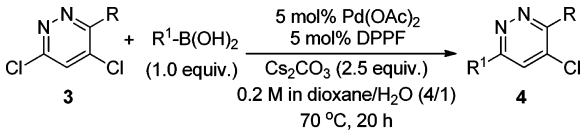
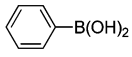
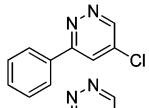
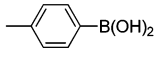
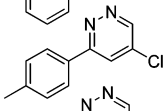
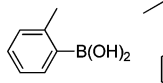
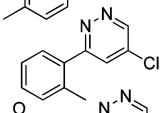
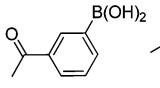
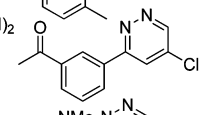
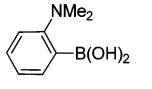
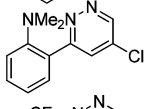
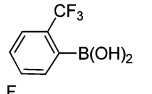
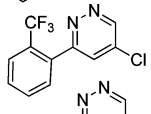
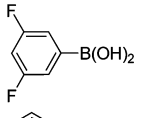
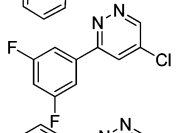
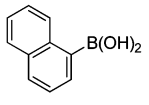
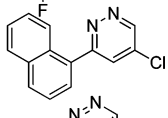
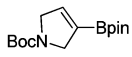
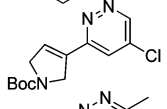
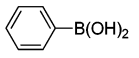
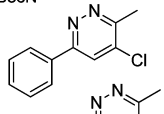
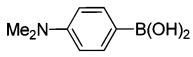
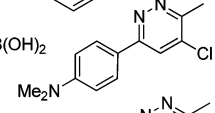
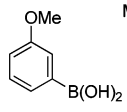
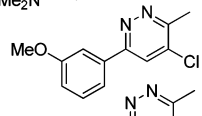
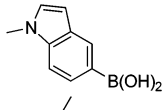
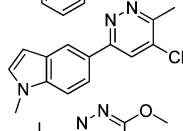
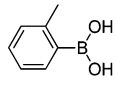
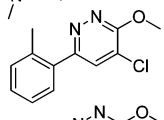
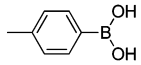
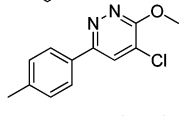
Table 2. C3-Coupling with DPPF[a]

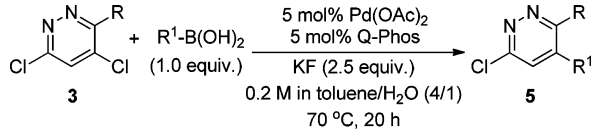


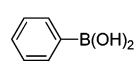
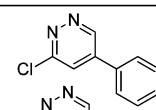
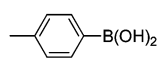
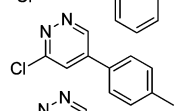
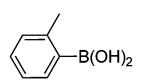
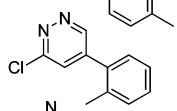
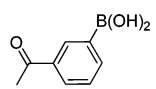
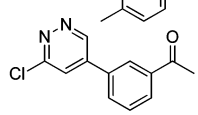
entry	3	R^1-B(OH)$_2$	product (4)		yield/%
1	R = H **3a**			**4a**	73
2	**3a**			**4b**	79
3	**3a**			**4c**	92
4	**3a**			**4d**	82
5	**3a**			**4e**	89[b]
6	**3a**			**4f**	90[b]
7	**3a**			**4g**	74
8	**3a**			**4h**	75
9	**3a**			**4i**	66[c]
10	R = Me **3b**			**4j**	77
11	**3b**			**4k**	70[b]
12	**3b**			**4l**	73
13	**3b**			**4m**	89
14	R = OMe **3c**			**4n**	57
15	**3c**			**4o**	58[b]

[a]All reactions were performed on a 1 mmol scale without glovebox. [b]The final product contains <5% of the other isomer product. [c]The final product contains <10% of the borate dimer.

Phos showed that the reaction with 5 mol % of Pd(OAc)$_2$, 5 mol % of Q-Phos, and 2.5 equiv of KF in toluene and water (4 to 1 ratio) at 70 °C for 20 h afforded the desired product with the best yields. These conditions were then applied to cross-couple a wide variety of electron-rich, electron-poor, and sterically hindered arylboronic acids (Table 3), identical to those utilized in the previously mentioned couplings with DPPF (Table 2). Under these conditions, the selectivity instead showed preference for substitution at the C5 position regardless of the boronic acids that was employed.

Table 3. C5-Coupling with Q-Phos[a]



entry	3	R^1-B(OH)$_2$	product (5)		yield/%
1	R = H **3a**			**5a**	76
2	**3a**			**5b**	61
3	**3a**			**5c**	78
4	**3a**			**5d**	57
5	**3a**			**5e**	57[b]
6	**3a**			**5f**	61[b]
7	**3a**			**5g**	74
8	**3a**			**5h**	53
9	**3a**			**5i**	56
10	R = Me **3b**			**5j**	65
11	**3b**			**5k**	62[b]
12	**3b**			**5l**	57
13	**3b**			**5m**	60[b]
14	R = OMe **3c**			**5n**	67
15	**3c**			**5o**	68[b]

[a]All reactions were performed on a 1 mmol scale without glovebox. [b]The final product contains <5% of the other isomer product.

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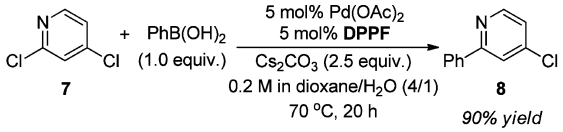
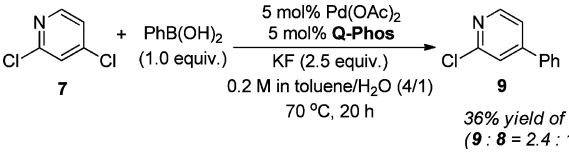
Like dichloropyridazines, dichloropyridines are very important and commonly used synthetic building blocks. While many efforts have been done to achieve site selectivity, most have been in the presence of directing groups.[1,4] Moreover, it is almost impossible to reverse the selectivity based on the recent work by Houk and Merlic, which indicated about 1000 fold of C2/C4 selectivity (Figure 2).[6b] By simply applying Table 2 conditions to 2,4-dichloropyridine (**7**), we were able to achieve predominant C2-coupling and obtain the 2-substituted product (**8**) in 90% yields (eq 1). When the ligand was switched from



(1)



(2)

DPPF to Q-Phos, the regioselectivity was reversed and the 4-substituted product (**9**) was isolated in 36% yields (eq 2). To the best of our knowledge, this is the first example of a C4-coupling of 2,4-dichloropyridine in the absence of a directing group. Further optimization of the conditions for the site-selective cross-coupling of dichloropyridines is under investigation.

CONCLUSIONS

In summary, we have reported the first ligand-dependent site-selective Suzuki coupling of 3,5-dichloropyridazines. In the presence of $Pd(OAc)_2$ and the bidentate ligand DPPF, the 3-substituted product can be obtained, while switching to the monodentate ligand Q-Phos affords the 5-substituted analogs. These reactions exhibit a broad substrate scope with numerous aryl, heteroaryl, and alkenyl boronic acids having been selectively coupled. The ability to cross-couple at either C−Cl bond has allowed us to install a specific aryl or alkenyl group at either of the two positions, leaving open the opportunity to add a wide variety of coupling partners at the other C−Cl bond.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 or 500 NMR spectrometer and calibrated using residual undeuterated solvent as an internal reference. The high-resolution LC/ESI-MS analysis was performed on a LTQ Orbitrap mass spectrometer operated at a resolution of 30000. An aliquot of each compound was injected into an HPLC system consisting of an YMC C18 column, 150 × 4.6 mm, 3.0 μm particle size. The ratio of the crude products is based on crude HNMR or LCMS.

General Procedure for Table 1: Screening Palladium-Catalyzed Suzuki Coupling Conditions with Respect to Ligand, Solvent, Base and Order of Addition. All operations were carried out in a nitrogen-filled glovebox. Commercially available materials were used as received. Reactions for high-throughput screening were performed in 8 × 30 mm borosilicate glass shell vials arranged in 96 well metal blocks with magnetic stirring. Ligands were dispensed to the vials as solutions followed by evaporation of the solvent in vacuo in the nitrogen-filled glovebox. Materials were dispensed to the vials as solution/slurry in the reaction solvent via micropipets. Bases such as Cs_2CO_3 and KF were dispensed either from arrays of 96 vials into which the bases were preweighted robotically in the glovebox or as aqueous solution via micropipets. The palladium source and ligand were premixed in reaction solvent at 25 °C for 15 min before addition of subsequent reagents and starting materials. The metal 96-well block was sealed with a prefluoroelastomeric backed metal top plate, heated to the indicated temperature, and holded for 16 h. Analysis was acomplished by reversed-phase HPLC using an internal standard such as naphthalene to facilitate quantitative HPLC solution assay yield determination.

Representative Procedure A for Table 2 (Table 2, Entry 1, as an Example) and Compound 8. A mixture of 3,5-dichloropyridazine (149 mg, 1.00 mmol), phenylboronic acid (122 mg, 1.00 mmol), palladium(II) acetate (11.23 mg, 0.05 mmol), 1,1′-bis-(diphenylphosphino)ferrocene (27.7 mg, 0.05 mmol), and cesium carbonate(815 mg, 2.50 mmol) in 1,4-dioxane (4.0 mL) and water (1.0 mL) was degassed for 10 min with N_2 and sealed in a microwave vial. The reaction was heated at 70 °C for 20 h. The reaction was cooled to room temperature, diluted with ethyl acetate (20 mL), filtered through Celite, and concentrated. The residue was purified by flash column chromatography (0−100% EtOAc/hexanes) and afforded the product 5-chloro-3-phenylpyridazine (**4a**, 139.9 mg, 0.734 mmol, 73.4% yield) as a white solid. The ratio of the crude products is 82:4:14 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (s, 1 H), 8.08 (d, J = 6.06 Hz; 2 H), 7.89 (s, 1 H), 7.55 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.9, 149.8, 138.8, 135.2, 130.8, 129.3, 127.4, 123.6; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{10}H_8N_2Cl$ 191.0371, found 191.0370.

Compound ***4b***. Representative procedure A in 79% yield (161 mg) as an amorphous solid. The ratio of the crude products is 85:3:12 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 9.07 (s, 1 H), 7.93 (d, J = 7.98 Hz, 2 H), 7.79 (s, 1 H), 7.31−7.27 (m, 2 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.0, 149.6, 141.3, 138.7, 132.4, 130.1, 127.4, 123.3, 21.6; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{11}H_{10}N_2Cl$ 205.0527, found 205.0525.

Compound ***4c***. Representative procedure A in 92% yield (188 mg) as an amorphous solid. The ratio of the crude products is 96:2:2 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.38 (s, 1H), 7.15−7.03 (m, 4H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 149.3, 137.9, 136.4, 136.0, 131.2, 130.0, 129.7, 126.8, 126.3, 20.4; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{11}H_{10}N_2Cl$ 205.0527, found 205.0526.

Compound ***4d***. Representative procedure A in 82% yield (190 mg) as an amorphous solid. The ratio of the crude products is 87:2:11 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.58 (s, 1H), 8.25 (d, J = 7.5 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.60−7.57 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 159.1, 150.2, 139.1, 138.0, 135.8, 131.9, 130.6, 129.8, 127.2, 123.8, 27.0; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{12}H_{10}ON_2Cl$ 233.0476, found 233.0474.

Compound ***4e***. Representative procedure A in 89% yield (209 mg) as an amorphous solid. The ratio of the crude products is 91:2:7 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.19 (s, 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.15 (m, 2H), 2.62 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 152.0, 149.8, 137.6, 132.2, 131.2, 128.8, 127.3, 122.9, 118.5, 44.4; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{12}H_{13}N_3Cl$ 234.0793, found 234.0791.

Compound ***4f***. Representative procedure A in 90% yield (233 mg) as an amorphous solid. The ratio of the crude products is 92:1:5 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.69−7.61 (m, 3H), 7.54 (d, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 150.5, 138.0, 135.5, 132.3, 132.0, 131.9, 130.1, 127.0, 126.9, 124.0 (q, J = 272 Hz); HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{11}H_7N_2ClF_3$ 259.0244, found 259.0242.

Compound ***4g***. Representative procedure A in 74% yield (167 mg) as an amorphous solid. The ratio of the crude products is 83:3:14 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.88 (s, 1H), 7.64−7.62 (m, 2H), 6.99−6.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (d, J = 248 Hz); 163.7 (d, J = 248 Hz); 157.5, 150.7, 139.3, 138.5, 123.7, 110.6 (d, J = 21.0 Hz);

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110.5 (d, J = 21.0 Hz); 106.3 (t, d = 25.0); HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{10}H_6N_2ClF_2$ 227.0182, Found 227.0181.

Compound ***4h***. Representative procedure A in 75% yield (181 mg) as an amorphous solid. The ratio of the crude products is 84:3:13 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.02−7.90 (m, 3H), 7.72 (s, 1H), 7.62−7.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 149.7, 138.1, 134.0, 133.9, 130.8, 130.5, 128.7, 128.6, 127.6, 127.3, 126.4, 125.4, 125.0; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{14}H_{10}N_2Cl$ 241.0527, found 241.0526.

Compound ***4i***. Representative procedure A in 66% yield (185 mg) as an amorphous solid. The ratio of the crude products is 78:3:19 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1 H); 7.70 (s, 1 H); 6.64 (m, 1 H); 4.68−4.62 (m, 2 H); 4.39−4.34 (m, 2 H); 1.19 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 154.5, 150.2, 138.5, 136.1, 128.7, 123.1, 80.2, 54.3, 53.2, 28.7; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{13}H_{17}O_2N_3Cl$ 282.1004, found 282.0999.

Compound ***4j***. Representative procedure A in 77% yield (158 mg) as an amorphous solid. The ratio of the crude products is 86:2:12 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (t, J = 5.88 Hz, 2 H); 7.53−7.55 (m, 1 H); 7.24−7.29 (m, 3 H); 2.58 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 157.2, 138.8, 135.2, 130.3, 129.1, 127.0, 123.5, 20.3; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{11}H_{10}N_2Cl$ 205.0527, found 205.0526.

Compound ***4k***. Representative procedure A in 70% yield (174 mg) as an amorphous solid. The ratio of the crude products is 81:3:16 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 2H), 7.69 (s, 1H), 6.77 (d, J = 9.0 Hz, 2H), 3.03 (s, 6H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 155.8, 152.0, 138.7, 130.0, 128.1, 126.7, 122.6, 40.4, 20.4; HRMS (ESI-Orbitrap) m/z $[M + H]+$ calcd for $C_{13}H_{15}N_3Cl$ 248.0949, found 248.0947.

Compound ***4l***. Representative procedure A in 73% yield (171 mg) as an amorphous solid. The ratio of the crude products is 83:2:15 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.55 (s, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.27−7.23 (m, 1H), 6.88 (d, J = 7.5 Hz, 1H), 3.75 (s, 3H), 2.68 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 158.2, 157.5, 138.9, 136.6, 130.1, 123.7, 119.3, 116.6, 112.0, 55.5, 20.3; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{12}H_{12}ON_2Cl$ 235.0633, found 235.0630.

Compound ***4m***. Representative procedure A in 89% yield (230 mg) as an amorphous solid. The ratio of the crude products is 94:1:5 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 6.58 (s, 1H), 3.80 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 156.4, 130.4, 129.1, 126.7, 123.8, 120.9, 120.4, 110.1, 102.4, 33.2, 25.1; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{14}H_{13}N_3Cl$ 258.0793, found 258.0791.

Compound ***4n***. Representative procedure A in 57% yield (135 mg) as an amorphous solid. The ratio of the crude products is 72:4:24 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.41−7.30 (m, 4H), 4.29 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.3, 158.5, 136.5, 136.2, 131.3, 129.9, 129.5, 127.4, 126.4, 56.1, 20.7; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{12}H_{12}ON_2Cl$ 235.0633, found 235.0631.

Compound ***4o***. Representative procedure A in 58% yield (152 mg) as an amorphous solid. The ratio of the crude products is 74:7:19 (C3 coupling/C5 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 4.18 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 155.9, 140.1, 132.5, 129.9, 127.8, 126.6, 126.3, 55.9, 21.5; HRMS (ESI-Orbitrap) m/z $[M + H]+$ calcd for $C_{12}H_{12}ON_2Cl$ 235.0633, found 235.0630.

Compound ***8***. Representative procedure A in 92% yield (174 mg) as an amorphous solid. The ratio of the crude products is >98:<1:<1 (C2 coupling/C4 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 5.5 Hz, 1H), 8.01 (d, J = 7.0 Hz, 2H), 7.77 (s, 1H), 7.54−7.47 (m, 3H), 7.28−7.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 150.8 144.9, 138.4, 129.9, 129.1, 127.3, 122.5, 121.0; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{11}H_9NCl$ 190.0418, found 190.0417.

Representative Procedure B for Table 3 (Table 3, Entry 1, as an Example) and Compound 9. A mixture of 3,5-dichloropyridazine (149 mg, 1.00 mmol), phenylboronic acid (122 mg, 1.00 mmol), and potassium fluoride (145 mg, 2.50 mmol) in toluene (4.0 mL) and water (1.0 mL) was degassed for 10 min with N_2. Palladium(II) acetate (11.23 mg, 0.05 mmol) and 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene (35.5 mg, 0.05 mmol) were then added, and the solution was further degassed for an additional 5 min. The vial was sealed, and the reaction was heated at 70 °C for 20 h. The reaction was cooled to room temperature and diluted with EtOAc (20 mL), filtered through Celite, and concentrated. The residue was purified by flash column chromatography (0 to 100% EtOAc/hexanes) and afforded the product 3-chloro-5-phenylpyridazine (**5a**, 145.3 mg, 0.762 mmol, 76.2% yield). The ratio of the crude products is 84:7:9 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.40 (s, 1 H), 7.71 (m, 3 H), 7.59 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 149.2, 141.4, 133.3, 131.1, 130.0, 127.5, 124.9; HRMS (ESI-Orbitrap) m/z $[M + H]+$ calcd for $C_{10}H_8N_2Cl$ 191.0371, found 191.0370.

Compound ***5b***. Representative procedure B in 61% yield (124 mg) as an amorphous solid. The ratio of the crude products is 74:8:18 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.07 (s, 1 H), 7.93 (d, J = 7.98 Hz, 2 H), 7.79 (s, 1 H), 7.31−7.27 (m, 2 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.0, 149.6, 141.3, 138.7, 132.4, 130.1, 127.4, 123.3, 21.6; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{11}H_{10}N_2Cl$ 205.0527, found 205.0526.

Compound ***5c***. Representative procedure B in 78% yield (160 mg) as an amorphous solid. The ratio of the crude products is 84:6:10 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 3.0 Hz, 1H), 7.37 (d, J = 3.0 Hz, 1H), 7.20−7.10 (m, 4H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 151.2, 142.8, 135.6, 133.8, 131.4, 130.1, 129.7, 127.7, 126.9, 20.3; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{11}H_{10}N_2Cl$ 205.0527, found 205.0526.

Compound ***5d***. Representative procedure B in 57% yield (134 mg) as an amorphous solid. The ratio of the crude products is 74:8:18 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.29 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.78−7.70 (m, 2H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 157.7, 149.0, 140.5, 138.6, 134.1, 131.7, 130.8, 130.4, 127.2, 125.2, 27.0; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{12}H_{10}ON_2Cl$ 233.0476, found 233.0474.

Compound ***5e***. Representative procedure B in 57% yield (133 mg) as an amorphous solid. The ratio of the crude products is 75:9:16 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.77 (s, 1H), 7.44 (d, J = 6.5, 1H), 7.29 (d, J = 7.5, 1H), 7.20−7.15 (m, 2H), 2.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 152.2, 151.0, 143.2, 131.5, 126.4, 126.3, 123.0, 119.2, 44.2; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{12}H_{13}N_3Cl$ 234.0793, found 234.0790.

Compound ***5f***. Representative procedure B in 61% yield (158 mg) as an amorphous solid. The ratio of the crude products is 78:9:13 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.70−7.62 (m, 2H), 7.53 (s, 1H), 7.35 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 150.4, 140.1, 132.9, 132.6, 131.5, 130.2, 127.8, 127.1, 127.0, 123.8 (q, J = 272 Hz); HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{11}H_7N_2ClF_3$ 259.0244, found 259.0243.

Compound ***5g***. Representative procedure B in 74% yield (168 mg) as an amorphous solid. The ratio of the crude products is 84:6:10 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, acetone-d_6) δ 9.64 (s, 1 H), 8.19 (s, 1 H), 7.71 (d; J = 7.39 Hz; 2 H), 7.28 (t; J = 8.91 Hz; 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.9 (d, J = 246 Hz), 163.7 (d, J = 246 Hz), 157.4, 149.1, 138.8, 138.8, 137.1, 125.4, 111.3 (d, J = 21.0 Hz), 111.2 (d, J = 21 Hz), 105.9 (t, d = 25.4); HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{10}H_6N_2ClF_2$ 227.0182, found 227.0180.

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Compound ***5h***. Representative procedure B in 53% yield (128 mg) as an amorphous solid. The ratio of the crude products is 75:9:16 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.95−7.90 (m, 2H), 7.69 (m, J = 8.0, 1H), 7.60 (s, 1H), 7.56−7.48 (m, 4H), 7.39 (d, J = 6.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 151.8, 142.0, 134.0, 132.0, 130.8, 130.5, 129.2, 128.5, 128.2, 127.9, 127.0, 125.7, 124.2; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{14}H_{10}N_2Cl$ 241.0527, Found 241.0526.

Compound ***5i***. Representative procedure B in 56% yield (157 mg) as an amorphous solid. The ratio of the crude products is 80:7:13 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.31 (s, 1H), 6.67 (d, J = 23 Hz, 1H), 4.23 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 154.0, 147.5, 133.8, 132.2, 130.0, 123.2, 80.5, 54.5, 52.4, 28.7; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{13}H_{17}O_2N_3Cl$ 282.1004, found 282.1001.

Compound ***5j***. Representative procedure B in 65% yield (133 mg) as an amorphous solid. The ratio of the crude products is 82:6:12 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.36 (m, 3H), 7.27−7.22 (m, 3H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 155.1, 143.0, 135.3, 129.6, 129.2, 128.6, 127.5, 21.0; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{11}H_{10}N_2Cl$ 205.0527, found 205.0528.

Compound ***5k***. Representative procedure B in 62% yield (152 mg) as an amorphous solid. The ratio of the crude products is 78:8:14 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 3.00 (s, 6H), 2.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 155.1, 151.2, 143.3, 129.9, 126.6, 122.2, 112.2, 40.4, 21.5; HRMS (ESI-Orbitrap) m/z [M + H]+ calcd for $C_{13}H_{15}N_3Cl$ 248.0949, found 248.0950.

Compound ***5l***. Representative procedure B in 57% yield (134 mg) as an amorphous solid. The ratio of the crude products is 75:8:17 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.85 (s, 1H), 3.84 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 158.1, 155.2, 143.0, 136.8, 130.4, 127.5, 120.8, 114.9, 114.5, 55.7, 21.0; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{12}H_{12}ON_2Cl$ 235.0633, found 235.0632.

Compound ***5m***. Representative procedure B in 60% yield (171 mg) as an amorphous solid. The ratio of the crude products is 79:7:14 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.39 (d, J = 8.53 Hz, 1 H), 7.27 (s, 1 H), 7.13 (m, 2 H), 6.51 (d, J = 3.12 Hz, 1 H), 3.80 (s, 3 H), 2.64 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 155.1, 144.6, 137.0, 130.8, 128.8, 127.7, 126.4, 121.9, 121.6, 110.0, 101.8, 33.3, 21.4; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{14}H_{13}N_3Cl$ 258.0793, found 258.0792.

Compound ***5n***. Representative procedure B in 67% yield (157 mg) as an amorphous solid. The ratio of the crude products is 83:6:11 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 1H), 7.33−7.30 (m, 3H), 7.17 (d, J = 7.5 Hz, 1H), 4.13 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 151.3, 136.5, 134.2, 132.6, 130.6, 130.5, 129.7, 129.5, 126.3, 55.6, 20.0; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{12}H_{12}ON_2Cl$ 235.0633, found 235.0631.

Compound ***5o***. Representative procedure B in 68% yield (161 mg) as an amorphous solid. The ratio of the crude products is 81:7:12 (C5 coupling/C3 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.0 Hz, 2 H), 7.30 (s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 4.11 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 151.6, 140.5, 132.9, 129.6, 129.4, 129.2, 128.4, 55.6, 21.6; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{12}H_{12}ON_2Cl$ 235.0633, found 235.0631.

Compound ***9***. Representative procedure B in 36% yield (68 mg) as an amorphous solid. The ratio of the crude products is 60:25:15 (C4 coupling/C2 coupling/bis coupling): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47−8.45 (m, 1H), 7.68−7.40 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 151.8, 150.3, 137.0, 130.0, 129.5, 127.3, 122.3, 120.7; HRMS (ESI-Orbitrap) m/z [M + H]$^+$ calcd for $C_{11}H_9NCl$ 190.0418, found 190.0413.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Gregory Fu on the occasion of his 50th birthday.

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