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Ligand-Dependent Site-Selective Suzuki Cross-Coupling of 4-Bromopyrazol-5-yl Triflates

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ABSTRACT

Ligand-dependent Suzuki cross-coupling of 4-bromopyrazol-5-yl triflates has been developed. This approach enabled selective introduction of an aryl substituent at the C4 or C5 position in the pyrazoles. This protocol is the first example in which the cross-coupling proceeded predominantly at the C4 position in pyrazoles, which is generally recognized as the least reactive position. The selection of phosphine ligands switched the order of the arylation. This method should be highly useful for preparing diverse poly-substituted pyrazole derivatives.

INTRODUCTION

Pyrazoles appear as potent scaffolds in many pharmaceuticals with a wide range of biological activities.[1] The most general methods for their preparation are the condensation of 1,3-dicarbonyl compounds with hydrazine derivatives or the cycloaddition of diazoalkanes with alkynes.[2] Although these methods are reliable and straightforward, one must prepare precursors bearing the desired substituents for the condensation or cycloaddition reactions. For these reasons, there has been a growing interest in new synthetic methods which allow for the efficient synthesis of poly-substituted pyrazole derivatives from a common intermediate. Pd-catalyzed cross-coupling is one of the useful approaches for installing aryl substituents to fully assembled pyrazoles in a late stage of the reaction sequence. Especially, site-selective cross coupling of poly(pseudo)halopyrazoles is an attractive approach for preparation of poly-substituted pyrazoles, which enables the production of pyrazoles with various substituents from common intermediates.

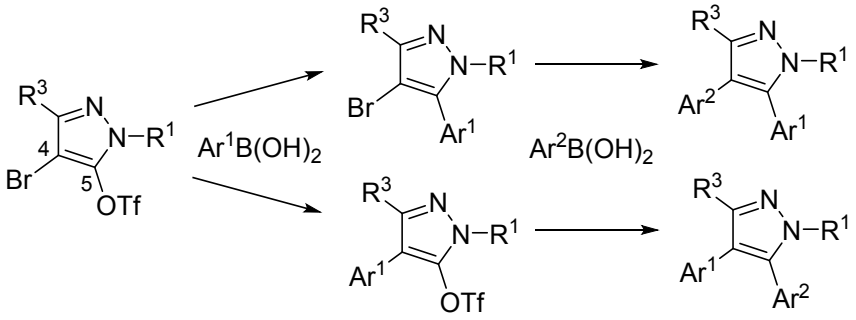
Collins and coworkers reported that 1-methyl-3-bromopyrazol-5-yl nonaflate underwent highly selective Pd-catalyzed cross-couplings at the C-O bond in the nonaflate moiety, followed by

coupling at the C-Br bond, achieving selective introduction of two distinct aryl substituents at the C3 and C5 positions in pyrazoles.[3] Langer and coworkers reported site-selective Suzuki cross-coupling of *N*-protected tribromopyrazoles.[4] Under the reported reaction conditions, arylation proceeded sequentially at C5, C3, and C4 positions with very good selectivity to afford mono-, di-, or tri-arylated pyrazoles, depending on the amount of aryl boronic acids. Diarylation of pyrazole derivatives at the C4 and C5 positions via C-H bond activation was also reported by Doucet and coworkers; the C4 halo-substituted pyrazole derivatives were selectively arylated at the C5 position by Pd-catalyzed C-H bond arylation and the the remaining C-halogen bond at the C4 position are arylated by Suzuki cross-coupling.[5] Site-selectivity of these reactions is based on the different reactivity of the two or three carbon-(pseudo)halogen bonds or carbon-hydrogen bonds in the substrates. Furthermore, an alternative approach, ligand-dependent site-selective Suzuki cross-coupling, has been also reported for several dihaloarenes. Dai and coworkers examined the effect of different phosphine ligands on the site-selectivity of Suzuki cross-coupling of 3,5-dichloropyridazines and discovered that dppf and Qphos ligands promoted coupling at C5 and C3, respectively.[6] Similarly, Strotman and Chobanian and coworkers reported ligand-dependent Suzuki cross-coupling of 2,4-diiodooxazoles and 2,4-diiodoimidazoles.[7] In addition to examples of dihaloarenes with the identical halogens, Fu and coworkers reported ligand-dependent site-selective Suzuki cross-coupling of 4-chlorophenyl triflate.[8] Although their approaches are attractive because a line of analogues can be obtained from common intermediates by changing only the ligand used, no examples of di(pseudo)halopyrazoles have been reported.

Here, we describe a general method for ligand-dependent highly selective Suzuki cross-coupling of di(pseudo)halopyrazoles, 4-bromopyrazol-5-yl triflates (Figure 1). In this approach,

two distinct aryl substituents could be introduced selectively to the C4 and C5 positions of pyrazoles and the order of C4- and C5-arylations could be switched by simply changing the phosphine ligand.

Figure 1. Ligand-dependent site-selectivity switching in Suzuki cross-coupling of 4-bromopyrazol-5-yl triflates.

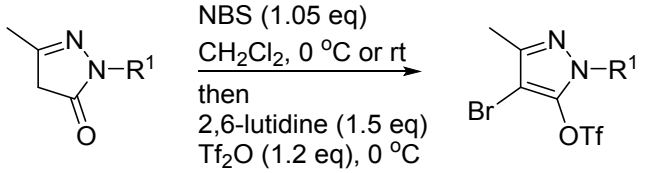


RESULT AND DISCUSSION

Pyrazole-5-yl triflates are useful substrates for Suzuki cross-coupling and can be readily prepared from 5-pyrazolones.[9] Because the α-position of 5-pyrazolone can be easily brominated,[10] we chose 4-bromopyrazol-5-yl triflates **2** as substrates for investigating site-selective Suzuki cross-coupling. We first prepared 4-bromopyrazol-5-yl triflate derivatives **2a**, **2b** from commercially available 5-pyrazolones **1a**, **1b**. 5-Pyrazolone derivatives are generally obtained by the condensation of β-ketoesters with alkyl or arylhydrazines.[2] Combined with the methodology of α-bromination of 5-pyrazolones[9] and triflation of 5-pyrazolones,[11] we established a very efficient one-pot method to prepare 4-bromopyrazol-5-yl triflates. We treated 5-pyrazolones **1a**, **1b** with equal equivalents of *N*-bromosuccinimide (NBS) in dichloromethane

followed by the reaction of triflic anhydride in the presence of 2,6-lutidine in one pot to afford the corresponding 4-bromopyrazol-5-yl triflate derivatives **2a**, **2b** in good yields (Table 1).

Table 1. Synthesis of 4-bromopyrazol-5-yl triflates **2a**, **2b**.



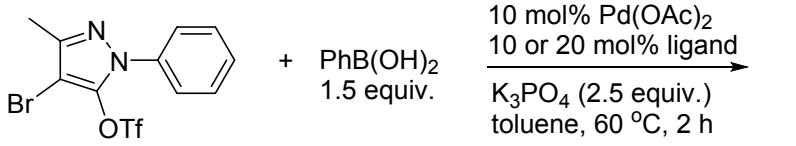
1 **2**

pyrazolone **1**	R^1	triflate **2**	yield (%)
1a	Ph	**2a**	86
1b	Me	**2b**	66

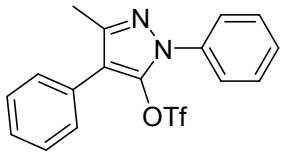
Next, we examined the effect of the ligand for Suzuki cross-coupling of 4-bromopyrazol-5-yl triflates **2a** with phenylboronic acid (Table 2). Monodentate ligands showed marked ligand-dependent selectivity (Table 2, entries 1−4). The PPh_3 ligand predominantly gave C5 coupling product **4a**, whereas the selectivity was completely reversed by using $P(Cy)_3$, $P\textit{t}Bu_3$, and Amphos ligands. Especially, the electron-rich and sterically demanding monodentate ligand Amphos gave the C4 coupling product **3a** in excellent yield with prefect site-selectivity (entry 4). Therefore, Amphos was an optimal ligand for the C4 coupling. In the case of bidentate ligands, electron-deficient ligands Xantphos, DPPF, and DPPP preferentially coupled at C5, but their selectivities were inferior to that of PPh_3 ligand (entries 5−7 vs. entry 1). Meanwhile, the electron-rich ferrocene-type bidentate ligand DTBPF had the opposite selectivity compared to the DPPF ligand (entry 8). The modification of the reaction conditions (the use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ with PPh_3, the higher loading of the catalyst and elevation of the reaction temperature) using PPh_3 ligand improved the conversion of the reaction with retention of high

C5-selectivity (entry 11). It is noteworthy that Buchwald's ligands Xphos and Sphos preferentially gave bis-coupling product **5a** (entries 9−10).

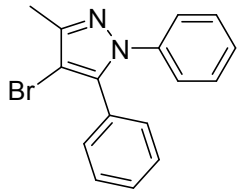
Table 2. Effect of ligand for Suzuki coupling of 4-bromopyrazol-5-yl triflate and phenylboronic acid[a]



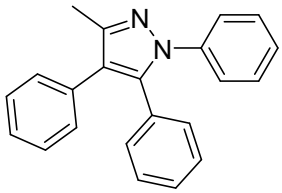
2a



3a



4a



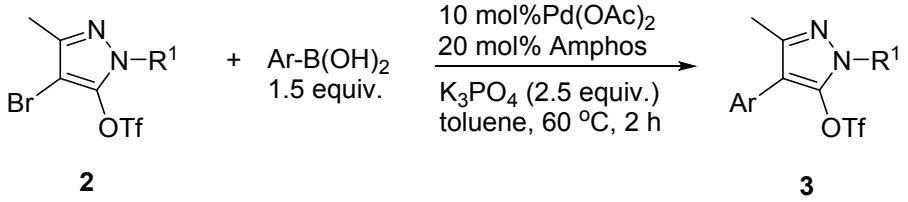
5a

entry	ligand	conversion (%)[b]	ratio of product[b] **3a** : **4a** : **5a**
1	PPh_3	40	<1 : 99 : 1
2	$P(Cy)_3$	70	91 : <1 : 9
3	$PtBu_3$ HBF_4	8	>99 : <1 : <1
4	**Amphos**	**97**	**>99 : <1 : <1**
5	Xantphos	51	1.5 : 96 : 3
6	DPPF	13	29 : 71 : <1
7	DPPP	7	33 : 67 : <1
8	DTBPF	81	95 : <1 : 5
9	Xphos	75	34 : 29 : 35
10	Sphos	28	15 : 22 : 63
11	**PPh_3[c]**	**>99**	**<1 : 99 : 1**

[a] 1:2 Pd/ligand ratio for monodentate ligands and 1:1 Pd/ligand ratio for bidentate ligands. [b] Conversion and ratio of products were determined by HPLC analysis. [c] The reaction was performed using 20 mol% $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ and ligand at 100 °C.

With the optimal ligands for C4 (Amphos) and C5 (PPh_3) selective Suzuki cross-coupling in hand, we then investigated the scope of the reactions. Table 3 shows the results of Suzuki cross-coupling using the Amphos ligand. 4-Bromopyrazol-5-yl triflate **2a** could be coupled with electron-neutral or electron-rich phenylboronic acids in good yields (entries 1−4), whereas the yields were moderate when either electron-deficient phenylboronic acids or heteroaryl boronic acids were used. In such cases, substrate **2a** was not consumed completely since catalysts were deactivated as a result of the formation of inactive palladium black (entries 5−8). We also examined the Suzuki cross-coupling of the *N*-methyl substrate **2b** to obtain C4 coupling products **3i**−**3l** in good yields without any C5 coupling products (entries 9−12).

Table 3. Scope of Suzuki cross-coupling using Amphos ligand.

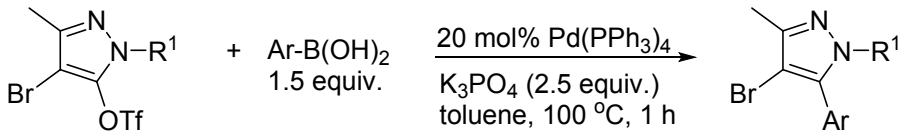


2 **3**

entry	**2**	R^1	Ar	product **3**	yield%
1	**2a**	Ph	Ph	**3a**	86
2	**2a**	Ph	4-MePh	**3b**	67
3	**2a**	Ph	3-Me_2NPh	**3c**	90
4	**2a**	Ph	2-MeOPh	**3d**	82
5	**2a**	Ph	2,4-F_2Ph	**3e**	52
6	**2a**	Ph	3-ClPh	**3f**	49
7	**2a**	Ph	3-Furyl	**3g**	33
8	**2a**	Ph	3-Thienyl	**3h**	53
9	**2b**	Me	Ph	**3i**	78
10	**2b**	Me	3-Me_2NPh	**3j**	82
11	**2b**	Me	2-MeOPh	**3k**	92
12	**2b**	Me	3-Thienyl	**3l**	87

The results of Suzuki cross-coupling with various boronic acids under $Pd(PPh_3)_4$ conditions are summarized in Table 4. The scope of the boronic acids was broad and the C5 selectivity as compared to C4 was complete in all reactions. Furthermore, yields of cross-coupling with electron-deficient boronic acids and heteroaryl boronic acids under $Pd(PPh_3)_4$ conditions were improved in comparison with those under Amphos conditions (Table 4, entries 5−8 vs. Table 3, entries 5−8). *N*-Methyl substrate **2b** also coupled with various boronic acids to afford C5 coupling products in good yields (entries 9−12).

Table 4. Scope of Suzuki cross-coupling using PPh_3 ligand.



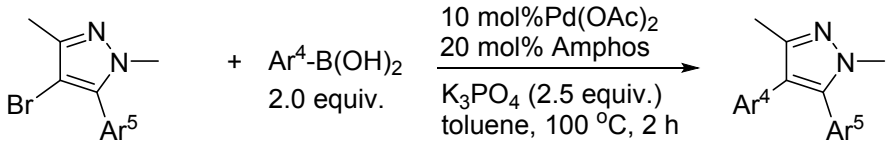
2 **4**

entry	**2**	R^1	Ar	product **4**	yield%
1	**2a**	Ph	Ph	**4a**	77
2	**2a**	Ph	4-MePh	**4b**	85
3	**2a**	Ph	3-Me_2NPh	**4c**	84
4	**2a**	Ph	2-MeOPh	**4d**	81
5	**2a**	Ph	2,4-F_2Ph	**4e**	80
6	**2a**	Ph	3-ClPh	**4f**	65
7	**2a**	Ph	3-Furyl	**4g**	39
8	**2a**	Ph	3-Thienyl	**4h**	92
9	**2b**	Me	Ph	**4i**	75
10	**2b**	Me	3-Me_2NPh	**4j**	97
11	**2b**	Me	2-MeOPh	**4k**	90
12	**2b**	Me	3-Thienyl	**4l**	82

The second arylation of the obtained bromide **4** and triflate **3** progressed smoothly (Tables 5 and 6). Under Amphos conditions, the various aryl substituents were installed at the C4 position of the obtained bromide **4** (entries 1−5), but higher reaction temperature was required. Similarly,

the second arylation of the obtained triflates **3** under $Pd(PPh_3)_4$ conditions proceeded easily to afford 4,5-diarylpyrazoles **5** in good yields (Table 6, entries 1−5). The order of sequential diarylation at the C4 and C5 positions provided almost no influence on the efficiency of 4,5-diarylpyrazole **5b**−**5e** synthesis from 4-bromopyrazol-5-yl triflate **2b** (Table 5, entries 1−4 vs. Table 6, entries 1−4). Two distinct aryl substituents can be introduced efficiently by each method.

Table 5. Second arylation using Amphos ligand.

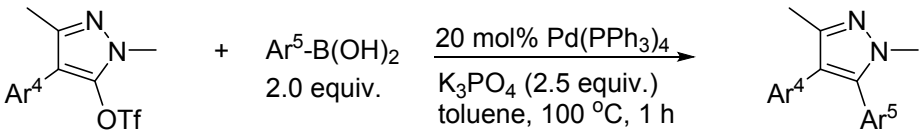


4 **5**

entry	**4**	Ar^4	Ar^5	product **5**	yield% [a]
1	**4i**	2-MeOPh	Ph	**5b**	86 (65)
2	**4i**	3-Me_2NPh	Ph	**5c**	97 (73)
3	**4k**	Ph	2-MeOPh	**5d**	72 (65)
4	**4j**	Ph	3-Me_2NPh	**5e**	52 (50)
5	**4i**	4-MePh	Ph	**5f**	83 (62)

[a] Yields in parentheses were calculated for two steps: 1st arylation (Table 4) and 2nd arylation (Table 5).

Table 6. Second arylation using PPh_3 ligand.



3 **5**

entry	**3**	Ar^4	Ar^5	product **5**	yield% [a]
1	**3k**	2-MeOPh	Ph	**5b**	55 (51)
2	**3j**	3-Me_2NPh	Ph	**5c**	89 (73)
3	**3i**	Ph	2-MeOPh	**5d**	67 (52)

4	**3i**	Ph	3-Me_2NPh	**5e**	87 (68)
5	**3i**	Ph	4-MePh	**5g**	88 (69)

[a] Yields in parentheses were calculated for two steps: 1st arylation (Table 3) and 2nd arylation (Table 6).

The oxidative addition step in Suzuki cross-coupling is generally considered as the site-selectivity determining step, and the bond dissociation energies (BDEs) are one of the important factors determining the oxidative addition site.[12] The calculated C-Cl BDEs of 1*H*-pyrazole are reported to be higher at the C4 position than at the C3 and C5 positions.[13,14] Indeed the order of the calculated BDEs is consistent with the order of the reacted sites of *N*-protected tribromopyrazole reported by Langer.[4] The gas-phase homolytic dissociation energy of the C-OTf bond was much larger than that of the C-Br bond using DFT calculations in 4-bromophenyl triflate.[15] As 4-bromopyrazol-5-yl triflates **2** are heterocycles having different kinds of (pseudo)halides, it is difficult to predict the more reactive site due to both the inherent relative site reactivities of pyrazole and the nature of the (pseudo)halide. However, Langer's results[4] suggested that the C4-Br bond in *N*-substituted pyrazoles was the least reactive. To the best of our knowledge, these Amphos reaction conditions are the first report of the site-selective Suzuki cross-coupling of pyrazoles with the C4 selectivity. In our developed method, the ligand demonstrated remarkable effects on the site-selective Suzuki cross-coupling at the C4 (C-Br bond) and C5 (C-OTf bond) positions of pyrazoles. Influences of the ligand for site-selectivity were examined using DFT calculations by Houk and Schoenebeck; the site-selectivity by these kinds of ligands was explained by the ligation state between mono-ligated Pd complex (PdL) and di-ligated Pd complex (PdL_2); PdL preferred the C-halogen bond with lower BDE (the distortion-controlled reaction): PdL_2 favored the C-OTf bond with lower LUMO energy (the interaction-controlled reaction).[16] Subsequent theoretical and experimental studies have

concluded that the sterically bulky ligands were generally advantageous for the formation of PdL, whereas the sterically less-hindered ligands generally stabilized the PdL_2 state.[17] These well-recognized studies explain our results (Table 2); bulky ligands such as Amphos, P*t*Bu_3, and DTBPF would interact with the substrate in the PdL state to provide the C4 coupling products (activation of the C4-Br bond), whereas less sterically demanding ligands such as PPh_3, DPPF, and Xantphos would react with the substrate in the PdL_2 state to afford the C5 coupling product (activation of the C-OTf bond).

CONCLUSIONS

We developed the ligand-dependent site-selective Suzuki cross-coupling of 4-bromopyrazol-5-yl triflates. The selective cross-coupling at C4 (C-Br bond) and C5 (C-OTf bond) was achieved by using the Amphos ligand and the PPh_3 ligand, respectively. These reaction conditions were applicable to coupling of a wide range of phenyl boronic acids with various substituents and heteroaryl boronic acids. The second aryl substituent could also be introduced smoothly. Our developed methods would be highly useful for preparing diverse pyrazole derivatives. Additionally, the method provided the first examples of the ligand-dependent C4 site-selective Suzuki cross-coupling of pyrazoles having different kinds of (pseudo)halides.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were obtained from commercial suppliers and were used without further purification. For reactions that require heating, a heating mantle was used. Nuclear magnetic resonance (NMR) spectra were recorded on an Agilent Technologies VXR-400NMR for ^{1}H NMR and ^{13}C NMR. Chemical shifts were reported as δ values (ppm)

reference to tetramethylsilane. Mass spectra (MS) were obtained on JMS-AX505HA, JMS-700 MStation, or JMS-100LP instrument by applying an electrospray ionization (ESI)/TOF or fast atom bombardment (FAB)/double-focusing magnetic sector mass spectrometer method. The progress of the reaction was determined on Merck Silica Gel Art. 5715 (TLC). Purification was carried out using a EPCLC W-prep 2XY purification system (Yamazen Corporation) with prepacked normal phase SiO_2 cartridges eluted with optimized gradients of either *n*-hexane-ethyl acetate or chloroform-methanol as described.

Synthesis of 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (2a). *N*-Bromosuccinimide (2150 mg, 12.1 mmol) was added to a solution of 3-methyl-1-phenyl-1*H*-pyrazol-5-one (2000 mg, 11.5 mmol**)** in dichloromethane (40 mL) at 0 °C and allowed to warm to room temperature. After stirring at the same temperature for 1 h, 2,6-lutidine (2.00 mL, 17.2 mmol) and triflic anhydride (2.32 mL, 13.8 mmol) were added to the mixture at 0 °C. After stirring at the same temperature for 30 min, the reaction mixture was poured into saturated $NaHCO_3$ aqueous solution, extracted with chloroform. Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate, 100:0 to 96:4) to yield compound **2a** (3870 mg, 10.0 mmol, 87%) as a colorless solid. mp: 43.0-44.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40−7.51 (m, 5H), 2.34 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.5, 138.8, 136.8, 129.5, 128.9, 123.9, 118.1 (q, $J_{C\text{-}F}$ = 320 Hz), 87.6, 13.2. HRMS-FAB m/z $[M+H]^+$ calcd. for $C_{11}H_9BrF_3N_2O_3S$, 384.9469; found 384.9462.

Synthesis of 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (2b). *N*-Bromosuccinimide (3330 mg, 18.7 mmol) was added to a solution of 1,3-dimethyl-1*H*-pyrazol-5-one (2000 mg, 17.8 mmol**)** in dichloromethane (60 mL) at 0 °C. After stirring at the same

temperature for 30 min, 2,6-lutidine (4.15 mL, 35.7 mmol) and triflic anhydride (3.60 mL, 21.4 mmol) were added to the mixture at 0 °C. After stirring at the same temperature for 30 min, the reaction mixture was poured into saturated $NaHCO_3$ aqueous solution, extracted with chloroform. Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate, 98:2 to 92:8) to yield compound **2b** (3830 mg, 11.9 mmol, 66%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 2.23 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.2, 139.0, 118.4 (q, J_{C-F} = 320 Hz), 84.9, 36.2, 13.0. HRMS-FAB m/z $[M+H]^+$ calcd. for $C_6H_7BrF_3N_2O_3S$, 322.9313; found 322.9305.

General Procedure: Screening Suzuki cross-coupling conditions with respect to ligand (Table 2). A mixture of 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol), phenyboronic acid (48mg, 0.39 mmol), palladium(II) acetate (5.8 mg, 0.026 mmol), indicated ligand (0.052 mmol for monodentate ligand, 0.026 mmol for bidentate ligand), and potassium phosphate (138 mg, 0.65 mmol) in toluene (3.0 mL) was heated at 60 °C for 2 h under an Ar atmosphere. The mixture was cooled to room temperature and diluted with chloroform. After filtration through Celite pad, the filtrate was concentrated under reduced pressure. The conversion and the ratio of products were determined by normal phase HPLC analysis (column: Senshu Pak PEGASIL Silica SP100-3 (4.6φ x 250 mm) , mobile phase: isocratic *n*-hexane/*i*-PrOH = 99.8/0.2, flow rate: 0.5 mL/min, Wavelength of UV detection: 254 nm) of the residue using an external standard.

Representative Procedure: Suzuki cross-coupling using Amphos ligand (Table 3, entry 9, 3i). A mixture of 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 800 mg, 2.48 mmol), phenylboronic acid (453 mg, 3.72 mmol), palladium(II) acetate (56 mg, 0.25

mmol), 4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline (132 mg, 0.50 mmol), and potassium phosphate (1580 mg, 7.43 mmol) in toluene (20 mL) was heated at 60 °C for 2 h under an Ar atmosphere. The mixture was cooled to room temperature and diluted with chloroform. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate, 100:0 to 94:6) to yield 1,3-dimethyl-4-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3i**, 621 mg, 1.94 mmol, 78%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39−7.44 (m, 2H), 7.29−7.36 (m, 3H), 3.84 (s, 3H), 2.28 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.1, 138.0, 129.7, 129.0, 128.7, 127.6, 118.2 (q, $J_{C\text{-}F}$ = 319 Hz), 110.6, 35.5, 13.4. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{12}H_{12}F_3N_2O_3S$, 321.0521; found 321.0506.

3-Methyl-1,4-diphenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3a**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and phenylboronic acid (48 mg, 0.39 mmol), **3a** (85 mg, 0.22 mmol, 86%) was obtained as a colorless solid. mp: 55.5-57.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57−7.61 (m, 2H), 7.35−7.54 (m, 8H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.7, 137.6, 137.0, 129.5, 129.4, 129.1, 128.8, 128.5, 127.9, 123.9, 117.9 (q, $J_{C\text{-}F}$ = 320 Hz), 112.6, 13.6. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{17}H_{14}F_3N_2O_3S$, 383.0677; found 383.0667.

3-Methyl-1-phenyl-4-(*p*-tolyl)-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3b**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and *p*-tolylboronic acid (53 mg, 0.39 mmol), **3b** (69 mg, 0.17 mmol, 67%) was obtained as a colorless solid. mp: 64.5-66.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56−7.60 (m, 2H), 7.48−7.54 (m, 2H), 7.42 (tt, J = 6.6, 1.3 Hz, 1H), 7.25−7.33 (m, 4H), 2.41 (s, 3H), 2.38 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.7, 137.7, 137.5, 137.0, 129.5, 129.4, 128.9, 128.4, 126.4, 123.9, 117.9

(q, $J_{C\text{-}F}$ = 320 Hz), 112.6, 21.3, 13.6. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{16}F_3N_2O_3S$, 397.0834; found 397.0817.

4-(3-(Dimethylamino)phenyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3c**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (3-(dimethylamino)phenyl)boronic acid (64 mg, 0.39 mmol), **3c** (100 mg, 0.24 mmol, 90%) was obtained as a colorless solid. mp: 87.0-89.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56−7.62 (m, 2H), 7.48−7.54 (m, 2H), 7.14 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.28−7.34 (m, 1H), 6.72−6.79 (m, 3H), 3.00 (s, 6H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.8, 147.8, 137.5, 137.0, 130.0, 129.4, 129.4, 128.4, 123.9, 117.9 (q, $J_{C\text{-}F}$ = 320 Hz), 117.2, 113.4, 113.0, 112.0, 40.5, 13.8. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{19}H_{19}F_3N_3O_3S$, 426.1099; found 426.1090.

4-(2-Methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3d**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (2-methoxyphenyl)boronic acid (59 mg, 0.39 mmol), **3d** (88 mg, 0.21 mmol, 82%) was obtained as a pale yellow liquid. ^{1}H NMR ($CDCl_3$) ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.58−7.62 (m, 2H), 7.47−7.54 (m, 2H), 7.36−7.44 (m, 2H), 7.28 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.04 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.99 (dd, *J* = 8.3, 0.9 Hz, 1H), 3.87 (s, 3H), 2.29 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.1, 148.7, 137.9, 137.1, 131.4, 129.8, 129.3, 128.2, 123.9, 120.6, 118.1, 117.9 (q, $J_{C\text{-}F}$ = 320 Hz), 110.9, 108.9, 55.4, 13.7. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{16}F_3N_2O_4S$, 413.0783; found 413.0768.

4-(2,4-Difluorophenyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3e**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (2,4-difluorophenyl)boronic acid (62 mg, 0.39 mmol), **3e** (57 mg, 0.14 mmol, 52%)

was obtained as a colorless solid. mp: 57.0-58.0 ºC. ^{1}H NMR ($CDCl_3$) ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56−7.61 (m, 2H), 7.49−7.54 (m, 2H), 7.43 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.35 (ddd, *J* = 8.5, 8.5, 6.3 Hz, 1H), 6.93−7.03 (m, 2H), 2.31 (d, *J* = 0.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.1 (dd, $J_{C\text{-}F}$ = 251, 14 Hz), 160.3 (dd, $J_{C\text{-}F}$ = 249, 12 Hz), 148.4, 138.0, 136.8, 132.3 (dd, $J_{C\text{-}F}$ = 9.7, 4.4 Hz), 129.5, 128.7, 124.0, 118.0 (q, $J_{C\text{-}F}$ = 320 Hz), 113.4 (dd, $J_{C\text{-}F}$ = 16, 3.8 Hz), 111.8 (dd, $J_{C\text{-}F}$ = 21, 3.8 Hz), 105.7, 104.6 (dd, $J_{C\text{-}F}$ = 26, 26 Hz), 13.4 (d, $J_{C\text{-}F}$ = 2.4 Hz). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{17}H_{12}F_5N_2O_3S$, 419.0489; found 419.0472.

4-(3-Chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3f**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (3-chlorophenyl)boronic acid (61 mg, 0.39 mmol), **3f** (53 mg, 0.13 mmol, 49%) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56−7.60 (m, 2H), 7.49−7.55 (m, 2H), 7.34−7.46 (m, 4H), 7.31 (ddd, *J* = 7.3, 1.6, 1.6 Hz, 1H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.5, 137.6, 136.8, 134.8, 131.3, 130.1, 129.5, 129.0, 128.7, 128.0, 127.2, 124.0, 117.9 (q, $J_{C\text{-}F}$ = 320 Hz), 111.3, 13.6. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{17}H_{13}ClF_3N_2O_3S$, 417.0288; found 417.0287.

4-(Furan-3-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3g**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and 3-furylboronic acid (44 mg, 0.39 mmol), **3g** (32 mg, 0.086 mmol, 33%) was obtained as pale brown solid. mp: 95.0-97.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 1.4, 0.9 Hz, 1H), 7.47−7.56 (m, 5H), 7.42 (dddd, *J* = 8.1, 6.4, 1.6, 1.6 Hz, 1H), 6.61 (dd, *J* = 1.9, 0.9 Hz, 1H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.7, 143.6, 140.3, 137.3, 136.9, 129.4, 128.5, 123.9, 118.0 (q, $J_{C\text{-}F}$ = 320 Hz), 113.8, 110.0, 104.4, 14.0. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{15}H_{12}F_3N_2O_4S$, 373.0470; found 373.0479.

3-Methyl-1-phenyl-4-(thiophen-3-yl)-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3h**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and 3-thienylboronic acid (50 mg, 0.39 mmol), **3h** (54 mg, 0.14 mmol, 53%) was obtained as a colorless solid. mp: 80.0-81.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55−7.59 (m, 2H), 7.48−7.54 (m, 2H), 7.39−7.46 (m, 2H), 7.38 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.23 (dd, *J* = 5.0, 1.2 Hz, 1H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.7, 137.4, 136.9, 129.4, 129.1, 128.5, 127.4, 126.2, 123.9, 123.4, 117.9 (q, $J_{C\text{-}F}$ = 320 Hz), 108.1, 13.9. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{15}H_{12}F_3N_2O_3S_2$, 389.0241; found 389.0237.

4-(3-(Dimethylamino)phenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3j**). From 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 84 mg, 0.26 mmol) and (3-(dimethylamino)phenyl)boronic acid (64 mg, 0.39 mmol), **3j** (77 mg, 0.21 mmol, 82%) was obtained as a colorless solid. mp: 59.5-60.5 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24−7.30 (m, 1H), 6.64−6.74 (m, 3H), 3.83 (s, 3H), 2.96 (s, 6H), 2.30 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.7, 146.2, 137.9, 130.3, 129.3, 118.2 (q, $J_{C\text{-}F}$ = 320 Hz), 117.3, 113.1, 111.8, 111.4, 40.5, 35.4, 13.6. HRMS-FAB m/z $[M+H]^+$ calcd. for $C_{14}H_{17}F_3N_3O_3S$, 364.0943; found 364.0942.

4-(2-Methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3k**). From 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 84 mg, 0.26 mmol) and (2-methoxyphenyl)boronic acid (59 mg, 0.39 mmol), **3k** (84 mg, 0.24 mmol, 92%) was obtained as a pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.99 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.2, 0.8 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.19 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.0, 147.0, 138.4, 131.4, 129.6, 120.5, 118.4, 118.2 (q, $J_{C\text{-}F}$ = 319 Hz), 110.8, 106.8, 55.3, 35.3, 13.4. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{13}H_{14}F_3N_2O_4S$, 351.0626; found 351.0611.

1,3-Dimethyl-4-(thiophen-3-yl)-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3l**). From 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 84 mg, 0.26 mmol) and 3-thienylboronic acid (50 mg, 0.39 mmol), **3l** (74 mg, 0.23 mmol, 87%) was obtained as a pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J = 5.0, 3.0 Hz, 1H), 7.26 (dd, J = 3.0, 1.2 Hz, 1H), 7.13 (dd, J = 5.0, 1.2 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.19 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.1, 137.8, 129.4, 127.5, 125.9, 123.0, 118.3 (q, $J_{C\text{-}F}$ = 319 Hz), 106.2, 35.5, 13.7. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{10}H_{10}F_3N_2O_3S_2$, 327.0085; found 327.0076.

Representative Procedure: Suzuki cross-coupling using Amphos ligand (Table 4, entry 9, 4i). A mixture of 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 800 mg, 2.48 mmol), phenylboronic acid (453 mg, 3.72 mmol), tetrakis(triphenylphosphine)palladium(0) (570 mg, 0.496 mmol) and potassium phosphate (1580 mg, 7.43 mmol) in toluene (20 mL) was heated at 100 °C for 1 h under an Ar atmosphere. The mixture was cooled to room temperature and diluted with chloroform. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate, 100:0 to 92:8) to yield 4-Bromo-1,3-dimethyl-5-phenyl-1*H*-pyrazole (**4i**, 467 mg, 1.86 mmol, 75%) as a colorless solid. mp: 45.0-46.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38−7.50 (m, 5H), 3.76 (s, 3H), 2.29 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.5, 141.6, 129.7, 129.1, 129.0, 128.7, 94.0, 37.9, 12.3. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{11}H_{12}BrN_2$, 251.0184; found 251.0169.

4-Bromo-3-methyl-1,5-diphenyl-1*H*-pyrazole (**4a**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and phenylboronic acid (48 mg, 0.39 mmol), **4a** (63 mg, 0.20 mmol, 77%) was obtained as a pale yellow solid. mp: 72.0-74.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32−7.36 (m, 3H), 7.17−7.31 (m, 7H), 2.39 (s, 3H). ^{13}C-NMR

(100 MHz, $CDCl_3$): δ 148.4, 140.7, 139.9, 129.9, 129.1, 128.8, 128.8, 128.4, 127.3, 124.7, 96.9, 12.5. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{16}H_{14}BrN_2$, 313.0340; found 313.0323.

4-Bromo-3-methyl-1-phenyl-5-(*p*-tolyl)-1*H*-pyrazole (**4b**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and *p*-tolylboronic acid (53 mg, 0.39 mmol), **4b** (71 mg, 0.22 mmol, 85%) was obtained as a colorless solid. a colorless solid. mp: 80.0-82.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.18−7.32 (m, 5H), 7.14−7.17 (m, 4H), 2.38 (s, 3H), 2.36 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.4, 140.7, 140.0, 138.8, 129.7, 129.2, 128.8, 127.2, 126.2, 124.7, 96.7, 21.4, 12.5. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{17}H_{16}BrN_2$, 327.0497; found 327.0469.

3-(4-Bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylaniline (**4c**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (3-(dimethylamino)phenyl)boronic acid (64 mg, 0.39 mmol), **4c** (78 mg, 0.22 mmol, 84%) was obtained as a pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.15−7.32 (m, 6H), 6.70 (ddd, *J* = 8.6, 2.3, 1.3 Hz, 1H), 6.67−6.62 (m, 2H), 2.85 (s, 6H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.2, 148.3, 141.5, 140.2, 129.6, 129.0, 128.7, 127.1, 124.7, 117.9, 114.0, 112.7, 96.6, 40.3, 12.6. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{19}BrN_3$, 356.0762; found 356.0740.

4-Bromo-5-(2-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazole (**4d**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (2-methoxyphenyl)boronic acid (59 mg, 0.39 mmol), **4d** (72 mg, 0.21 mmol, 81%) was obtained as a colorless solid. mp: 128.0-129.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H), 7.31 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.16−7.26 (m, 5H), 7.02 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 3.41 (s, 3H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.8, 148.1,

140.8, 138.2, 131.8, 131.0, 128.5, 126.8, 123.3, 120.7, 118.5, 111.4, 97.6, 55.1, 12.6. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{17}H_{16}BrN_2O$, 343.0446; found 343.0433.

4-Bromo-5-(2,4-difluorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole (**4e**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (2,4-difluorophenyl)boronic acid (62 mg, 0.39 mmol), **4e** (73 mg, 0.21 mmol, 80%) was obtained as a pale yellow solid. mp: 81.5-83.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23−7.33 (m, 4H), 7.18−7.22 (m, 2H), 6.94 (ddd, J = 9.5, 8.9, 2.5 Hz, 1H), 6.82 (dddd, J = 8.7, 7.9, 2.6, 0.9 Hz, 1H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.3 (dd, $J_{C\text{-}F}$ = 252, 12 Hz), 157.5 (dd, $J_{C\text{-}F}$ = 253, 13 Hz), 148.5, 139.8, 134.8, 133.0 (dd, $J_{C\text{-}F}$ = 9.7, 3.8 Hz), 129.0, 127.6, 123.8, 113.8 (dd, $J_{C\text{-}F}$ = 15, 4.0 Hz), 111.9 (dd, $J_{C\text{-}F}$ = 21, 3.8 Hz), 104.7 (dd, $J_{C\text{-}F}$ = 18, 18 Hz), 98.5, 12.5. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{16}H_{12}BrF_2N_2$, 349.0152; found 349.0135.

4-Bromo-5-(3-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazole (**4f**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and (3-chlorophenyl)boronic acid (61 mg, 0.39 mmol), **4f** (59 mg, 0.17 mmol, 65%) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24−7.35 (m, 6H), 7.17−7.22 (m, 2H), 7.10 (ddd, J = 7.7, 1.4, 1.4 Hz, 1H), 2.39 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.6, 139.6, 139.2, 134.4, 130.9, 129.8, 129.7, 129.0, 129.0, 128.1, 127.6, 124.7, 97.2, 12.5. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{16}H_{13}BrClN_2$, 346.9951; found 346.9937.

4-Bromo-5-(furan-3-yl)-3-methyl-1-phenyl-1*H*-pyrazole (**4g**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and 3-furylboronic acid (44 mg, 0.39 mmol), **4g** (31 mg, 0.10 mmol, 39%) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, J = 1.5, 0.9 Hz, 1H), 7.31−7.42 (m, 6H), 6.16 (dd, J = 1.9, 0.8 Hz, 1H), 2.36 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.5, 142.6, 142.0, 140.0, 133.7,

129.0, 128.1, 125.4, 114.1, 110.2, 96.2, 12.5. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{12}BrN_2O$, 303.0133; found 303.0128.

4-Bromo-3-methyl-1-phenyl-5-(thiophen-3-yl)-1*H*-pyrazole (**4h**). From 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2a**, 100 mg, 0.26 mmol) and 3-thienylboronic acid (50 mg, 0.39 mmol), **4h** (76 mg, 0.24 mmol, 92%) was obtained as a pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, J = 3.0, 1.3 Hz, 1H), 7.22−7.36 (m, 6H), 6.90 (dd, J = 5.1, 1.3 Hz, 1H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.5, 140.0, 136.5, 129.0, 128.8, 127.9, 127.7, 126.2, 125.5, 124.9, 96.6, 12.5. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{12}BrN_2S$, 318.9905; found 318.9893.

3-(4-Bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl-aniline (**4j**). From 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 84 mg, 0.26 mmol) and (3-(dimethylamino)phenyl)boronic acid (64 mg, 0.39 mmol), **4j** (74 mg, 0.25 mmol, 97%) was obtained as a colorless solid. mp: 59.0-61.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, J = 8.0, 8.0 Hz, 1H), 6.78−6.82 (m, 1H), 6.68−6.72 (m, 2H), 3.77 (s, 3H), 2.99 (s, 6H), 2.29 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.4, 146.4, 142.5, 129.7, 129.3, 117.4, 113.6, 112.9, 93.8, 40.4, 37.9, 12.3. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{13}H_{17}BrN_3$, 294.0606; found 294.0631.

4-Bromo-5-(2-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazole (**4k**). From 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 84 mg, 0.26 mmol) and (2-methoxyphenyl)boronic acid (59 mg, 0.39 mmol), **4k** (66 mg, 0.21 mmol, 90%) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45 (ddd, J = 8.4, 7.5, 1.8 Hz, 1H), 7.26 (dd, J = 7.5, 1.8 Hz, 1H), 7.07 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 7.01 (dd, J = 8.4, 0.8 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 2.29 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.2, 146.1, 138.9, 132.1,

131.1, 120.7, 117.8, 111.3, 94.6, 55.5, 37.7, 12.4. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{12}H_{14}BrN_2O$, 281.0290; found 281.0285.

4-Bromo-1,3-dimethyl-5-(thiophen-3-yl)-1*H*-pyrazole (**4l**). From 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**2b**, 84 mg, 0.26 mmol) and 3-thienylboronic acid (50 mg, 0.39 mmol), **4l** (55 mg, 0.21 mmol, 82%) was obtained as a pale yellow solid. mp: 54.0-55.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, J = 3.0, 1.4 Hz, 1H), 7.46 (dd, J = 4.9, 3.0 Hz, 1H), 7.24 (dd, J = 5.0, 1.4 Hz, 1H), 3.81 (s, 3H), 2.28 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.5, 137.1, 128.8, 127.8, 126.1, 126.0, 94.2, 38.1, 12.3. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_9H_{10}BrN_2S$, 256.9748; found 256.9740.

Representative Procedure: The second Suzuki cross-coupling using Amphos ligand (Table 5, entry 1, 5b). A mixture of 4-bromo-1,3-dimethyl-5-phenyl-1*H*-pyrazole (**4i**, 75 mg, 0.30 mmol), 2-methoxyphenylboronic acid (91 mg, 0.60 mmol), palladium(II) acetate (6.7 mg, 0.030 mmol), 4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline (16 mg, 0.060 mmol), and potassium phosphate (159 mg, 0.75 mmol) in toluene (3.0 mL) was heated at 100 °C for 2 h under an Ar atmosphere. The mixture was cooled to room temperature and diluted with chloroform. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate, 90:10 to 70:30) to yield 4-(2-Methoxyphenyl)-1,3-dimethyl-5-phenyl-1*H*-pyrazole (**5b**, 72 mg, 0.26 mmol, 86%) as a pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27−7.34 (m, 3H), 7.16−7.23 (m, 3H), 6.99 (dd, J = 7.4, 1.8 Hz, 1H), 6.81−6.86 (m, 2H), 3.81 (s, 3H), 3.55 (s, 3H), 2.19 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.1, 146.6, 141.9, 132.2, 131.0, 129.4, 128.2, 128.1, 127.9, 122.5, 120.3, 115.9, 110.8, 55.0, 37.1, 12.5. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{19}N_2O$, 279.1497; found 279.1523.

3-(1,3-Dimethyl-5-phenyl-1*H*-pyrazol-4-yl)-*N*,*N*-dimethyl-aniline (**5c**). From 4-bromo-1,3-dimethyl-5-phenyl-1*H*-pyrazole (**4i**, 75 mg, 0.30 mmol) and (3-(dimethylamino)phenyl)boronic acid (90 mg, 0.60 mmol), **5c** (85 mg, 0.29 mmol, 97%) was obtained as a yellow solid. mp: 118.0-120.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31−7.39 (m, 3H), 7.23−7.27 (m, 2H), 7.11 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.57 (ddd, *J* = 8.2, 2.7, 0.8 Hz, 1H), 6.53 (ddd, *J* = 7.6, 1.5, 1.1 Hz, 1H), 6.41 (dd, *J* = 2.5, 1.6 Hz, 1H), 3.76 (s, 3H), 2.77 (s, 6H), 2.38 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.3, 145.6, 141.2, 134.1, 130.9, 130.1, 128.7, 128.5, 128.2, 120.2, 118.0, 114.3, 110.4, 40.4, 36.9, 12.9. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{19}H_{22}N_3$, 292.1814; found 292.1802.

5-(2-Methoxyphenyl)-1,3-dimethyl-4-phenyl-1*H*-pyrazole (**5d**). From 4-bromo-5-(2-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazole (**4k**, 51 mg, 0.18 mmol) and phenylboronic acid (44 mg, 0.36 mmol), **5d** (36 mg, 0.13 mmol, 72%) was obtained as a pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.18−7.24 (m, 2H), 7.13 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.06−7.10 (m, 2H), 7.01 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.96 (dd, *J* = 8.7, 0.8 Hz, 1H), 6.89 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 157.7, 145.3, 138.1, 134.0, 132.2, 130.4, 129.1, 128.0, 125.7, 120.7, 120.0, 119.4, 111.1, 55.4, 36.7, 12.9. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{19}N_2O$, 279.1497; found 279.1506.

3-(1,3-Dimethyl-4-phenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl-aniline (**5e**). From 3-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl-aniline (**4j**, 37 mg, 0.13 mmol) and phenylboronic acid (31 mg, 0.25 mmol), **5e** (19 mg, 0.065 mmol, 52%) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19−7.27 (m, 3H), 7.11−7.18 (m, 3H), 6.70 (ddd, *J* = 8.5, 2.7, 0.7 Hz, 1H), 6.58 (ddd, *J* = 7.5, 1.0, 1.0 Hz, 1H), 6.50 (dd, *J* = 2.6, 1.5 Hz, 1H), 3.79 (s, 3H), 2.84 (s, 6H), 2.34 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.3, 145.5, 142.1, 133.9, 131.0, 129.6,

129.1, 128.0, 125.8, 119.4, 118.0, 114.2, 112.3, 40.3, 37.0, 12.7. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{19}H_{22}N_3$, 292.1814; found 292.1817.

1,3-Dimethyl-5-phenyl-4-(*p*-tolyl)-1*H*-pyrazole (**5f**). From 4-bromo-1,3-dimethyl-5-phenyl-1*H*-pyrazole (**4i**, 75 mg, 0.30 mmol) and *p*-tolylboronic acid (82 mg, 0.60 mmol), **5f** (65 mg, 0.25 mmol, 83%) was obtained as a pale yellow solid. mp: 147.0-148.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32−7.40 (m, 3H), 7.20−7.24 (m, 2H), 7.02−7.06 (m, 2H), 6.96−7.00 (m, 2H), 3.76 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.6, 141.1, 135.5, 130.6, 130.6, 130.1, 129.4, 128.9, 128.5, 128.3, 119.5, 36.9, 21.1, 12.7. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{19}N_2$, 263.1548; found 263.1548.

Representative Procedure: The second Suzuki cross-coupling using PPh_3 ligand (Table 6, entry 1, 5b). A mixture of 4-(2-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3k**, 74 mg, 0.21 mmol), phenylboronic acid (52 mg, 0.42 mmol), tetrakis(triphenylphosphine)palladium(0) (49 mg, 0.042 mmol) and potassium phosphate (112 mg, 0.53 mmol) in toluene (3.0 mL) was heated at 100 °C for 2 h under an Ar atmosphere. The mixture was cooled to room temperature and diluted with chloroform. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate, 90:10 to 70:30) to yield 4-(2-methoxyphenyl)-1,3-dimethyl-5-phenyl-1*H*-pyrazole (**5b**, 32 mg, 0.12 mmol, 55%) as a pale yellow liquid.

3-(1,3-Dimethyl-5-phenyl-1*H*-pyrazol-4-yl)-*N*,*N*-dimethyl-aniline (**5c**). From 4-(3-(dimethylamino)phenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3j**, 56 mg, 0.15 mmol) and phenylboronic acid (38 mg, 0.21 mmol), **5c** (40 mg, 0.14 mmol, 89%) was obtained as a yellow solid.

5-(2-Methoxyphenyl)-1,3-dimethyl-4-phenyl-1*H*-pyrazole (**5d**). From 1,3-dimethyl-4-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3i**, 96 mg, 0.30 mmol) and 2-methoxyphenylboronic acid (91 mg, 0.60 mmol), **5d** (56 mg, 0.20 mmol, 67%) was obtained as a pale yellow liquid.

3-(1,3-Dimethyl-4-phenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl-aniline (**5e**). From 1,3-dimethyl-4-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3i**, 96 mg, 0.30 mmol) and (3-(dimethylamino)phenyl)boronic acid (99 mg, 0.60 mmol), **5e** (76 mg, 0.26 mmol, 87%) was obtained as a colorless liquid.

1,3-Dimethyl-4-phenyl-5-*(p*-tolyl)-1*H*-pyrazole (**5g**). From 1,3-dimethyl-4-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (**3i**, 96 mg, 0.30 mmol) and *p*-tolylboronic acid (82 mg, 0.60 mmol), **5g** (69 mg, 0.26 mmol, 88%) was obtained as a pale yellow solid. mp: 68.5-69.5 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26−7.20 (m, 2H), 7.13−7.19 (m, 3H), 7.07−7.12 (m, 4H), 3.76 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.6, 141.3, 138.2, 133.8, 129.9, 129.6, 129.3, 128.1, 127.5, 125.9, 119.4, 36.9, 21.3, 12.7. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{18}H_{19}N_2$, 263.1548; found 263.1569.

3-Methyl-1,4,5-triphenyl-1*H*-pyrazole (**5a**). A mixture of 4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl trifluoromethanesulfonate (100 mg, 0.26 mmol), phenylboronic acid (160 mg, 1.30 mmol), palladium(II) acetate (5.8 mg, 0.026 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (25 mg, 0.052 mmol) and potassium phosphate (138 mg, 0.65 mmol) in toluene (3.0 mL) was heated at 60 °C for 2 h under an Ar atmosphere, and then warmed to 80 °C for 2 h. Then, additional phenylboronic acid (160 mg, 1.30 mmol), palladium(II) acetate (5.8 mg, 0.026 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (25 mg, 0.052 mmol) and potassium phosphate (138 mg, 0.65 mmol) were added to the mixture. After stirring at 80 °C for 1.5 h, the reaction mixture was poured into water, extracted with ethyl acetate. The combined

organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate, 98:2 to 90:10) to yield compound **5a** (61 mg, 0.20 mmol, 76%) as a colorless solid. mp: 179.0-181.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.12−7.30 (m, 13H), 7.02−7.06 (m, 2H), 2.40 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.8, 140.3, 140.0, 133.3, 130.3, 130.3, 129.9, 128.7, 128.3, 128.2, 128.0, 126.9, 126.4, 125.1, 121.4, 12.8. HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{22}H_{19}N_2$, 311.1548; found 311.1548.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectrum and synthetic procedure of compound **5a** as reference standard of HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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