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Facile Access to 3,5-Dihalogenated Pyrazoles by Sydnone Cycloaddition and their Versatile Functionalization by Pd-Catalyzed Cross-Coupling Processes

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The 1,3-dipolar cycloaddition of diversely *N*-substituted 4-iodosydnones with 3-halopropiolates produces easily separable mixtures of dihalogenated pyrazolylcarboxylic esters at a preparative scale level, with the 3,5-dihalogenopyrazole regioisomers always predominating. Further decarboxylation of the major isomers provided the corresponding 3,5-dihalogenopyrazoles with a free C-4 position. These were found to be valuable scaffolds for the elaboration of unsymmetrically 1,3,5-trisubstituted pyrazole derivatives by site-selective Pd-catalyzed cross-coupling reactions. Notably, the flexible and site-selective introduction of different (hetero)aryl, vinyl, or alkyl substituents at the C-5 and C-3 positions of the pyrazole core could be achieved through sequential Suzuki-type reactions with various boron compounds. Furthermore, the Suzuki coupling sequence could be amenable to a one-pot procedure that enables rapid generation of the targeted compounds.

Introduction

Multiple aryl- and heteroaryl-substituted heterocycles are high-value targets in the pharmaceutical and agrochemical industries. While there exist a plethora of methods to access such compounds, one strategy that provides the high levels of flexibility needed in library elaboration procedures is the sequential, site-selective installation of the aryl or heteroaryl groups onto polyhalogenated heterocycles through metal-catalyzed cross-coupling processes with organometallic reagents.[1,2] In this area, Suzuki-type reactions are particularly attractive, as they are largely unaffected by the presence of water and allow not only (hetero)aryl, but also vinyl and alkyl boron compounds, to participate in the coupling process.[3]

Pyrazole derivatives are important building blocks in organic synthesis and have found numerous applications as pharmaceuticals and agrochemicals.[4] Among these, poly(hetero)aromatic pyrazoles are particularly important compounds with a broad spectrum of biological effects, including kinase inhibitory,[5] estrogen receptor binding,[6] anti-inflammatory,[7] and herbicidal activities,[8] as illustrated in Figure 1. It is also of interest to note that the pyrazole nucleus of biologically relevant derivatives may also incorporate halogen atoms. Recently, we became interested in exploring new flexible synthetic routes to 1,3,5-trisubstituted pyrazoles that would allow rapid production of diverse arrays of analogues for biological evaluation with a particular emphasis on (hetero)aromatic derivatives. For this purpose we identified *N*-substituted 3,5-dihalogenated pyrazoles as highly attractive intermediates because of their inherent potential for diversification by established cross-coupling processes. Surprisingly, a search of the literature seemingly indicated that palladium-catalyzed coupling reactions had not been previously investigated on such substrates, and therefore, no experimental data regarding the selectivities of the coupling were available. This lack of precedence provided further impetus for us to explore this class of reactions. We naturally focused our attention on the use of pyrazoles bearing distinguishable halides at C-3 and C-5, as they would be normally considered as being the most favorable candidates for highly selective cross-coupling reactions. However, no practical and flexible approach to this class of compounds was available from the literature, which somehow reflected the difficulties inherent to selective halogenations of the pyrazole core at the carbon atoms adjacent to the nitrogen atom, most notably at C-3.[9] Within this context, we envisioned that direct assembly of *N*-substituted pyrazoles bearing suitable halides at C-3 and C-5 would normally be accessible by 1,3-dipolar cycloaddition of 4-halosydnones **1** with 3-halopropiolates **2**. 4-Halosydnones are well-documented, readily available mesoionic compounds that have been reported to cycloadd to alkynes efficiently to yield 5-halopyrazoles.[10] However, the participation of haloalkynes in this process had apparently not been

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previously investigated. 3-Halopropiolates appeared to be ideally suited for this purpose given the high reactivity of alkynyl esters in sydnone cycloaddition.[11] Furthermore, they are relatively stable, easily available compounds that should ultimately allow access to pyrazole derivatives with a free C-4 position upon decarboalkoxylation (Scheme 1).

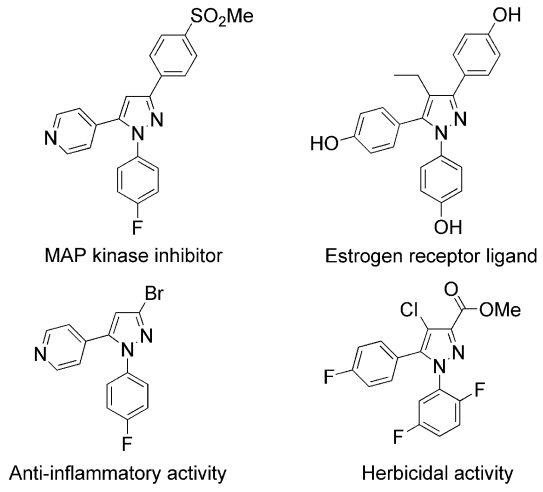
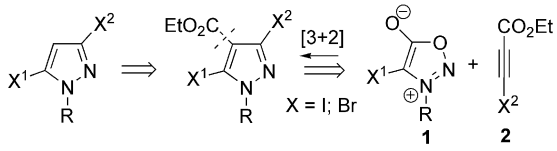


Figure 1. Some biologically active poly(hetero)aromatic pyrazoles.



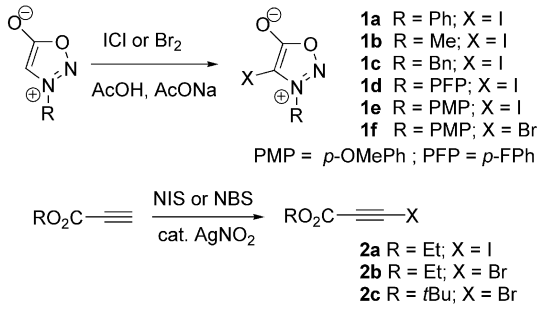
Scheme 1. Retrosynthetic analysis of 3,5-dihalopyrazoles.

In a previous report,[12] we demonstrated the viability of this strategy by the synthesis of *N*-*p*-methoxyphenyl (PMP) 3-bromo-5-iodopyrazole as a valuable scaffold for the one-pot preparation of dissymmetrical 3,5-(hetero)aromatic pyrazoles through successive Suzuki–Miyaura cross-coupling reactions. The PMP protecting group offers additional opportunity to access NH-pyrazole derivatives. Because of our interests in the synthesis of drug-like chemical collections for biological screening, we have investigated further the scope and limitations of the cycloaddition/cross-coupling approach to polysubstituted pyrazoles. In this context, we wish to disclose herein the results of our exploratory studies toward 1,3,5-trisubstituted pyrazoles.

Results and Discussion

Preparation of 4-Halosydnones and 1-Haloalkynes

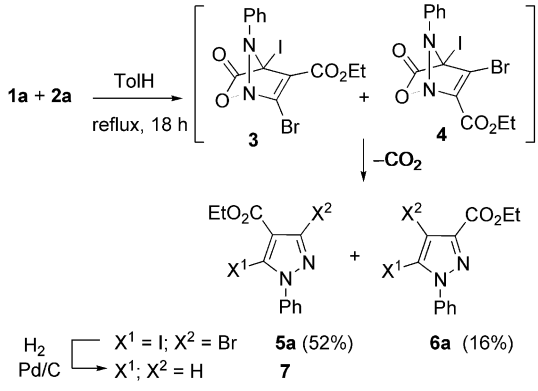
N-Substituted 4-halosydnones **1a**–**f**[10] and ethyl halopropiolates **2a**–**c**[13] were easily prepared following previously reported halogenation procedures (Scheme 2). *p*-Methoxyphenyl- and benzyl-protected sydnones are of particular interest, should 1*H*-pyrazoles be desired.[14]



Scheme 2.

1,3-Dipolar Cycloaddition: Access to 3,5-Dihalogenopyrazole-4-carboxylates

With the halo compounds in hand, the viability of haloalkynes participating in the sydnone 1,3-dipolar cycloaddition process was soon confirmed, and a representative experimental procedure is the following preparation of 3-bromo-5-iodopyrazole **5a** (Scheme 3). An equimolar mixture of iodosydnone **1a** and bromoalkyne **2b** was heated overnight in refluxing xylene. The reaction mixture was then cooled and concentrated in vacuo to furnish a crude 3:1 mixture of regioisomeric dihalopyrazoles **5a** and **6a**. The pyrazoles were easily separated by silica gel chromatography eluting with cyclohexane/AcOEt, which furnished desired pyrazole **5a** in an acceptable 52% isolated yield. The structure assignment was confirmed by comparison of the NMR spectroscopic data of the corresponding dehalogenated pyrazole **7**, obtained by hydrogenolysis of **5a** (50 mol-% Pd/C, 30 bar H_2, EtOH, 80 °C, 18 h, 39%) with the previously reported data.[15]

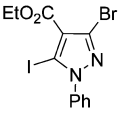
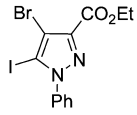
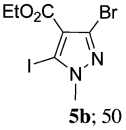
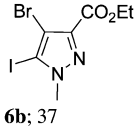
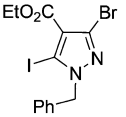
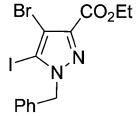
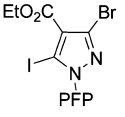
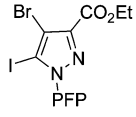
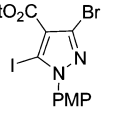
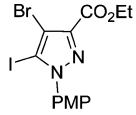
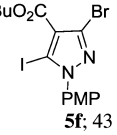
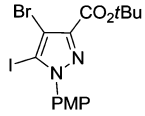
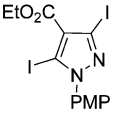
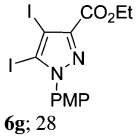
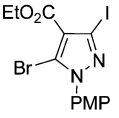
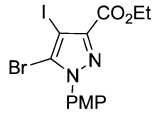


Scheme 3.

The scope of the reaction was then investigated by using various combinations of halosydnones and haloalkynes. The results are summarized in Table 1. The reaction toler-

ates various substitution patterns of the sydnones at N-1, including alkyl, benzyl, and aryl substituents. Firstly, a series of pairs of isomeric 3(4)-bromo-5-iodopyrazoles were obtained in good to excellent combined yields (64–87%).

Table 1. Cycloaddition of halosydnones with halopropiolates.[a]

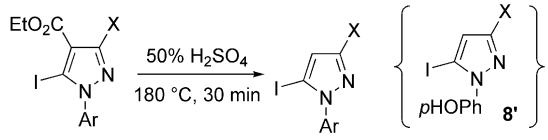
Entry	Substrates		Products; Isolated yields [%]		
1	**1a**	**2b**	 **5a**; 52	76:24[b] (68)[c]	 **6a**; 16
2	**1b**	**2b**	 **5b**; 50	58:42 (87)	 **6b**; 37
3	**1c**	**2b**	 **5c**; 39	59:41 (66)	 **6c**; 27
4	**1d**	**2b**	 **5d**; 48	75:25 (64)	 **6d**; 16
5	**1e**	**2b**	 **5e**; 63	75:25 (84)	 **6e**; 21
6	**1e**	**2c**	 **5f**; 43	77:23 (56)	 **6f**; 13
7	**1e**	**2a**	 **5g**; 58	60:40 (86)	 **6g**; 28
8	**1f**	**2a**	 **5h**; –	(0)	 **6h**; –

[a] Reactions were conducted in boiling xylene. [b] Ratios of crude reaction products as determined by ^{1}H NMR spectroscopy. [c] Combined isolated yields.

Although regioselectivities generally remained moderate (ratios 1.5:1 to 3:1), desired 3,5-dihalogenopyrazoles **5a**–**e** were always isolated as the major compounds in satisfying yields (39–63%; Table 1, Entries 1–5). Importantly, the reactions may be performed on a 10-mmol preparative scale without noticeable variations in yields. It is worth noting that the size of the ester group had essentially no influence on the regioselectivity (Table 1, Entry 6). Next, the methodology was successfully extended to the synthesis of diiodopyrazoles, as illustrated with the synthesis of pyrazoles **5g** and **6g** (Table 1, Entry 7). Finally, it was observed that our model bromosydnone **1f** was unstable under the reaction conditions, which is consistent with prior observations in the literature[16] and thus prevented access to isomeric 5-bromo-3-iodopyrazole **5h** (Table 1, Entry 8).

Dealkoxycarbonylation Step

N-Arylpyrazoles **5d**–**f** underwent facile deethoxycarbonylation in refluxing 50% aq. sulfuric acid to provide the corresponding dihalogenopyrazoles **8a**–**c** as the selected candidates for site-selective cross-coupling reactions. Clean and complete conversion of the starting materials was normally achieved within 30 min. However, it is important to note that in the case of *N*-*p*-anisylpyrazoles, much longer reaction times led to the production of undesired demethylated pyrazoles **8′** (Scheme 4).

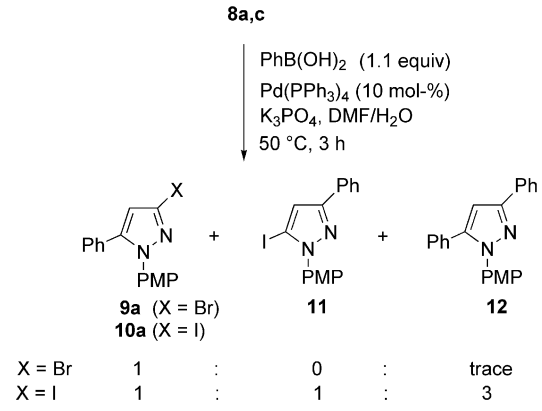


8a Ar = PMP; X = Br; 65%
8b Ar = PFP; X = Br; 95%
8c Ar = PMP; X = I; 51%

Scheme 4.

Pyrazole Functionalization by Suzuki-Type Cross-Coupling Reactions

With these results in hand, we next focused our attention on their application in C(sp^2)–C(sp^2) bond formation by Pd-catalyzed cross-coupling reactions. We chose the reaction of **8a** and **8c** with phenylboronic acid (1.1 equiv.) under Suzuki-type conditions as our starting point for the evaluation of the effectiveness and selectivity of the cross-coupling reactions. As expected, the cross-coupling reaction was shown to be highly selective for the C-5 position in the case of 3-bromo-5-iodopyrazole **8a**. Thus, under the optimum set of reaction conditions [10 mol-% $Pd(PPh_3)_4$, 2 equiv. K_3PO_4, DMF/H_2O (4:1), 50 °C, 2.5 h], **9a** was cleanly obtained as the only monocoupled product in 69% isolated yield. In contrast, the reaction of 3,5-diiodopyrazole **8c** proved nonselective under identical conditions, affording inseparable mixtures of mono- and bis-arylated adducts (compounds **10a**, **11**, and **12** obtained in a 1:1:3 ratio as determined by GC–MS; Scheme 5).[17]

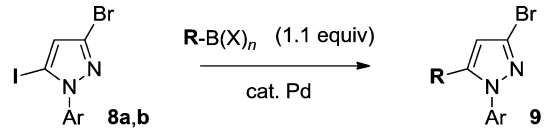


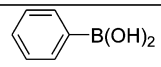
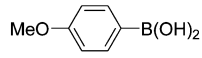
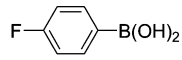
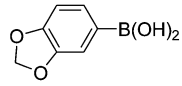
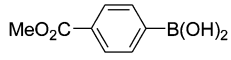
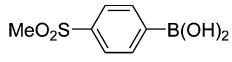
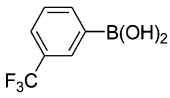
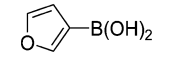
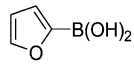
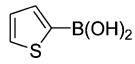
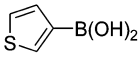
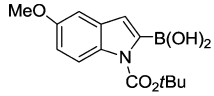
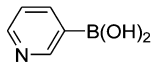
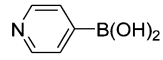
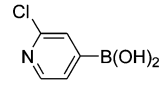
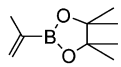
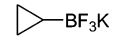
Scheme 5.

Accordingly, application of this strategy to a variety of electron-poor and electron-rich arylboronic acids, as well as to a series of heteroarylboronic acids, including 3(4)-pyridyl-, 2(3)-furyl-, 2(3)-thienyl-, and 2-indolylboronic acids, generally furnished the corresponding coupling products in good to excellent yields (Table 2, Entries 1–17). The low yields obtained in the synthesis of **9e** and **9l** (Table 2, Entries 5 and 12) was attributed to the poor stability of the corresponding boronic acids under the reaction conditions. It is interesting to note that 3-bromo-1-(4-fluorophenyl)-5-(4-pyridinyl)pyrazole (**9f**) has been previously shown to possess very potent anti-inflammatory properties.[7] In an effort to further diversify and broaden the range of 5-C(sp^2)-functionalized 3-bromopyrazoles, it was shown that isopropenyl boronic acid pinacol ester could be successfully entered into the Suzuki–Miyaura coupling of **8a** under the previous reaction conditions to provide the corresponding pyrazole derivative **9r** in 77% isolated yield (Table 2, Entry 18). The introduction of a cyclopropyl group to the pyrazole moiety was also attempted. The cyclopropyl group is increasingly incorporated into pharmaceuticals and agrochemicals due to its particular spatial and electronic properties as well as its high metabolic stability.[18] Interestingly, **8b** underwent selective cross-coupling with potassium cyclopropyl trifluoroborate (1.1 equiv.) at C-5 by using $Pd(OAc)_2$/RuPhos as a catalyst system[19] in aqueous toluene to give 5-cyclopropylpyrazole **9s** in 45% isolated yield (Table 2, Entry 19).

We then briefly investigated the reactivity of the remaining halogen atom at C-3 of compounds **9** toward Pd-catalyzed C–C bond-forming reactions. As illustrated by the synthesis of pyrazoles **13a**–**d**, Suzuki cross-coupling reactions of bromine derivatives **9j**,**o** with (hetero)aryl and alkyl boron compounds proved very successful using the previous reaction conditions at a slightly higher reaction temperature, thereby opening access to unsymmetrically 3,5-bisfunctionalized pyrazoles (Table 3). The possibility of introducing two different (hetero)aryl substituents at the C-5 and C-3 positions of the pyrazole nucleus in a one-pot sequential fashion was then investigated. Although one-pot

Table 2. Monocoupling of 3-bromo-5-iodopyrazoles with various boron compounds.

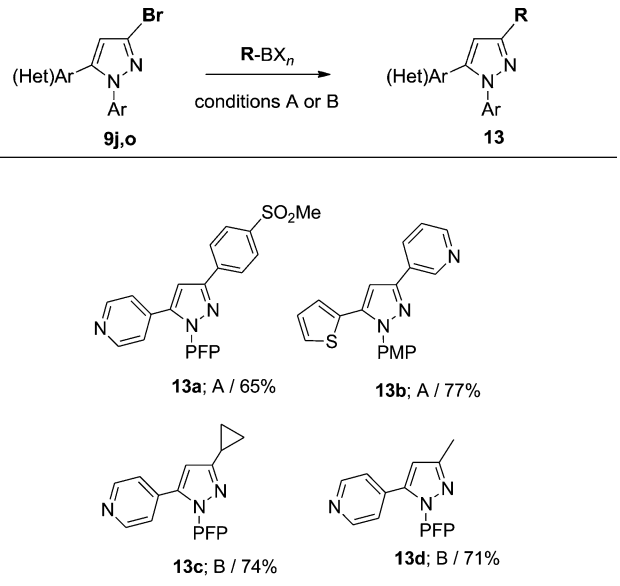


Entry	Substrate / conditions[a]	Boron compound	Product/ Yield [%]
1	**8a** / A		**9a** / 69
2	**8a** / A		**9b** / 94
3	**8a** / A		**9c** / 87
4	**8b** / A		**9d** / 81
5	**8b** / A		**9e** / 38
6	**8b** / A		**9f** / 69
7	**8b** / A		**9g** / 79
8	**8b** / A		**9h** / 81
9	**8a** / A		**9i** / 95
10	**8a** / A		**9j** / 91
11	**8a** / A		**9k** / 91
12	**8a** / A		**9l** / 30
13	**8a** / A		**9m** / 83
14	**8a** / A		**9n** / 69[b]
15	**8b** / A		**9o** / 64[b]
16	**8a** / A		**9p** / 51[b]
17	**8b** / A		**9q** / 54[b]
18	**8b** / A		**9r** / 77[b]
19	**8b** / B		**9s** / 45

[a] Single runs conducted on 0.2-mmol scale. Conditions A: $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (2 equiv.), DMF/H_2O (4:1), 50 °C, 2–3 h; conditions B: $Pd(OAc)_2$ (10 mol-%), Ruphos (20 mol-%), K_3PO_4 (3 equiv.), toluene/H_2O (10:1), 100 °C, 6 h. [b] Reaction conducted at 80 °C.

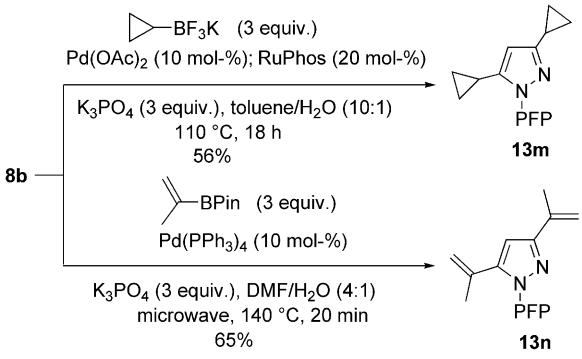
double Suzuki–Miyaura cross-coupling reactions remain rare, recent years have witnessed heightened efforts in this area[20] that also address important economical and environmental issues. Efficient processes should preferably avoid the need for additional base, catalyst, or ligand to cross-couple the second boronic acid efficiently.

Table 3. Suzuki coupling of 3-bromopyrazoles.[a]



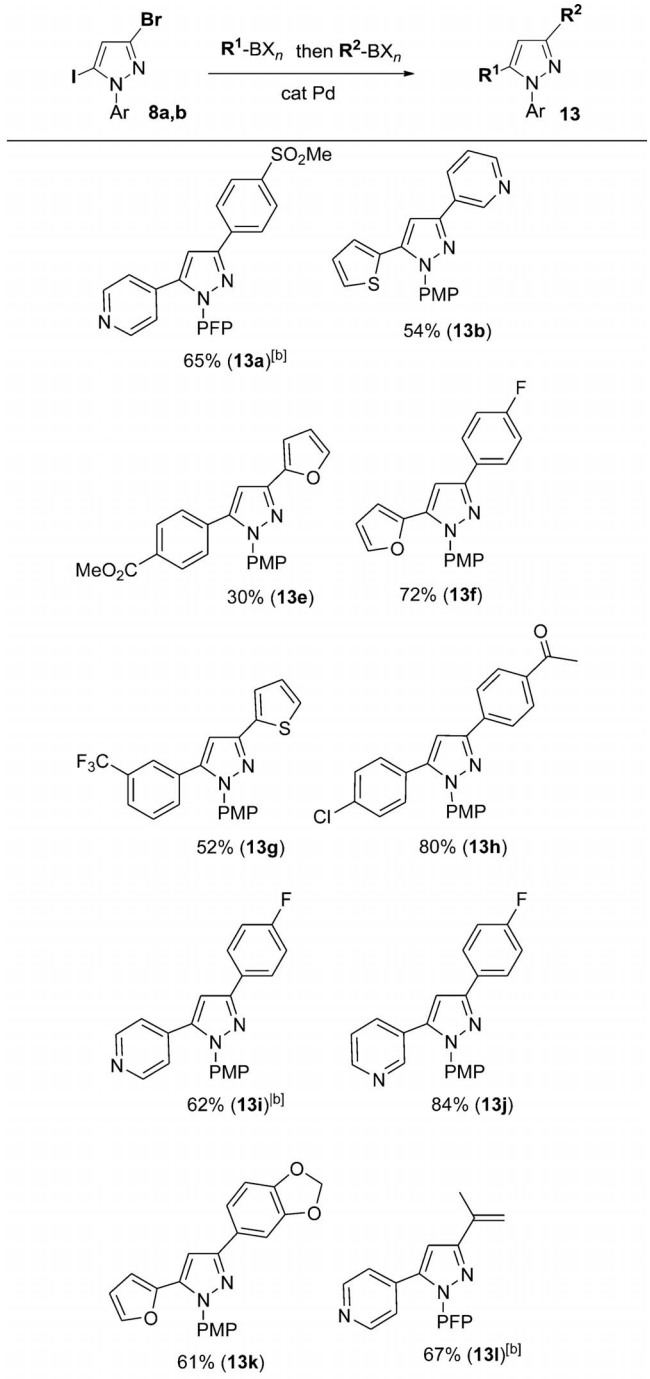
[a] Single runs conducted on 0.2-mmol scale. Conditions A: $RB(OH)_2$ (1.3 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (3 equiv.), DMF/H_2O (4:1), 80 °C, 18 h; conditions B: RBF_3K (2 equiv.), $Pd(OAc)_2$ (10 mol-%), Ruphos (20 mol-%), K_3PO_4 (3 equiv.), toluene/H_2O (10:1), 110 °C, 12 h.

Fortunately, a synthetic procedure based on the previous set of reaction conditions and Pd catalyst could be established for the rapid synthesis of a small array of 3,5-bis(heteroaromatic) pyrazoles that essentially only required a temperature adjustment. Thus, the dihalogenopyrazoles (1.0 equiv.) and a first boronic acid (1.1 equiv.) underwent the Suzuki–Miyaura cross-coupling reaction under the previous conditions [10 mol-% $Pd(PPh_3)_4$, 2 equiv. of K_3PO_4, DMF/H_2O (4:1), 50 °C]. Once the reaction had reached completion, as judged by TLC (ca. 2–3 h), the second boronic acid (1.3 equiv.) was added, and the reaction was left to stir overnight at 80 °C to afford the corresponding bis-cross-coupled pyrazole derivatives in satisfying yields. As illustrated with the synthesis of 3-isopropenyl-5-(4-pyridyl)-pyrazole **13l**, the procedure allows different boron reagents



Scheme 6. Synthesis of symmetrically substituted pyrazoles.

Table 4. One-pot Suzuki bis-coupling.[a]



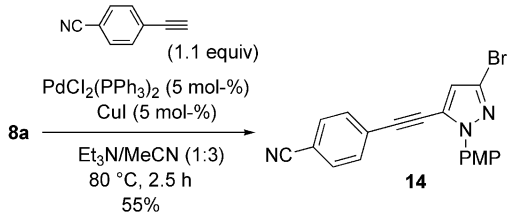
[a] Single runs conducted on 0.2-mmol scale. Conditions: $R^1B(OH)_2$ (1.1 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (3 equiv.), DMF/H_2O (4:1), 50 °C, 3 h; then $R^2B(OH)_2$ (1.3 equiv.; or isopropenylboronic acid pinacol ester), 80 °C, 18 h. [b] First coupling was performed at 80 °C.

(i.e., boronic acid and pinacol ester) to take part in the process (Table 4).

As illustrated in Scheme 6, symmetrically disubstituted pyrazoles may also be easily accessed. It is worth mentioning that a high temperature, short-time microwave procedure may be used for the heating.

Pyrazole Functionalization by Sonogashira Cross-Coupling Reactions

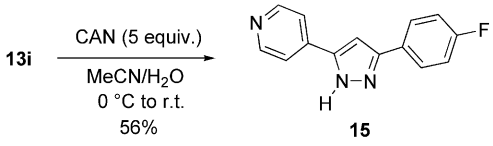
Next, the participation of dihalogenopyrazoles in the Sonogashira cross-coupling process was also briefly explored given the high synthetic and biological value of acetylenic pyrazoles.[21] For instance, **8a** underwent cross-coupling with 4-cyanophenylacetylene to give the corresponding 3-alkynyl-furopyridinone **14** in 55% isolated yield (Scheme 7).



Scheme 7. Sonogashira cross-coupling.

PMP Protecting Group Removal: Access to 1-Unsubstituted Pyrazoles

Finally, as illustrated with the synthesis of **15** (Scheme 8) it was shown that *N*-PMP-pyrazoles may be easily deprotected with ceric ammonium nitrate, thus expanding the synthetic potential of our strategy.



Scheme 8. PMP protecting group removal.

Conclusions

The 1,3-dipolar cycloaddition of 4-halosydnones with 1-haloalkynes opens straightforward access to 3,5-dihalopyrazoles of potential utility as scaffolds for drug discovery. The somewhat modest regioselectivities achieved in this process are compensated by repeatability, scalability, and high global yields as well as by the ease of separation of the regioisomers. These halo compounds proved to be valuable substrates for the elaboration of unsymmetrically 3,5-substituted pyrazole derivatives by Pd-catalyzed cross-coupling reactions. Notably, the flexible and site-selective introduction of different (hetero)aryl, vinyl, or alkyl substituents at the C-5 and C-3 positions of the pyrazole core could be achieved through sequential Suzuki-type reactions with various boron compounds. Furthermore, the Suzuki coupling sequence may be amenable to a one-pot procedure to enable rapid generation of targeted compounds. Overall, the procedures introduced here allow rapid, practical, and modular access to diversely functionalized pyrazole derivatives from readily available substrates, and reagents and should find broad applications in the preparation of chemical libraries of potentially biologically active compounds.

Experimental Section

General Methods: All reactions were run under open atmosphere by using commercial-grade solvents except for reactions catalyzed by palladium, which were carried out under an argon atmosphere. Analytical thin-layer chromatography (TLC) was carried out on Merck silica 60/F-240 aluminum-backed plates. Visualization of the developed chromatogram was done by UV absorbance. Flash chromatography was performed by using Merck silica gel 60 (40–63 μm). NMR spectra were recorded with either a 300 or 400 MHz spectrometer in the indicated solvent. Chemical shifts (δ) are given from TMS (δ = 0.00 ppm) in parts per million (ppm) with the residual signals of deuterated solvent used as standards [$CDCl_3$: ^1H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm (t)]. Coupling constants (J) are expressed in Hertz (Hz) and spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), and br. (broad). Commercially available reagents were used as purchased. Halosydnones **1a**–**f** were prepared in three steps from the corresponding *N*-arylglycines according to published procedures.[10b,22] Haloalkynes **2a**–**c** were obtained by silver-catalyzed halogenation of ethyl or *tert*-butyl propiolates with *N*-bromo- or *N*-iodosuccinimide.[23]

General Procedure for the Synthesis of Halopyrazoles 5 and 6: A mixture of the selected halosydnone (11 mmol) and halopropiolate (11 mmol) in xylene (10 mL) was heated at reflux overnight. The reaction mixture was then cooled and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt) to give, in a first fraction, the 3,5-dihalogenopyrazole **5** and, in a second fraction, the isomeric 4,5-dihalogenopyrazole **6**.

Ethyl 3-Bromo-5-iodo-1-phenyl-1*H*-pyrazole-4-carboxylate (5a): Yield: 2.40 g (52%), white solid, m.p. 88 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.2 Hz, 3 H, CH_3), 4.39 (q, J = 7.1 Hz, 2 H, CH_2), 7.42–7.51 (m, 5 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6 (CH_3), 61.5 (CH_2), 91.1 (5-C), 119.0 (3-C), 127.4, 129.5, 130.3, 130.7 (arom.), 139.9 (4-C), 161.2 (CO) ppm. HRMS (EI): calcd. for $C_{12}H_{10}BrIN_2O_2$ $[M]^+$ 419.8970; found 419.8971.

Ethyl 3-Bromo-5-iodo-1-methyl-1*H*-pyrazole-4-carboxylate (5b): Yield: 1.97 g (50%), white solid, m.p. 77 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 3 H, CH_3), 3.97 (s, 3 H, NCH_3), 4.35 (q, J = 7.1 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_3), 41.5 (CH_3), 61.2 (CH_2), 91.0 (5-C), 117.7 (3-C), 128.8 (4-C), 161.0 (CO) ppm. HRMS (EI): calcd. for $C_7H_8BrIN_2O_2$ $[M]^+$ 357.8814; found 357.8813.

Ethyl 1-Benzyl-3-bromo-5-iodo-1*H*-pyrazole-4-carboxylate (5c): Yield: 1.86 g (39%), white solid, m.p. 92 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 3 H, CH_3), 4.29 (q, J = 7.1 Hz, 2 H, CH_2), 5.39 (s, 2 H, CH_2), 7.18–7.28 (m, 5 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 57.0 (CH_2), 61.0 (CH_2),

90.3 (5-C), 117.8 (3-C), 127.7, 128.4, 128.9, 129.3, 134.8 (arom. + 4-C), 160.8 (CO) ppm. HRMS (CI): calcd. for $C_{13}H_{13}BrIN_2O_2$ [M + H]$^+$ 434.9205; found 434.9205.

Ethyl 3-Bromo-1-(4-fluorophenyl)-5-iodo-1*H*-pyrazole-4-carboxylate (5d): Yield: 2.31 g (48%), white solid, m.p. 116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3 H, CH_3), 4.32 (q, J = 7.1 Hz, 2 H, CH_2), 7.09–7.15 (m, 2 H, arom.), 7.36–7.40 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 61.0 (CH_2), 91.4 (5-C), 116.0 (d, $^2J_{C,F}$ = 23.2 Hz), 118.6 (3-C), 128.9 (d, $^3J_{C,F}$ = 9.3 Hz), 130.2 (4-C), 135.5 (d, $^4J_{C,F}$ = 3.3 Hz), 160.5 (CO), 162.8 (d, $^1J_{C,F}$ = 250.8 Hz) ppm. HRMS (CI): calcd. for $C_{12}H_{10}BrFIN_2O_2$ [M + H]$^+$ 438.8954; found 438.8955.

Ethyl 3-Bromo-5-iodo-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylate (5e): Yield: 3.12 g (63%), white solid, m.p. 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 4.39 (q, J = 7.1 Hz, 2 H, CH_2), 6.99 (d, J = 8.9 Hz, 2 H, arom.), 7.35 (d, J = 8.9 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_3), 55.7 (OCH_3), 61.1 (CH_2), 91.7 (5-C), 114.2 (arom.), 118.3 (3-C), 128.3, 130.0, 132.6 (arom. + 4-C), 160.5 (CO), 160.9 (CO) ppm. HRMS (CI): calcd. for $C_{13}H_{13}BrIN_2O_3$ [M + H]$^+$ 450.9154; found 450.9155.

***tert*-Butyl 3-Bromo-5-iodo-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylate (5f):** Yield: 2.26 g (43%), white solid, m.p. 75–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 9 H, $3CH_3$), 3.87 (s, 3 H, OCH_3), 6.97 (d, J = 8.8 Hz, 2 H, arom.), 7.32 (d, J = 8.8 Hz, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 ($3CH_3$), 55.7 (OCH_3), 82.6 (CMe_3), 91.0 (5-C), 114.3 (arom.), 119.3 (3-C), 128.5, 130.0, 132.8, 144.5 (arom. + 4-C), 160.1 (CO), 160.6 (CO) ppm.

Ethyl 3,5-Diiodo-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxylate (5g): Yield: 3.18 g (58%), white solid, m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 4.37 (q, J = 7.1 Hz, 2 H, CH_2), 6.96 (d, J = 8.9 Hz, 2 H, arom.), 7.35 (d, J = 8.9 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3), 55.7 (OCH_3), 61.1 (CH_2), 90.7 (5-C), 100.4 (3-C), 114.2, 121.8, 128.4, 132.7 (arom. + 4-C), 160.5 (CO), 160.9 (CO) ppm. HRMS (EI): calcd. for $C_{13}H_{12}I_2N_2O_3$ [M]$^+$ 497.8937; found 497.8936.

Spectroscopic Data for the Isomeric 4,5-Dihalopyrazoles 6

Ethyl 4-Bromo-5-iodo-1-phenyl-1*H*-pyrazole-3-carboxylate (6a): Yield: 0.74 g (16%), white solid, m.p. 108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 3 H, CH_3), 4.45 (q, J = 7.1 Hz, 2 H, CH_2), 7.50 (s, 5 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 61.7 (CH_2), 92.3 (5-C), 108.3 (4-C), 126.6, 129.2, 129.9, 140.1, 143.0 (arom. + 3-C), 160.4 (CO) ppm. HRMS (EI): calcd. for $C_{12}H_{10}BrIN_2O_2$ [M]$^+$ 419.8970; found 419.8970.

Ethyl 4-Bromo-5-iodo-1-methyl-1*H*-pyrazole-3-carboxylate (6b): Yield: 1.46 g (37%), white solid, m.p. 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 3 H, CH_3), 4.06 (s, 3 H, NCH_3), 4.42 (q, J = 7.1 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7 (CH_3), 42.4 (NCH_3), 61.9 (CH_2), 92.2 (5-C), 107.0 (4-C), 141.8 (3-C), 160.6 (CO) ppm. HRMS (EI): calcd. for $C_7H_8BrIN_2O_2$ [M]$^+$ 357.8814; found 357.8814.

Ethyl 1-Benzyl-4-bromo-5-iodo-1*H*-pyrazole-3-carboxylate (6c): Yield: 1.29 g (27%), white solid, m.p. 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 3 H, CH_3), 4.43 (q, J = 7.1 Hz, 2 H, CH_2), 5.53 (s, 2 H, CH_2), 7.20–7.22 (m, 2 H, arom.), 7.30–7.32 (m, 3 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 58.1 (CH_2), 61.6 (CH_2), 91.4 (5-C), 107.3 (4-C), 127.6, 128.4, 128.9, 134.7, 142.1 (arom. + 3-C), 160.4 (CO) ppm. HRMS (CI): calcd. for $C_{13}H_{13}BrIN_2O_2$ [M + H]$^+$ 434.9205; found 434.9203.

Ethyl 4-Bromo-1-(4-fluorophenyl)-5-iodo-1*H*-pyrazole-3-carboxylate (6d): Yield: 0.77 g (16%), white solid, m.p. 112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, J = 7.1 Hz, 3 H, CH_3), 4.45 (q, J = 7.1 Hz, 2 H, CH_2), 7.12–7.19 (m, 2 H, arom.), 7.42–7.48 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 61.7 (CH_2), 92.6 (5-C), 108.2 (4-C), 116.1 (d, $^2J_{C,F}$ = 23.0 Hz), 128.6 (d, $^3J_{C,F}$ = 10.0 Hz), 136.1, 143.0 (arom. + 3-C), 160.2 (CO), 163.0 (d, $^1J_{C,F}$ = 250.8 Hz) ppm. HRMS (CI): calcd. for $C_{12}H_9BrFIN_2O_2$ [M + H]$^+$ 438.8954; found 438.8954.

Ethyl 4-Bromo-5-iodo-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (6e): Yield: 1.04 g (21%), white solid, m.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 4.41 (q, J = 7.1 Hz, 2 H, CH_2), 6.96 (d, J = 8.7 Hz, 2 H, arom.), 7.36 (d, J = 8.7 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_3), 55.7 (OCH_3), 61.6 (CH_2), 93.0 (5-C), 107.8 (4-C), 114.2, 127.9, 133.2, 142.7 (arom. + 3-C), 160.5 (CO), 160.8 (CO) ppm. HRMS (ESI): calcd. for $C_{13}H_{13}BrIN_2O_3$ [M + H]$^+$ 450.9147; found 450.9165.

***tert*-Butyl 4-Bromo-5-iodo-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (6f):** Yield: 0.68 g (13%), white solid, m.p. 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 9 H, $3CH_3$), 3.87 (s, 3 H, OCH_3), 6.97 (d, J = 8.8 Hz, 2 H, arom.), 7.39 (d, J = 8.8 Hz, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4 ($3CH_3$), 55.8 (OCH_3), 83.0 (CMe_3), 107.3 (4-C), 114.2, 128.0, 133.5, 144.1 (arom. + 3-C), 159.7 (CO), 160.5 (CO) ppm.

Ethyl 4,5-Diiodo-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (6g): Yield: 1.53 g (28%), white solid, m.p. 138–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 4.44 (q, J = 7.1 Hz, 2 H, CH_2), 6.94 (d, J = 8.8 Hz, 2 H, arom.), 7.35 (d, J = 8.8 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3), 56.0 (OCH_3), 62.1 (CH_2), 100.2 (5-C), 114.5, 121.1, 128.4, 134.0, 146.3 (arom. + 3-C + 4-C), 160.9 (CO), 161.0 (CO) ppm. HRMS (EI): calcd. for $C_{13}H_{12}I_2N_2O_3$ [M]$^+$ 497.8937; found 497.8938.

General Procedure for the Synthesis of Pyrazole 8a-c: A solution of the selected ethyl 3-bromo-5-iodo-1*H*-pyrazole-4-carboxylate **5** (1.5 mmol) in 50% aqueous H_2SO_4 (20 mL) was heated at 180 °C for 30 min. The reaction mixture was then cooled to room temperature, diluted with water (50 mL), and extracted with AcOEt (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, cyclohexane/AcOEt, 90:10).

3-Bromo-5-iodo-1-(4-methoxyphenyl)-1*H*-pyrazole (8a): Yield: 0.37 g (65%), white solid, m.p. 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.58 (s, 1 H, 4-H), 6.97 (d, J = 8.8 Hz, 2 H, arom.), 7.36 (d, J = 8.8 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 83.8 (5-C), 114.1, 118.9, 127.9, 129.2, 132.8, (arom. + 3-C + 4-C), 160.1 (CO) ppm. HRMS (ESI): calcd. for $C_{10}H_9BrIN_2O$ [M + H]$^+$ 378.8934; found 378.8943.

3-Bromo-1-(4-fluorophenyl)-5-iodo-1*H*-pyrazole (8b): Yield: 0.52 g (95%), white solid, m.p. 101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (s, 1 H, 4-H), 7.14–7.19 (m, 2 H, arom.), 7.44–7.48 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.4 (5-C), 115.0 (d, $^2J_{C,F}$ = 23.1 Hz), 119.5 (4-C), 128.4 (d, $^3J_{C,F}$ = 8.8 Hz), 129.8 (3-C), 135.8 (d, $^4J_{C,F}$ = 2.8 Hz), 162.5 (d, $^1J_{C,F}$ = 250.3 Hz) ppm. HRMS (CI): calcd. for $C_9H_6BrFIN_2$ [M + H]$^+$ 366.8743; found 366.8743.

3,5-Diiodo-1-(4-methoxyphenyl)-1*H*-pyrazole (8c): Yield: 0.33 g (51%), white solid, m.p. 110–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, CH_3), 6.70 (s, 1 H, 4-H), 6.96 (d, J = 9.1 Hz, 2 H,

arom.), 7.36 (d, J = 9.1 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0 (OCH_3), 84.1 (5-C), 98.4 (3-C), 114.4, 125.0, 128.2, 133.1 (arom. + 4-C), 160.4 (CO) ppm. HRMS (EI): calcd. for $C_{10}H_8I_2N_2O$ $[M]^+$ 425.8726; found 425.8726.

Suzuki Cross-Coupling at C-5/Synthesis of 5-(Hetero)arylpyrazoles 9

General Procedure for the Coupling of Boronic Acids and Boronic Acid Pinacol Esters (Conditions A): In a glass tube fitted with a Teflon screw seal, $Pd(PPh_3)_4$ (0.02 mmol), K_3PO_4 (0.40 mmol) and the selected boronic acid (0.22 mmol) were added to a solution of the selected 3-bromo-5-iodopyrazole **5** (0.20 mmol) in a degassed mixture of DMF/H_2O (4:1; 2 mL). The reactor was flushed with argon, and the reaction mixture was left to stir at the indicated temperature (50 or 80 °C) until complete consumption of the starting material as judged by TLC (2–3 h). The reaction mixture was then diluted with water (20 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt).

3-Bromo-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole (9a): Yield: 45 mg (69%), white solid, m.p. 80–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OCH_3), 6.50 (s, 1 H, 4-H), 6.83 (d, J = 8.9 Hz, 2 H, arom.), 7.16–7.22 (m, 4 H, arom.), 7.30–7.38 (m, 3 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 109.7 (4-C), 114.2, 126.8, 127.2, 128.7, 128.8, 128.9, 129.5, 132.7 (arom. + 3-C), 148.7 (5-C), 159.2 (CO) ppm. HRMS (ESI): calcd. for $C_{16}H_{14}BrN_2O$ $[M + H]^+$ 329.0284; found 329.0287.

3-Bromo-1,5-bis(4-methoxyphenyl)-1*H*-pyrazole (9b): Yield: 67 mg (94%), white solid, m.p. 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.43 (s, 1 H, 4-H), 6.80–6.85 (m, 4 H, arom.), 7.11 (d, J = 8.7 Hz, 2 H, arom.), 7.19 (d, J = 8.9 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 55.6 (OCH_3), 109.1 (4-C), 114.1, 114.2, 121.8, 126.8, 127.1, 130.1, 132.7 (arom. + 3-C), 145.0 (5-C), 159.1 (CO), 159.9 (CO) ppm. HRMS (CI): calcd. for $C_{17}H_{15}BrN_2O_2$ $[M + H]^+$ 359.0395; found 359.0395.

3-Bromo-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazole (9c): Yield: 60 mg (87%), white solid, m.p. 108–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, OCH_3), 6.47 (s, 1 H, 4-H), 6.84 (d, J = 8.7 Hz, 2 H, arom.), 6.96–7.02 (m, 2 H, arom.), 7.15–7.18 (m, 4 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 109.7 (4-C), 114.3 (arom.), 115.9 (d, $^2J_{C,F}$ = 21.9 Hz), 125.6 (d, $^4J_{C,F}$ = 3.3 Hz), 126.8, 127.2 (arom. + 3-C), 130.7 (d, $^3J_{C,F}$ = 8.8 Hz), 132.4, 144.2 (arom. + 5-C), 159.3 (CO), 163.9 (d, $^1J_{C,F}$ = 249.7 Hz) ppm. HRMS (EI): calcd. for $C_{16}H_{12}BrFN_2O$ $[M]^+$ 346.0117; found 346.0117.

5-(Benzo[*d*][1,3]dioxol-5-yl)-3-bromo-1-(4-fluorophenyl)-1*H*-pyrazole (9d): Yield: 58 mg (81%), white solid, m.p. 138–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (s, 2 H, OCH_2O), 6.47 (s, 1 H, 4-H), 6.65–6.80 (m, 3 H, arom.), 7.04–7.10 (m, 2 H, arom.), 7.27–7.32 (m, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.6 (OCH_2O), 108.7, 109.1, 110.0 (arom. + 4-C), 116.0 (d, $^2J_{C,F}$ = 23.0 Hz), 122.8, 123.1 (arom.), 127.1 (d, $^3J_{C,F}$ = 8.8 Hz), 127.7 (3-C), 135.5 (d, $^4J_{C,F}$ = 3.3 Hz), 145.0, 148.0, 148.4 (2CO + 5-C), 160.9 (d, $^1J_{C,F}$ = 248.0 Hz) ppm. HRMS (CI): calcd. for $C_{16}H_{11}BrFN_2O_2$ $[M + H]^+$ 360.9982; found 360.9994.

Methyl 4-[3-Bromo-1-(4-fluorophenyl)-1*H*-pyrazol-5-yl]benzoate (9e): Yield: 28 mg (38%), white solid, m.p. 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 6.51 (s, 1 H, 4-H), 6.93–6.99 (m, 2 H, arom.), 7.14–7.20 (m, 4 H, arom.), 7.91 (d, J = 6.3 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.5 (OCH_3), 110.8 (4-C), 116.3 (d, $^2J_{C,F}$ = 23.6 Hz), 127.2 (d, $^3J_{C,F}$ = 8.8 Hz), 128.0, 128.7, 130.1, 130.6, 133.4 (arom. + 3-C), 135.3 (d, $^4J_{C,F}$ = 3.3 Hz), 144.2 (5-C), 162.2 (d, $^1J_{C,F}$ = 249.2 Hz), 166.4 (C=O) ppm. HRMS (ESI): calcd. for $C_{17}H_{13}BrFN_2O_2$ $[M + H]^+$ 375.0139; found 375.0146.

3-Bromo-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrazole (9f): Yield: 54 mg (69%), yellow solid, m.p. 183–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06 (s, 3 H, CH_3), 6.61 (s, 1 H, 4-H), 7.03–7.09 (m, 2 H, arom.), 7.21–7.26 (m, 2 H, arom.), 7.38 (d, J = 8.5 Hz, 2 H, arom.), 7.88 (d, J = 8.5 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.5 (CH_3), 111.3 (4-C), 116.5 (d, $^2J_{C,F}$ = 23.6 Hz), 127.3 (d, $^3J_{C,F}$ = 8.8 Hz), 128.0, 128.1, 129.5, 134.4 (arom. + 3-C), 135.0 (d, $^4J_{C,F}$ = 3.3 Hz), 141.0, 143.2 (C-SO_2Me + 5-C), 162.2 (d, $^1J_{C,F}$ = 249.7 Hz) ppm. HRMS (ESI): calcd. for $C_{16}H_{13}BrFN_2O_2S$ $[M + H]^+$ 394.9860; found 394.9869.

3-Bromo-1-(4-fluorophenyl)-5-(3-trifluorophenyl)-1*H*-pyrazole (9g): Yield: 61 mg (79%), yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1 H, 4-H), 7.03–7.07 (m, 2 H, arom.), 7.22–7.24 (m, 1 H, arom.), 7.31–7.34 (m, 1 H, arom.), 7.42–7.49 (m, 2 H, arom.), 7.59–7.61 (m, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.7 (4-C), 116.3 (d, $^2J_{C,F}$ = 23.5 Hz), 123.7 (q, $^1J_{C,F}$ = 272 Hz, CF_3), 125.5 (q, $^3J_{C,F}$ = 3.7 Hz), 125.8 (q, $^3J_{C,F}$ = 3.7 Hz), 127.3 (d, $^3J_{C,F}$ = 8.8 Hz), 128.0, 129.4, 129.9, 131.9 (arom. + 3-C), 135.1 (d, $^4J_{C,F}$ = 3.6 Hz), 143.7 (5-C), 162.2 (d, $^1J_{C,F}$ = 249.7 Hz, C-F) ppm.

3-Bromo-1-(4-fluorophenyl)-5-(furan-3-yl)-1*H*-pyrazole (9h): Yield: 50 mg (81%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (s, 1 H, arom), 6.47 (s, 1 H, 4-H), 7.08–7.14 (m, 2 H, arom.), 7.23 (s, 1 H, arom.), 7.34–7.37 (m, 3 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.1, 109.9 (arom. + 4-C), 114.8 (3-C), 116.3 (d, $^2J_{C,F}$ = 23.0 Hz), 127.7 (arom.), 127.8 (d, $^3J_{C,F}$ = 8.8 Hz), 135.6 (d, $^4J_{C,F}$ = 3.29 Hz), 137.8 (5-C), 140.8, 143.6 (arom.), 162.5 (d, $^1J_{C,F}$ = 249.2 Hz) ppm. HRMS (ESI): calcd. for $C_{13}H_9BrFN_2O$ $[M + H]^+$ 306.9877; found 306.9889.

3-Bromo-5-(furan-2-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole (9i): Yield: 60 mg (95%), white solid, m.p. 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 5.88 (d, J = 3.5 Hz, 1 H, arom.), 6.31 (dd, J = 1.8 and 3.5 Hz, 1 H, arom.), 6.65 (s, 1 H, 4-H), 6.95 (d, J = 8.8 Hz, 2 H, arom.), 7.31 (d, J = 8.8 Hz, 2 H, arom.), 7.39 (d, J = 1.8 Hz, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 107.8 (4-C), 109.5, 111.4, 114.4 (arom.), 127.1 (3-C), 127.7, 132.6, 136.8, 143.0, 143.5 (arom.), 160.1 (CO) ppm. HRMS (CI): calcd. for $C_{14}H_{11}BrN_2O_2$ $[M + H]^+$ 319.0082; found 319.0081.

3-Bromo-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1*H*-pyrazole (9j): Yield: 61 mg (91%), white solid, m.p. 140–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, OCH_3), 6.52 (s, 1 H, 4-H), 6.80–6.92 (m, 4 H, arom.), 7.22–7.26 (m, 3 H, arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 109.2 (4-C), 114.4, 127.1, 127.2, 127.5, 127.8, 128.0, 130.1, 132.2 (arom. + 3-C), 139.5 (5-C), 160.1 (CO) ppm. HRMS (CI): calcd. for $C_{14}H_{11}BrN_2OS$ $[M + H]^+$ 334.9854; found 334.9855.

3-Bromo-1-(4-methoxyphenyl)-5-(thiophen-3-yl)-1*H*-pyrazole (9k): Yield: 61 mg (91%), yellow solid, m.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 6.51 (s, 1 H, 4-H), 6.50–6.90 (m, 3 H, arom.), 7.04 (dd, J = 2.8, 1.1 Hz, 1 H, arom.), 7.23–7.26 (m, 3 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 108.9 (4-C), 114.4, 124.4, 126.9, 127.3, 127.1, 127.4, 129.6, 132.7 (arom. + 3-C), 140.8 (5-C), 159.7 (CO) ppm. HRMS (EI): calcd. for $C_{14}H_{11}BrN_2OS$ $[M]^+$ 333.9776; found 333.9777.

3-Bromo-5-[*N*-Boc-5-methoxyindol]-2-yl-1-(4-methoxyphenyl)-1*H*-pyrazole (9l): Yield: 30 mg (30%), yellow solid, m.p. 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9 H, $3CH_3$), 3.74 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.49, 6.64 (2s, 2 H, 4-C + arom.), 6.75 (d, J = 9.1 Hz, 2 H, arom.), 6.98 (dd, J = 9.1 and 2.5 Hz, 1 H, arom.), 7.06 (d, J = 2.3 Hz, 1 H, arom.), 7.21 (d, J = 9.1 Hz, 2 H, arom.), 8.05 (d, J = 9.1 Hz, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 ($3CH_3$), 55.6 (OCH_3), 55.8 (OCH_3), 84.3 (CMe_3), 103.2 (4-C), 111.8, 113.3, 114.2, 114.8, 116.9, 124.0, 126.5, 127.3, 129.3, 131.8, 133.0 (arom. + 3-C), 137.6 (5-C), 149.1 (CO), 156.3 (CO), 158.7 (CO) ppm. HRMS (EI): calcd. for $C_{24}H_{24}BrN_3O_4$ $[M]^+$ 497.0949; found 497.0950.

3-[3-Bromo-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyridine (9m): Yield: 55 mg (83%), white solid, m.p. 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OCH_3), 6.57 (s, 1 H, 4-H), 6.85 (d, J = 8.7 Hz, 2 H, arom.), 7.17 (d, J = 8.9 Hz, 2 H, arom.), 7.18–7.26 (m, 1 H, arom.), 7.43 (d, J = 7.9 Hz, 1 H, arom.), 8.52 (s, 1 H, arom.), 8.55 (d, J = 4.5 Hz, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 110.2 (4-C), 114.5, 123.4, 125.7, 127.0, 127.4, 132.0, 135.9, 141.9 (arom. + 3-C + 5-C), 149.4, 149.9 (arom.), 159.6 (CO) ppm. HRMS (EI): calcd. for $C_{15}H_{12}BrN_3O$ $[M]^+$ 329.0164; found 329.0164.

4-[3-Bromo-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyridine (9n): Yield: 45 mg (69%), white solid, m.p. 88–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 6.62 (s, 1 H, 4-H), 6.87 (d, J = 8.8 Hz, 2 H, arom.), 7.07 (d, J = 5.8 Hz, 2 H, arom.), 7.18 (d, J = 8.8 Hz, 2 H, arom.), 8.55 (d, J = 3.5 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 110.5 (4-C), 114.5, 122.6, 126.9, 127.5, 132.0, 136.8, 142.3 (arom. + 3-C + 5-C), 150.3 (arom.), 159.8 (CO) ppm. HRMS (EI): calcd. for $C_{15}H_{12}BrN_2O_2$ $[M]^+$ 329.0164; found 329.0164.

4-[3-Bromo-1-(4-fluorophenyl)-1*H*-pyrazol-5-yl]pyridine (9o): Yield: 41 mg (64%), white solid, m.p. 88–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (s, 1 H, 4-H), 7.05–7.10 (m, 4 H, arom.), 7.23–7.27 (m, 2 H, arom.), 8.58 (d, J = 6.1 Hz, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.2 (4-C), 116.5 (d, $^2J_{C,F}$ = 23.5 Hz), 122.7 (arom.), 127.3 (d, $^3J_{C,F}$ = 8.8 Hz), 128.1 (3-C), 135.0 (d, $^4J_{C,F}$ = 2.9 Hz), 136.6, 142.5 (arom. + 5-C), 150.5 (arom.), 162.4 (d, $^1J_{C,F}$ = 249.4 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_9BrFN_3$ $[M]^+$ 316.9964; found 316.9965.

4-[3-Bromo-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-2-chloropyridine (9p): Yield: 27 mg (51%), white solid, m.p. 96–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 6.64 (s, 1 H, 4-H), 6.88–6.93 (m, 3 H, arom.), 7.16–7.26 (m, 3 H, arom.), 8.29 (d, J = 5.0 Hz, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 111.0 (4-C), 114.7, 121.3, 123.1, 126.9, 127.6, 131.7, 139.7, 141.0 (arom. + 3-C + 5-C), 150.1, 152.2 (arom.), 160.0 (CO) ppm. HRMS (CI): calcd. for $C_{15}H_{12}BrClN_3O$ $[M + H]^+$ 363.9852; found 263.9852.

4-[3-Bromo-1-(4-fluorophenyl)-1*H*-pyrazol-5-yl]-2-chloropyridine (9q): Yield: 38 mg (54%), white solid, m.p. 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (s, 1 H, 4-H), 6.99 (dd, J = 5.2 and 1.4 Hz, 2 H, arom.), 7.17–7.36 (m, 5 H, arom.), 8.39 (d, J = 5.2 Hz, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.5 (4-C), 116.5 (d, $^2J_{C,F}$ = 23.1 Hz), 121.3, 123.1 (arom.), 127.3 (d, $^3J_{C,F}$ = 8.8 Hz), 128.2 (3-C), 134.7 (d, $^4J_{C,F}$ = 3.3 Hz), 139.4, 141.1 (arom. + 5-C), 150.2, 152.3 (arom.), 162.5 (d, $^1J_{C,F}$ = 250.3 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_8BrClFN_3$ $[M]^+$ 350.9574; found 350.9573.

3-Bromo-1-(4-fluorophenyl)-5-(prop-1-en-2-yl)-1*H*-pyrazole (9r): Yield: 43 mg (77%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3 H, CH_3), 5.03 (s, 1 H, $=CH_2$), 5.19 (s, 1 H, $=CH_2$), 6.34 (s, 1 H, 4-H), 7.08–7.14 (m, 2 H, arom.), 7.38–7.42 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3 (CH_3), 109.5 (4-C), 116.2 (d, $^2J_{C,F}$ = 23.1 Hz), 119.6 ($=CH_2$), 126.8 (d, $^3J_{C,F}$ = 8.8 Hz), 127.3, 133.1 (C-Me + 3-C), 136.2 (d, $^4J_{C,F}$ = 3.3 Hz), 146.6 (5-C), 162.2 (d, $^1J_{C,F}$ = 248.6 Hz) ppm. HRMS (ESI): calcd. for $C_{12}H_{11}BrFN_2$ $[M + H]^+$ 281.0084; found 280.0096.

Procedure for the Coupling of Potassium Cyclopropyltrifluoroborate (Conditions B): In a glass tube fitted with a Teflon screw seal, $Pd(OAc)_2$ (0.02 mmol), RuPhos (0.04 mmol), K_3PO_4 (0.60 mmol), and the potassium trifluoroborate (0.22 mmol) were added to a solution of pyrazole **8b** (0.20 mmol) in a degassed mixture of toluene/H_2O (10:1; 2 mL). The reactor was flushed with argon, and the reaction mixture was left to stir at 100 °C for 6 h. The reaction mixture was then diluted with water (20 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt) to afford 3-bromo-5-cyclopropyl-1-(4-fluorophenyl)-1*H*-pyrazole (**9s**). Yield: 25 mg (45%), oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74–0.78 (m, 2 H, CH_{Cpr}), 0.96–1.03 (m, 2 H, CH_{Cpr}), 2.01–2.25 (m, 1 H, CH_{Cpr}), 5.97 (s, 1 H, 4-H), 7.12–7.18 (m, 2 H, arom.), 7.52–7.57 (m, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6 (CH_2), 9.1 (CH), 105.7 (4-C), 116.1 (d, $^2J_{C,F}$ = 22.7 Hz), 126.8 (d, $^3J_{C,F}$ = 8.1 Hz), 127.2 (3-C), 135.5 (d, $^4J_{C,F}$ = 3.7 Hz), 148.4 (5-C), 162.1 (d, $^1J_{C,F}$ = 248.0 Hz) ppm. HRMS (ESI): calcd. for $C_{12}H_{11}BrFN_2$ $[M + H]^+$ 281.0084; found 281.0091.

Suzuki Cross-Coupling at C-3/Synthesis of Pyrazoles 13a-d

General Procedure for the Introduction of (Hetero)aromatic Groups (Conditions A): In a glass tube fitted with a Teflon screw seal, $Pd(PPh_3)_4$ (0.02 mmol), K_3PO_4 (0.40 mmol), and the selected boronic acid (0.26 mmol) were added to a solution of the 3-bromopyrazole (0.20 mmol) in a degassed mixture of DMF/H_2O (4:1; 2 mL). The reactor was flushed with argon, and the reaction mixture was left to stir at 80 °C for 18 h. The reaction mixture was then diluted with water (20 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt).

4-{1-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1*H*-pyrazol-5-yl}pyridine (13a): Yield: 51 mg (65%), white solid, m.p. 192–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.09 (s, 3 H, CH_3), 7.02 (s, 1 H, 4-H), 7.10–7.17 (m, 4 H, arom.), 7.35–7.37 (m, 2 H, arom.), 7.80 (d, J = 8.3 Hz, 2 H, arom.), 8.09 (d, J = 8.3 Hz, 2 H, arom.), 8.62 (br. s, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (CH_3), 106.6 (4-C), 116.5 (d, $^2J_{C,F}$ = 22.7 Hz), 126.5, 127.3, 127.4, 128.1 (arom.), 135.6 (d, $^4J_{C,F}$ = 2.9 Hz), 137.4, 137.9, 140.0, 142.4, 150.4, 150.5 (arom. + 3-C + 5-C), 162.4 (d, $^1J_{C,F}$ = 249 Hz) ppm. HRMS (EI): calcd. for $C_{21}H_{17}FN_3O_2S$ $[M + H]^+$ 394.1026; found 394.1029.

3-[1-(4-Methoxyphenyl)-5-thiophen-2-yl-1*H*-pyrazol-3-yl]pyridine (13b): Yield: 51 mg (77%), white solid, m.p. 150–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 6.87–7.97 (m, 5 H, arom.), 7.27–7.38 (m, 4 H, arom.), 8.19 (d, J = 7.9 Hz, 1 H, arom.), 8.58 (br. s, 1 H, arom.), 9.10 (br. s, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 104.2 (4-C), 114.5, 126.8, 127.4, 127.5, 127.9, 131.1, 132.8, 133.1, 139.1, 147.3, 148.7, 149.1 (arom. + 3-C + 5-C), 160.0 (CO) ppm. HRMS (EI): calcd. for $C_{19}H_{15}N_3OS$ $[M]^+$ 333.0936; found 333.0932.

General Procedure for the Introduction of Alkyl Groups (Conditions B): In a glass tube fitted with a Teflon screw seal, $Pd(OAc)_2$

(0.02 mmol), RuPhos (0.04 mmol), K_3PO_4 (0.60 mmol), and the selected potassium trifluoroborate (0.40 mmol) were added to a solution of the 3-bromopyrazole (0.20 mmol) in a degassed mixture of toluene/H_2O (10:1; 2 mL). The reactor was flushed with argon, and the reaction mixture was left to stir at 110 °C for 12 h. The reaction mixture was then diluted with water (20 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt).

4-[3-Cyclopropyl-1-(4-fluorophenyl)-1*H*-pyrazol-5-yl]pyridine (13c): Yield: 41 mg (74%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (m, 2 H, CH_{Cpr}), 1.00 (m, 2 H, CH_{Cpr}), 2.02 (m, 1 H, CH_{Cpr}), 6.29 (s, 1 H, 4-H), 7.03–7.07 (m, 4 H, arom.), 7.22–7.24 (m, 2 H, arom.), 8.53 (d, J = 4.3 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.3 (CH_2), 9.2 (CH), 105.4 (4-C), 116.2 (d, $^2J_{C,F}$ = 22.7 Hz), 122.6 (arom.), 127.2 (d, $^3J_{C,F}$ = 8.8 Hz), 135.9, 138.0, 140.9, 150.2, 156.6 (arom. + 3-C + 5-C), 161.9 (d, $^1J_{C,F}$ = 248.0 Hz) ppm. HRMS (CI): calcd. for $C_{17}H_{15}FN_3$ $[M + H]^+$ 280.1250; found 280.1250.

4-[1-(4-Fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl]pyridine (13d): Yield: 36 mg (71%), white solid, m.p. 122–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 6.43 (s, 1 H, 4-H), 7.03–7.08 (m, 4 H, arom.), 7.22–7.27 (m, 2 H, arom.), 8.53 (d, J = 6.0 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 108.7 (4-C), 127.3 (d, $^2J_{C,F}$ = 23.5 Hz), 122.7 (arom.), 127.2 (d, $^3J_{C,F}$ = 8.1 Hz), 135.9 (d, $^4J_{C,F}$ = 2.9 Hz), 137.9, 141.1, 150.1, 150.2 (arom. + 3-C + 5-C), 162.0 (d, $^1J_{C,F}$ = 248.0 Hz) ppm. HRMS (CI): calcd. for $C_{15}H_{13}FN_3$ $[M + H]^+$ 254.1094; found 254.1095.

General Procedure for the Sequential Suzuki Cross-couplings at C-5 and C-3: Synthesis of Pyrazoles 13a,b and 13e-l: In a glass tube fitted with a Teflon screw seal, $Pd(PPh_3)_4$ (0.02 mmol), K_3PO_4 (0.60 mmol), and the selected boronic acid (0.22 mmol) were added to a solution of the 3-bromo-5-iodopyrazole (0.20 mmol) in a degassed mixture of DMF/H_2O (4:1, 2 mL). The reactor was flushed with argon, and the reaction mixture was left to stir at the indicated temperature (50 or 80 °C) for 3 h. The second boron compound (0.26 mmol) was then added, and the reaction mixture was left to stir overnight at 80 °C. Water (20 mL) was added, and the reaction mixture was extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt) to afford the corresponding 3,5-disubstituted pyrazole.

13a: 51 mg (65%). Analytical data were identical to those described above.

13b: 36 mg (54%). Analytical data were identical to those described above.

Methyl 4-[3-(Furan-2-yl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-benzoate (13e): Yield: 22 mg (30%), orange solid, m.p. 140–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.49 (dd, J = 3.3 and 1.8 Hz, 1 H, arom.), 6.77 (d, J = 3.3 Hz, 1 H, arom.), 6.81 (s, 1 H, 4-H), 6.86 (d, J = 9.1 Hz, 2 H, arom.), 7.23 (d, J = 9.1 Hz, 2 H, arom.), 7.25 (d, J = 8.4 Hz, 2 H, arom.), 7.49 (d, J = 1.8 Hz, 1 H, arom.), 7.97 (d, J = 8.4 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4 (OCH_3), 55.6 (OCH_3), 105.0, 106.5, 111.5, 114.4, 127.1, 128.7, 129.9, 133.0, 134.7, 142.3, 143.2, 144.6, 148.5 (arom.), 159.4 (CO), 166.7 (CO) ppm. HRMS (EI): calcd. for $C_{22}H_{18}N_2O_4$ $[M]^+$ 374.1267; found 374.1266.

3-(4-Fluorophenyl)-5-(furan-2-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole (13f): Yield: 48 mg (72%), orange solid, m.p. 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, OCH_3), 5.89 (d, J = 3.0 Hz, 1 H, arom.), 6.33 (dd, J = 3.3 and 1.8 Hz, 1 H, arom.), 6.92 (s, 1 H, 4-H), 6.99 (d, J = 8.8 Hz, 2 H, arom.), 7.10 (m, 2 H, arom.), 7.39 (d, J = 8.8 Hz, 2 H, arom.), 7.42 (d, J = 1.3 Hz, 1 H, arom.), 7.85 (dd, J = 8.8 and 5.5 Hz, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 102.5 (4-C), 108.8, 111.4, 114.5 (arom.), 115.6 (d, $^2J_{C,F}$ = 22.0 Hz), 127.6 (d, $^3J_{C,F}$ = 8.1 Hz), 127.8 (arom.), 129.3 (d, $^4J_{C,F}$ = 3.7 Hz), 133.4, 136.3, 142.6, 144.7, 151.0 (arom.), 160.0 (CO), 162.9 (d, $^1J_{C,F}$ = 246.0 Hz) ppm. HRMS (EI): calcd. for $C_{20}H_{15}FN_2O_2$ $[M]^+$ 334.1118; found 334.1114.

1-(4-Methoxyphenyl)-3-(thiophen-2-yl)-5-[3-(trifluoromethyl)-phenyl]-1*H*-pyrazole (13g): Yield: 42 mg (52%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 6.77 (s, 1 H, 4-H), 6.88 (d, J = 9.1 Hz, 2 H, arom.), 7.09 (dd, J = 5.0, 3.5 Hz, 1 H, arom.), 7.25 (d, J = 9.1 Hz, 2 H, arom.), 7.28 (dd, J = 5.4, 1.0 Hz, 1 H, arom.), 7.35–7.44 (m, 3 H, arom.), 7.55–7.58 (m, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 105.1 (4-C), 114.5 (arom.), 123.9 (q, $^1J_{C,F}$ = 272.0 Hz, CF_3), 124.3 (arom.), 125.1 (q, $^3J_{C,F}$ = 3.7 Hz), 125.1 (arom.), 125.5 (q, $^3J_{C,F}$ = 4.4 Hz), 127.1, 127.7, 129.1 (arom.), 131.2 (q, $^2J_{C,F}$ = 32.3 Hz), 131.9, 132.8, 136.1, 142.9, 147.4 (arom.), 159.4 (CO) ppm. HRMS (EI): calcd. for $C_{21}H_{15}F_3N_2OS$ $[M]^+$ 400.0857; found 400.0857.

1-{4-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]phenyl}ethanone (13h): Yield: 64 mg (80%), white solid, m.p. 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 6.84 (s, 1 H, 4-H), 6.87 (d, J = 8.8 Hz, 2 H, arom.), 7.17 (d, J = 8.6 Hz, 2 H, arom.), 7.29–7.33 (m, 4 H, arom.), 7.96–8.01 (m, 4 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (CH_3), 55.6 (OCH_3), 105.3 (4-C), 114.4, 125.8, 126.9, 128.8, 128.9, 129.0, 129.8, 130.0, 133.0, 134.6, 136.5, 137.6, 143.6, 150.6 (arom.), 159.3 (CO), 197.8 (C=O) ppm. HRMS (EI): calcd. for $C_{24}H_{19}ClN_2O_2$ $[M]^+$ 402.1135; found 402.1135.

4-[3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyridine (13i): Yield: 44 mg (62%), white solid, m.p. 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, OCH_3), 6.92–6.97 (m, 3 H, 4-H + arom.), 7.15–7.20 (m, 4 H, arom.), 7.29–7.32 (m, 2 H, arom.), 7.88–7.93 (m, 2 H, arom.), 8.60 (s, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 105.3 (4-C), 114.6 (arom.), 115.7 (d, $^2J_{C,F}$ = 21.3 Hz), 122.7, 126.9 (arom.), 127.6 (d, $^3J_{C,F}$ = 8.1 Hz), 132.8, 138.0, 141.7, 149.9, 151.3 (arom.), 159.6 (CO), 163.0 (d, $^1J_{C,F}$ = 288.6 Hz) ppm. HRMS (ESI): calcd. for $C_{21}H_{17}FN_3O$ $[M + H]^+$ 346.1363; found 356.1356.

3-[3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyridine (13j): Yield: 58 mg (84%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 6.87 (s, 1 H, 4-H), 6.93 (d, J = 8.8 Hz, 2 H, arom.), 7.13–7.18 (m, 2 H, arom.), 7.28–7.31 (m, 3 H, arom.), 7.58 (d, J = 8.1 Hz, 1 H, arom.), 7.91 (dd, J = 5.5 and 2.0 Hz, 1 H, arom.), 8.63 (d, J = 4.0 Hz, 1 H, arom.), 8.67 (s, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 105.0 (4-C), 114.5 (arom.), 115.7 (d, $^2J_{C,F}$ = 22.0 Hz), 123.6, 127.0 (arom.), 127.6 (d, $^3J_{C,F}$ = 8.1 Hz), 129.1 (d, $^4J_{C,F}$ = 2.9 Hz), 132.7, 136.2, 141.0, 148.7, 151.2 (arom.), 159.4 (CO), 162.9 (d, $^1J_{C,F}$ = 246.5 Hz) ppm. HRMS (CI): calcd. for $C_{21}H_{17}FN_3O$ $[M + H]^+$ 346.1356; found 346.1355.

3-(1,3-Benzodioxol-5-yl)-1-(4-methoxyphenyl)-5(-furan-2-yl)-1*H*-pyrazole (13k): Yield: 44 mg (61%), orange solid, m.p. 109–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 5.90 (d, J = 3.0 Hz, 1 H, arom.), 5.98 (s, 2 H, OCH_2O), 6.32 (dd, J = 3.4 and 1.9 Hz, 1 H, arom.), 6.84–6.88 (m, 2 H, 4-H + arom.), 6.97 (d, J = 8.8 Hz, 2 H, arom.), 7.36–7.42 (m, 5 H, arom.) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 101.2 (OCH_2O), 102.4 (4-C), 106.6, 108.6, 108.7, 111.4, 114.4, 119.7, 127.4, 127.7, 133.5, 136.1, 142.5, 144.8 (arom.), 147.6, 148.1, 151.6 (arom. + 2CO), 159.8 (CO) ppm. HRMS (EI): calcd. for $C_{22}H_{18}N_2O_4$ $[M]^+$ 361.1188; found 361.1188.

4-[1-(4-Fluorophenyl)-3-(1-methylethenyl)-1*H*-pyrazol-5-yl]pyridine (13l): Yield: 37 mg (67%), yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 5.27 (s, 1 H, $=CH_2$), 5.71 (s, 1 H, $=CH_2$), 6.84 (s, 1 H, 4-H), 7.13–7.18 (m, 2 H, arom.), 7.26 (br. s, 2 H, arom.), 7.35–7.39 (m, 2 H, arom.), 8.83 (br. s, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (CH_3), 105.8 (4-C), 113.4 ($=CH_2$), 116.3 (d, $^2J_{C,F}$ = 22.8 Hz), 127.3 (d, $^3J_{C,F}$ = 8.8 Hz), 135.9 (d, $^4J_{C,F}$ = 3.7 Hz), 136.5, 137.8, 149.8, 153.8 (arom. + C-Me), 162.1 (d, $^1J_{C,F}$ = 248.7 Hz) ppm. HRMS (CI): calcd. for $C_{17}H_{15}FN_3$ $[M + H]^+$ 280.1250; found 280.1251.

Synthesis of Symmetrically Substituted Pyrazoles 13m,n

3,5-Bis-cyclopropyl-1-(4-fluoro)phenyl-1*H*-pyrazole (13m): In a glass tube fitted with a Teflon screw seal, $Pd(OAc)_2$ (0.02 mmol), RuPhos (0.04 mmol), K_3PO_4 (0.60 mmol), and potassium cyclopropyltrifluoroborate (0.60 mmol) were added to a solution of 3-bromo-5-iodopyrazole **8b** (0.20 mmol) in a degassed mixture of toluene/H_2O (10:1; 2 mL). The reactor was flushed with argon, and the reaction mixture was left to stir at 110 °C for 18 h. The reaction mixture was then diluted with water (20 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt) to give **13m** (27 mg, 56%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.69–0.74 (m, 4 H, CH_{Cpr}), 0.89–0.95 (m, 4 H, CH_{Cpr}), 1.65–1.74 (m, 1 H, CH_{Cpr}), 1.88–1.97 (m, 1 H, CH_{Cpr}), 5.60 (s, 1 H, 4-H), 7.09–7.15 (m, 2 H, arom.), 7.53–7.58 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.8, 8.0, 8.8, 9.3 (C_{Cpr}), 99.3 (4-C), 115.8 (d, $^2J_{C,F}$ = 22.5 Hz), 126.5 (d, $^3J_{C,F}$ = 8.8 Hz), 136.5 (d, $^4J_{C,F}$ = 2.7 Hz), 146.6, 155.2 (3-C + 5-C), 161.6 (d, $^1J_{C,F}$ = 246.4 Hz) ppm. HRMS (ESI): calcd. for $C_{15}H_{16}FN_2$ $[M + H]^+$ 243.1292; found 243.1302.

3,5-Bis-isoprenyl-1-(4-fluoro)phenyl-1*H*-pyrazole (13n): $Pd(PPh_3)_4$ (0.02 mmol), K_3PO_4 (0.60 mmol), isopropenylboronic acid pinacol ester (0.6 mmol), and 3-bromo-5-iodopyrazole **8b** (0.20 mmol) were filled into an appropriate small microwave process vial containing a degassed mixture of DMF/H_2O (4:1, 2 mL). The vial was flushed with argon, sealed with a Teflon septum, and placed into a Biotage Initiator microwave cavity. After irradiation at 140 °C for 20 min and subsequent cooling, the reaction mixture was diluted with water (20 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt) to give **13n** (32.5 mg, 65%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 4.99, 5.11, 5.14, 5.55 (4s, $=CH_2$), 6.46 (s, 1 H, 4-H), 7.08–7.13 (m, 2 H, arom.), 7.43–7.47 (m, 2 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (CH_3), 20.6 (CH_3), 104.1 (4-C), 112.7 ($=CH_2$), 116.0 (d, $^2J_{C,F}$ = 22.7 Hz), 118.3 ($=CH_2$), 126.9 (d, $^3J_{C,F}$ = 8.1 Hz), 134.2, 136.9 (2 C-Me), 137.0 (d, $^4J_{C,F}$ = 2.9 Hz), 145.4, 153.0 (3-C + 5-C), 161.94 (d, $^1J_{C,F}$ = 229.6 Hz) ppm. HRMS (ESI): calcd. for $C_{15}H_{16}FN_2$ $[M + H]^+$ 243.1292; found 243.1297.

Sonogashira Cross-Coupling at C-5 for the Synthesis of 4-{[3-Bromo-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]ethynyl}benzonitrile (14): 3-Bromo-5-iodopyrazole **8a** (0.2 mmol), the alkyne (0.24 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), and CuI (0.01 mmol) were dissolved in a mixture of degassed MeCN (1 mL) and TEA (2 mL) in a glass tube fitted with a Teflon screw seal. The reactor was flushed with argon, and the reaction mixture was left to stir at 80 °C for 2.5 h, after which time it was diluted with water (20 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, appropriate mixture of cyclohexane/AcOEt) to afford **14** (41 mg, 55%) as a white solid. M.p. 189–192 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 6.69 (s, 1 H, 4-H), 6.99 (d, J = 8.6 Hz, 2 H, arom.), 7.48 (d, J = 8.6 Hz, 2 H, arom.), 7.60–7.64 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 81.3, 95.3 (2C≡), 112.7, 114.2 (arom.), 114.7 (4-C), 118.3 (CN), 125.3, 125.9, 126.5, 126.8, 132.1, 132.4 (arom.), 159.6 (CO) ppm. HRMS (CI): calcd. for $C_{19}H_{13}BrN_3O$ $[M + H]^+$ 378.0243; found 378.0243.

Removal of the PMP Protecting Group for the Synthesis of 3-[3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl]pyridine (15): A stirred, cooled solution (ice bath) of PMP-protected pyrazole **13i** (0.2 mmol) in a mixture of MeCN/H_2O (4:1, 5 mL) was treated dropwise with a cooled aqueous solution (3 mL) of ceric ammonium nitrate (1.0 mmol), and stirring was continued for 1 h at 0 °C and then 4 h at room temperature. The reaction mixture was then diluted with water (20 mL), and the organic solvent was removed under reduced pressure. The remaining aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL), dried with anhydrous $MgSO_4$, and concentrated in vacuo to give **15** (27 mg, 56%) as a white solid. M.p. 195–196 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 1 H, 4-H), 7.08–7.12 (m, 2 H, arom.), 7.32 (dd, J = 7.8 and 4.8 Hz, 1 H, arom.), 7.64 (dd, J = 8.8 and 5.3 Hz, 2 H, arom.), 8.03 (d, J = 7.8 Hz, 1 H, arom.), 8.56 (d, J = 3.5 Hz, 1 H, arom.), 9.01 (s, 1 H, arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.5 (4-C), 116.2 (d, $^2J_{C,F}$ = 22.0 Hz), 123.9, 126.7, 127.0 (arom.), 127.6 (d, $^3J_{C,F}$ = 8.1 Hz), 128.6, 133.1, 147.1, 149.2 (arom.), 163.0 (d, $^1J_{C,F}$ = 248.7 Hz) ppm. HRMS (CI): calcd. for $C_{14}H_{11}FN_3$ $[M + H]^+$ 240.0937; found 240.0937.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for new compounds.

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