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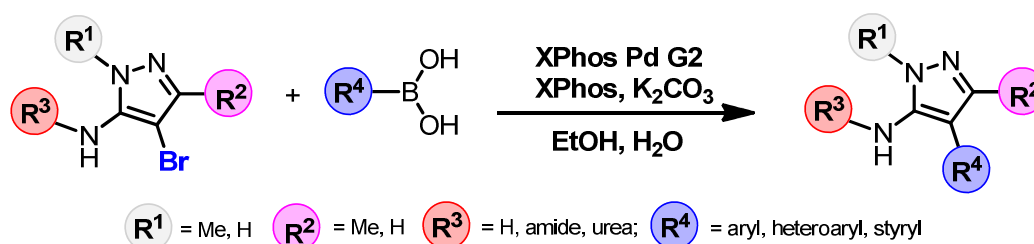
## The Suzuki-Miyaura cross-coupling reaction of halogenated aminopyrazoles: method development, scope, and mechanism of dehalogenation side reaction

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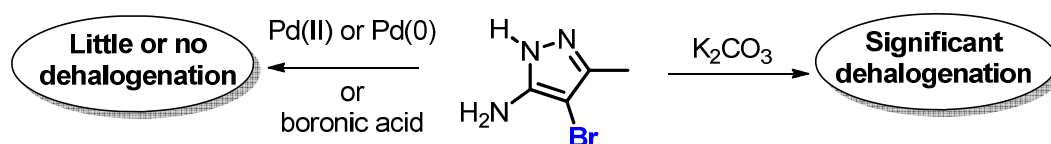
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### Including the study of pyrazole-Br dehalogenation



## ABSTRACT

The efficient Suzuki-Miyaura cross-coupling reaction of halogenated aminopyrazoles and their amides or ureas with a range of aryl, heteroaryl, and styryl boronic acids or esters has been developed. The method allowed incorporation of problematic substrates: aminopyrazoles bearing protected or unprotected pyrazole NH, as well as the free amino or *N*-amide group. Direct comparison of the chloro, bromo, and iodopyrazoles in the Suzuki-Miyaura reaction revealed that Br and Cl derivatives were superior to iodopyrazoles, as a result of reduced propensity to dehalogenation. Moreover, the mechanism and factors affecting the undesired dehalogenation side reaction were revealed.

## INTRODUCTION

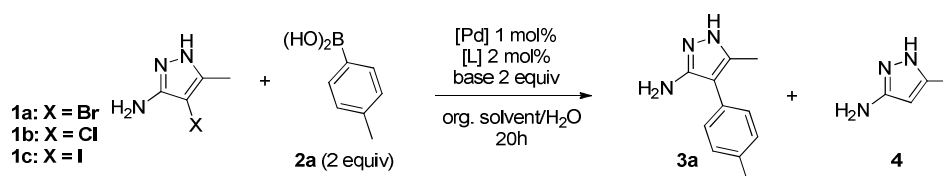
The Suzuki-Miyaura cross-coupling reaction is useful method allowing chemists to generate effectively more complex molecules from simpler fragments through the formation of sigma carbon – carbon bond.<sup>1,2</sup> This, among other reasons, caused that the Suzuki-Miyaura reaction has been implemented as a valuable tool for the synthesis of biologically active molecules, fine chemicals, and natural products.<sup>3,4</sup> On the other hand, several limitations and challenges occurred when the Suzuki-Miyaura and other transition metal catalyzed reactions were used in conjunction with heterocyclic compounds.<sup>5-7</sup> Given importance of heterocyclic systems for medicinal chemistry, many research groups spent great effort to implement transition metal catalyzed transformations into the syntheses and modifications of heteroarenes.<sup>8-10</sup>

In this context, there are two major problems with respect to the Suzuki-Miyaura reaction: (1) coordination of the heterocyclic substrate/product to the metal center resulting in the inhibition or deactivation of the catalyst,<sup>11,12</sup> and (2) instability and/or poor reactivity of some boronic acids (e.g. 2-heteroaryl and pyridyl boronic acids) leading to the undesired side reactions, such as protodeboronation and oxidative homo coupling.<sup>13</sup> The first issue has been largely solved by the use of new advanced palladium (pre)catalysts and ligands,<sup>14-18</sup> while the development of alternative organoboron reagents, particularly MIDA esters<sup>19</sup> and trifluoroborates,<sup>20</sup> solved the second issue. Nevertheless, the problems associated with electrophilic coupling partners, particularly electron-rich heteroaryl halides, and understanding the mechanism of their side reactions received inadequate attention. The reductive homo coupling and especially dehalogenation of (hetero)aryl halides accompanied many C-C a C-N cross-coupling reactions, which consequently led to lower yields and complicated isolation of product.<sup>21,22</sup>

We were interested in the synthesis of the 4-substituted aminopyrazoles, especially 4-styryl aminopyrazoles due to their structural similarity to 4-aryloxy pyrazoles, which were found as the potent inhibitors of cyclin-dependent kinases.<sup>23</sup> However, a parallel synthesis of 4-aryl aminopyrazoles using traditional step by step methods appeared less efficient in comparison to the synthetic strategies based on transition metal catalyzed cross-coupling chemistry. Moreover, the access to 4-styryl aminopyrazoles via traditional methods seemed to be difficult. Therefore we spent an effort on the development of a Suzuki-Miyaura cross-coupling method for 4-halogenated aminopyrazoles, which are challenging coupling partners for such reaction.<sup>24</sup>

Attention was paid to achieve two main targets: (1) manage substrate scope as broad as possible with respect to the both coupling partners, and (2) reach high conversion to a coupling product by suppression of impurities formation in order to simplify product purification. Herein, we reported our results on the Suzuki-Miyaura reaction using halogenated aminopyrazoles as problematic substrates for metal catalyzed cross-coupling reactions. In addition, we provided a deeper insight into the undesired and not well understood dehalogenation side reaction of NH containing heteroaromatic compounds. Despite the dehalogenation of simple aromatic halides can proceed through the  $\beta$ -elimination of alkoxypalladium complexes,<sup>25,26</sup> this mechanism is not the predominant pathway in the case of NH containing heteroarenes.

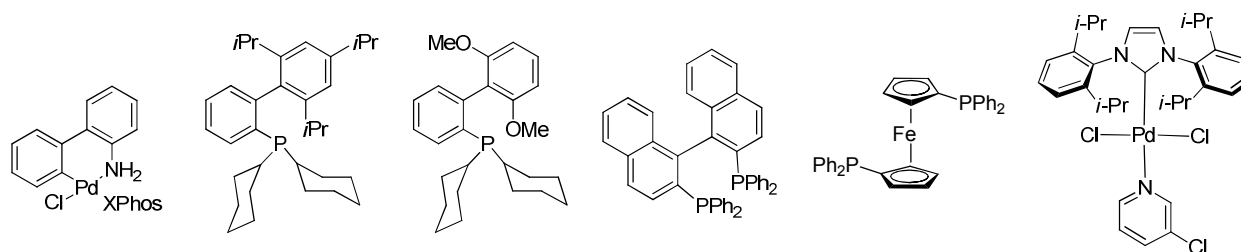
**Table 1. Optimization of reaction conditions**



entry	solvent	base	[Pd]	ligand	T (°C)	X	3a <sup>a</sup>	1 <sup>a</sup>	4 <sup>a</sup>
1	Dioxane	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	XPhos	100	Br	2	1	89

2	Dioxane	K <sub>2</sub> CO <sub>3</sub>	XPhos Pd G2	XPhos	100	Br	16	18	60
3	EtOH	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	XPhos	90	Br	57	11	24
4	MeCN	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	XPhos	90	Br	20	8	62
5	DMF	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	XPhos	100	Br	4	0	94
6	EtOH	Cs <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	XPhos	90	Br	33	0	59
7	EtOH	CsF	Pd(OAc) <sub>2</sub>	XPhos	90	Br	5	35	48
8	EtOH	K <sub>3</sub> PO <sub>4</sub>	Pd(OAc) <sub>2</sub>	XPhos	90	Br	16	0	79
9	EtOH	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	SPhos	90	Br	18	0	74
10	EtOH	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	BINAP	90	Br	8	33	40
11	EtOH	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	dppf	90	Br	9	16	65
12	EtOH	K <sub>2</sub> CO <sub>3</sub>	Pd(OAc) <sub>2</sub>	PAAd <sub>2</sub> Bu	90	Br	50	0	41
13	EtOH	K <sub>2</sub> CO <sub>3</sub>	PEPPSI	IPr	90	Br	44	14	30
14	EtOH	K <sub>2</sub> CO <sub>3</sub>	XPhos Pd G2	XPhos	90	Br	89	0	8
15	EtOH	K <sub>2</sub> CO <sub>3</sub>	XPhos Pd G2	XPhos	90	Br	33 <sup>b</sup>	0	59
16	EtOH	K <sub>2</sub> CO <sub>3</sub>	XPhos Pd G2	XPhos	90	Br	27 <sup>c</sup>	0	63
17	EtOH	K <sub>2</sub> CO <sub>3</sub>	XPhos Pd G2	XPhos	70	Br	36	42	18
<b>18</b>	<b>EtOH</b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>XPhos Pd G2</b>	<b>XPhos</b>	<b>135</b>	<b>Br</b>	<b>88<sup>d</sup></b>	<b>0</b>	<b>7</b>
19	EtOH	K <sub>2</sub> CO <sub>3</sub>	XPhos Pd G2	XPhos	135	Cl	87 <sup>d</sup>	0	6
20	EtOH	K <sub>2</sub> CO <sub>3</sub>	XPhos Pd G2	XPhos	135	I	11 <sup>d</sup>	0	84

## Structures of ligands and precatalysts

**XPhos Pd G2****XPhos****SPhos****rac-BINAP****dppf****PEPPSI-IPr**

<sup>a</sup> HPLC yield (%) determined from the crude reaction mixture (see Supporting Information for more details). <sup>b</sup> 3 equivalents of K<sub>2</sub>CO<sub>3</sub>. <sup>c</sup> 4 equivalents of K<sub>2</sub>CO<sub>3</sub>. <sup>d</sup> Reaction was carried out in a microwave reactor for 20 minutes.

## RESULTS AND DISCUSSION

Searching for optimal reaction conditions started with compound **1a** that contains free pyrazole NH, as well as primary amino group; all these features make compound **1a** challenging substrate for the Suzuki-Miyaura cross-coupling reaction. Indeed, when **1a** was reacted with *p*-tolylboronic acid **2a** in the presence of K<sub>2</sub>CO<sub>3</sub>, and a catalytic amount of Pd(OAc)<sub>2</sub> and XPhos, only 2% of the product **3a** was detected by LCMS (Table 1, entry 1). The product was accompanied with 1% of the starting material **1a** and 89% of the dehalogenated pyrazole **4**. In agreement with our previous results, the use of precatalyst XPhos Pd G2 instead of Pd(OAc)<sub>2</sub> increased the product formation to 16% (entry 2).<sup>27</sup> This can be further improved to 57% if the reaction is performed with Pd(OAc)<sub>2</sub>/XPhos in a mixture of EtOH/H<sub>2</sub>O (entry 3), while DMF and MeCN gave unsatisfactory results (entries 4 and 5). The use of various bases such as Cs<sub>2</sub>CO<sub>3</sub>, CsF, and K<sub>3</sub>PO<sub>4</sub> resulted only in diminished conversion or increased dehalogenation (entries 6 – 8). The combination of Pd(OAc)<sub>2</sub> and SPhos gave only 18% of the product **3a** (entry 9). Bidentate phosphine ligands BINAP and dppf furnished even lower amount of **3a** (entries 10 and 11). Trialkyl phosphine ligand PAd<sub>2</sub>Bu provided comparable result to XPhos (50% of **3a**, entry 12). From a range of available NHC-Pd catalysts, we tested 3-chloropyridyl stabilized Pd(II) precatalyst known as PEPPSI, which contained IPr as a supporting ligand. However, PEPPSI-IPr did not provide any improvement giving the mixture of **3a**, **1a** and **4** in a ratio of 44:14:30 (entry 13).

The nature of the palladium pre-catalyst (or Pd source) is of significance for the efficient cross-coupling, as it determines the formation and availability of the active L<sub>n</sub>Pd(0) species.<sup>28</sup> If the active ligated Pd(0) is formed readily and under mild conditions, it can diminish unwanted side reactions of both coupling partners, such as protodeboronation and oxidative homocoupling of

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3 boronic acids, and dehalogenation of aryl halides. When the XPhos derived precatalyst XPhos Pd  
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5 G2 was used instead of Pd(OAc)<sub>2</sub> in EtOH/H<sub>2</sub>O, the amount of the product **3a** considerably  
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7 increased to 89% (entry 14). LCMS of the reaction mixture showed that the starting material **1a**  
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9 was completely consumed and dehalogenated pyrazole **4** was formed in 8% after 20 hours.<sup>29</sup>  
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11 Increasing the amount of a base, or decreasing reaction temperature to 70 °C resulted in the  
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13 increased dehalogenation (entries 15 and 16), or incomplete conversion of the starting material  
14  
15 (entry 17). The reaction time was reduced to 20 minutes, when the reaction was heated in a  
16  
17 microwave reactor at 135 °C (entry 18).<sup>30</sup> Subsequently, 88% of the product **3a** and 7% of  
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19 dehalogenated pyrazole **4** were formed. The coupling product **3a** was then isolated in 78% yield  
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21 from either entry 14 or entry 18.  
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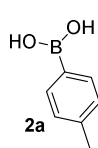
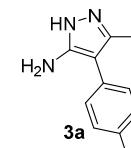
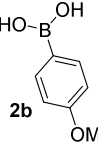
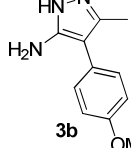
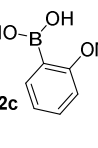
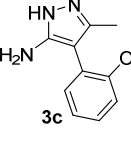
27  
28 Finally, the reactivity of chloro **1b** and iodo **1c** pyrazoles was compared to bromo derivative **1a**.  
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30 On heating in a microwave reactor at 135 °C for 20 minutes, chlorinated pyrazole **1b** displayed  
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32 nearly the same reactivity as **1a**, providing 87% of the coupling product **3a** and 6% of  
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34 dehalogenated pyrazole **4** (entry 19). On the other hand, iodo derivative **1c** showed the increased  
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36 tendency to deiodination, furnishing 84% of dehalogenated pyrazole **4** (entry 20) and only 11%  
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38 of product **3a**.  
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42  
43 Under the optimized conditions (Table 1, entry 18), the scope of the Suzuki reaction between  
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45 pyrazole **1a** and various aryl, heteroaryl, and styryl boronic acids was examined (Table 2).  
46  
47 Boronic acids bearing electron-donating groups reacted smoothly furnishing biaryls **3b** and **3c** in  
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49 high yields. Moreover, high yield of **3c** demonstrated that the reaction is somewhat tolerant to  
50  
51 sterically hindered boronic acids. Note that pyrazole **1a** itself is “*ortho*” disubstituted. Likewise,  
52  
53 the coupling of pyrazole **1a** with styrylboronic acid **2d** gave stilbene-like structure **3d** in 84%  
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55 isolated yield. As expected, electron-poor boronic acid **2e** gave lower conversion, as well as a  
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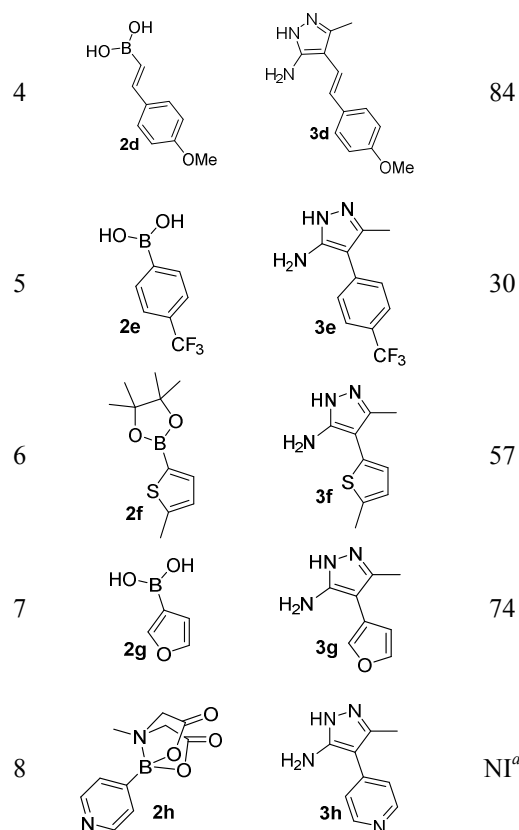
portion of unreacted starting material **1a** and dehalogenated pyrazole **4**. Thus, biaryl **3e** bearing strongly electron-withdrawing *p*-CF<sub>3</sub> group was isolated in only 30% yield.

In order to evaluate the Suzuki reaction of **1a** with heteroaromatic nucleophiles, we selected representatives of oxygen, sulfur, and nitrogen containing heteroarenes. The coupling with 2-thienylboronate **2f** afforded the respective biaryl product **3f** in 57% yield. A better result was achieved with 3-furanyl boronic acid **2g**, which afforded biaryl **3g** in 74% yield on coupling with pyrazole **1a**. Unfortunately, MIDA ester of problematic 4-pyridylboronic acid **2h** gave traces of coupling product **3h**, which precluded its isolation. Various solvents and additives, such as CuI and Cu(OAc)<sub>2</sub>, were employed in order to improve the product conversion; however, neither one improved the conversion of **3h** significantly.<sup>31</sup>

**Table 2. Scope of the Suzuki-Miyaura reaction using pyrazole 1a**

entry	nucleophile	product	yield (%)
1			78
2			87
3			82

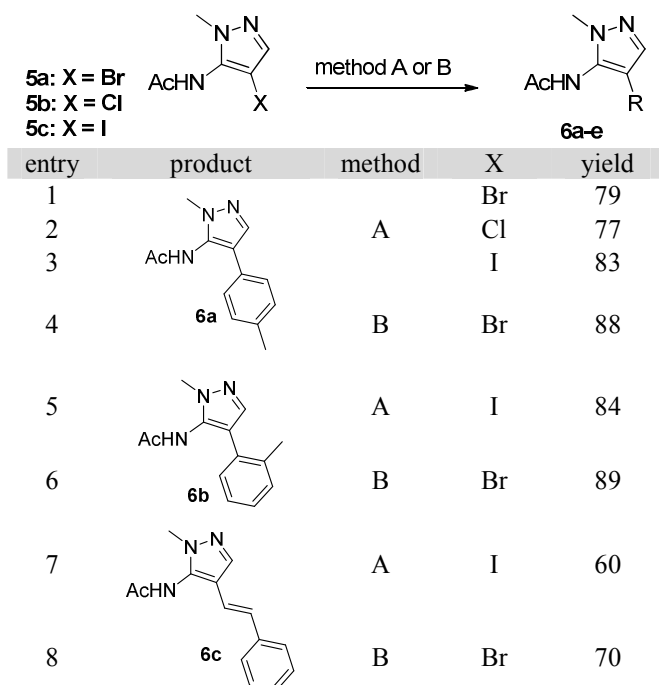


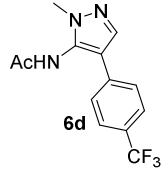
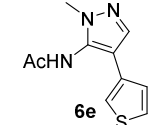


<sup>a</sup> Not isolated.

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**Table 3. Scope of the Suzuki-Miyaura reaction using pyrazole 5**



9		A	I	53
10	<b>6d</b>	B	Br	62
11		A	I	83
12	<b>6e</b>	B	Br	85

*Method A:* pyrazole **5** (1 mmol), K<sub>2</sub>CO<sub>3</sub> (2 mmol), boronic acid (2 mmol), XPhos Pd G2 (1 mol%), XPhos (2 mol%), dioxane/H<sub>2</sub>O, 100 °C, 24h. *Method B:* pyrazole **5a** (1 mmol), K<sub>2</sub>CO<sub>3</sub> (2 mmol), boronic acid (2 mmol), XPhos Pd G2 (1 mol%), XPhos (2 mol%), EtOH/H<sub>2</sub>O, μW 120 °C, 20 minutes.

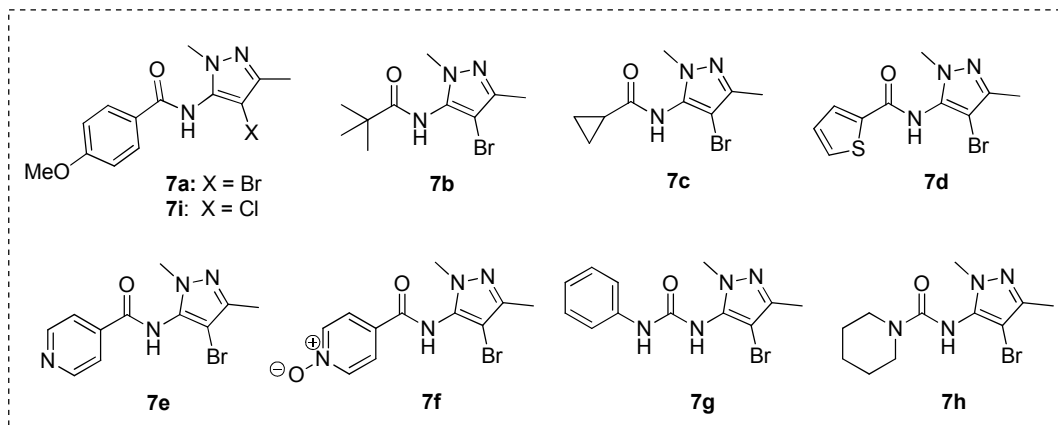
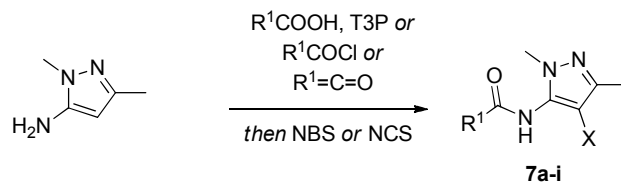
In the next step, we examined the Suzuki-Miyaura reaction of halogenated pyrazoles **5a-c** without substitution at C-3 (Table 3). These pyrazoles are structurally related to our previously reported ones, where Me or Ph was attached to this position.<sup>27</sup> We found that pyrazoles **5a-c** were less reactive in the Suzuki reaction and less susceptible to the dehalogenation (with respect to C3-substituted pyrazoles from the reference 27). Initially, the optimized reaction conditions from reference 27 were applied (method A). This method led to the incomplete consumption of brominated and chlorinated pyrazoles **5a** and **5b**, while iodide **5c** was completely consumed during the reaction. For instance, when chloride **5a** or bromide **5b** reacted with *p*-tolylboronic acid **2a** in a mixture of dioxane/H<sub>2</sub>O at 100 °C (method A), biaryl **6a** was isolated in 77% and 79%, respectively (entries 1 and 2). In both cases, unreacted starting material **5a/5b** was observed in a reaction mixture even after 24h. On the other hand, using the same conditions, iodide **5c** was completely consumed, providing **6a** in 83% yield (entry 3). The reaction rate can be further accelerated by elevating the temperature to 120 °C and switching a solvent system to EtOH/H<sub>2</sub>O (method B). Method B was derived from the optimized conditions in Table 1 However, we found that the reaction temperature for the substrate **5a** can be slightly lower (120 °C) than 135 °C

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3 required for pyrazole **1a**. The full conversion of bromide **5b** was achieved after just 20 minutes,  
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5 providing biaryl **6a** in 88% yield (entry 4).  
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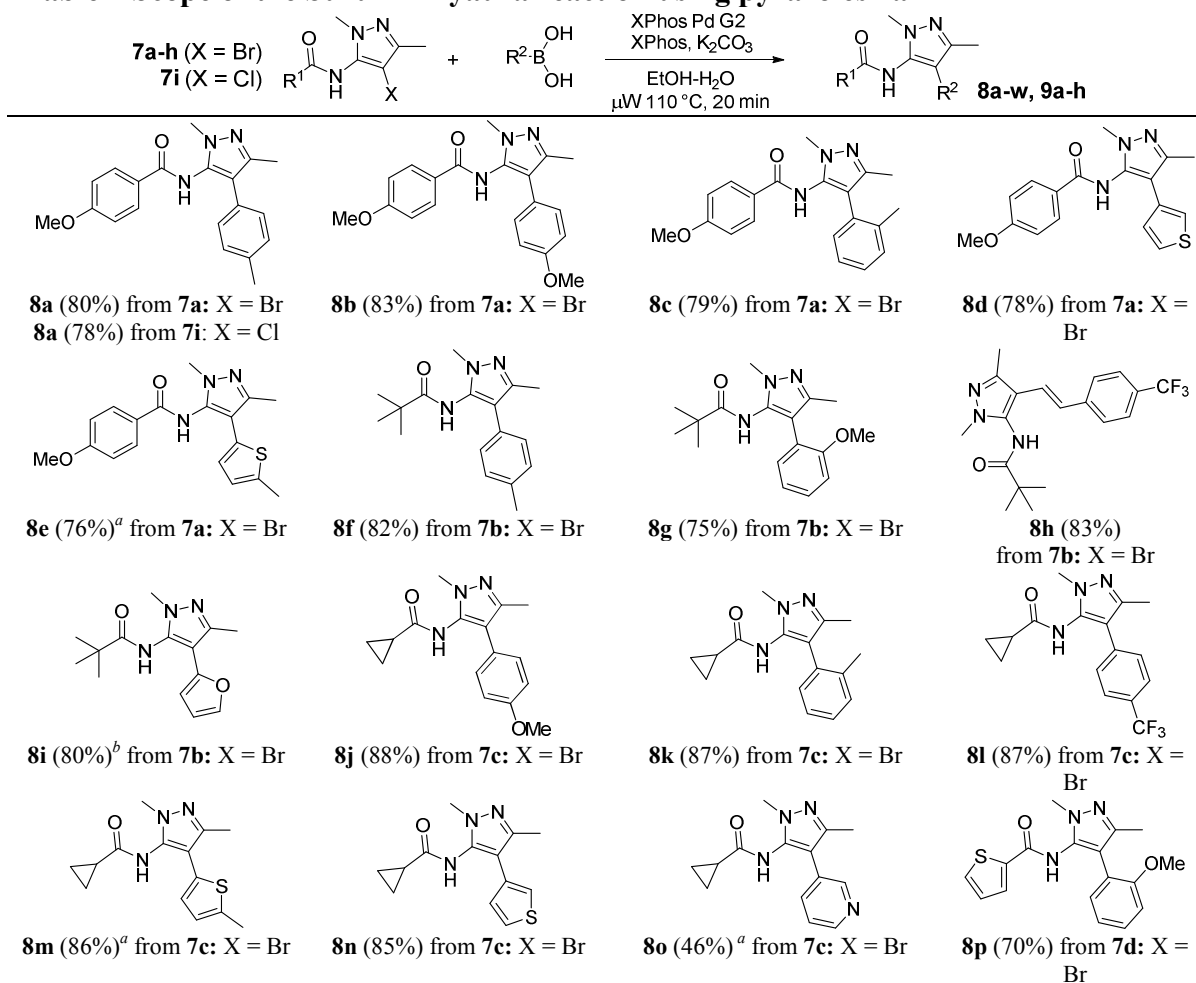
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9 In this context, iodinated pyrazole **5c** (method A) or brominated pyrazole **5a** (method B) were  
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11 coupled with a set of representative boronic acids yielding biaryls **6a-e** (Table 3). In all cases, the  
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13 reaction using bromide **5b**, higher temperature (120 °C), and a solvent system EtOH/H<sub>2</sub>O  
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15 provided higher yields of the respective coupling products. This was applied for the coupling of  
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17 sterically hindered boronic acid (entries 5 vs. 6), styrylboronic acid (entries 7 vs. 8), and  
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19 heteroarylboronic acid (entries 11 vs. 12). The lower reactivity of the electron poor boronic acid  
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21 resulted in the increased dehalogenation, therefore biaryl **6d** containing CF<sub>3</sub> group was isolated in  
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23 53% (method A, entry 9) and 62% yield (method B, entry 10), respectively.  
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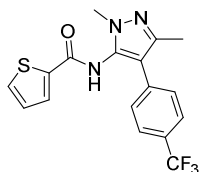
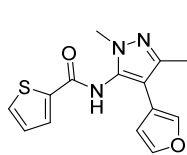
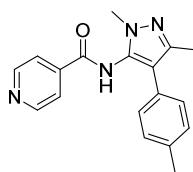
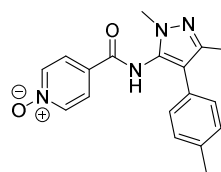
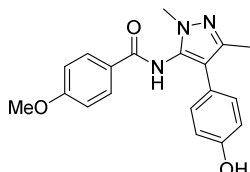
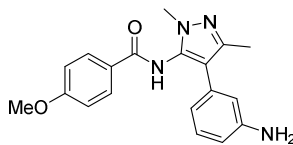
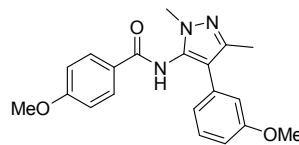
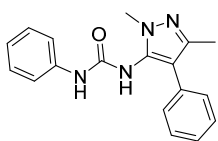
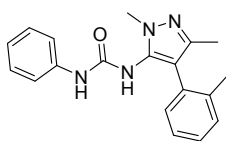
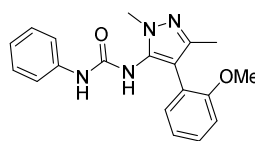
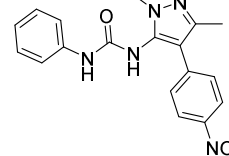
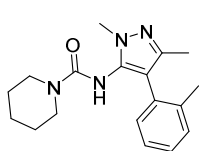
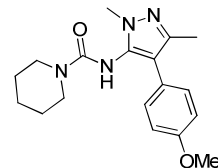
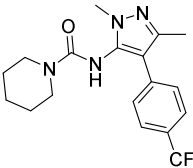
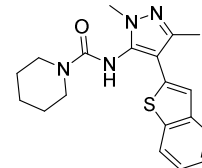
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29 Up to this point, we have explored the Suzuki coupling of aminopyrazoles featuring endocyclic  
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31 N-Me vs N-H (Table 2 vs. Table 3 and ref. 24), exocyclic NH<sub>2</sub> vs. NH-Ac (ref. 27 and Table 2),  
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33 and varying the C-3 substitution (Table 3 and ref. 27). Finally, we wished to explore the effect of  
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35 diverse substituents connected to the amino group on the cross-coupling reaction. Therefore we  
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37 synthesized 4-brominated aminopyrazoles **7a-h** and one chlorinated derivative **7i** bearing diverse  
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39 *N*-amide substitution in two steps using readily available starting materials (Scheme 1). The  
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41 cross-coupling of pyrazole amides **7a-d** and boronic acids (or esters in some cases) required just  
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43 20 minutes and 110 °C (Table 4), which was somewhat lower temperature compared to  
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45 unsubstituted pyrazoles **1a-c** (see Tables 1 and 2 for comparison).<sup>32</sup>  
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51 **Scheme 1. Preparation and structures of pyrazoles 7a-i**  
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**Table 4 Scope of the Suzuki-Miyaura reaction using pyrazoles 7a-i**



**8q** (28%) from **7d**: X = Br**8r** (59%) from **7d**: X = Br**8s** (NI) from **7e**: X = Br**8t** (NI) from **7f**: X = Br**8u** (77%) from **7i**: X = Cl**8v** (85%) from **7i**: X = Cl**8w** (NI)<sup>e</sup> from **7i**: X = Cl  
**8w** (90%)<sup>e</sup> from **7a**: X = Br**9a** (77%)<sup>c</sup> from **7g**: X = Br**9b** (44%)<sup>c</sup> from **7g**: X = Br**9c** (76%)<sup>c</sup> from **7g**: X = Br**9d** (50%)<sup>c</sup> from **7g**: X = Br**9e** (63%)<sup>c</sup> from **7h**: X = Br**9f** (89%)<sup>c</sup> from **7h**: X = Br**9g** (45%)<sup>c,d</sup> from **7h**: X = Br**9h** (81%)<sup>c</sup> from **7h**: X = Br

<sup>a</sup> Pinacol ester was used. <sup>b</sup> MIDA ester was used. <sup>c</sup> Reaction temperature 60 °C. <sup>d</sup> Reaction time 40 minutes.

<sup>e</sup> Potassium 3-methoxyphenyltrifluoroborate was used.

We speculated that bulky substituents around C-Br can potentially hinder the cross-coupling reaction. To our delight, phenyl, cyclopropyl, and *tert*-butylcarboxamides **7a-c** reacted smoothly with a range of electron-rich, electron-poor, sterically hindered, and heteroaryl boronic acids producing biaryls **8a-n** in high yields (75 – 88%). The exception was the coupling with pinacol ester of 3-pyridylboronic acid, which gave a lower yield of the respective product **8o** (46%). Amides **7d-f** featuring substituent with additional coordinating heteroatoms possessed a negative effect on the reaction. Thus biaryls **8p**, **8q**, and **8r** bearing lateral 2-thienyl scaffold were obtained from the amide **7d** in diminished yields (70, 28 and 59%, respectively). Lateral pyridine substituent of **7e** displayed pronounced inhibitory effect on the reaction; therefore the coupling of

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3 **7e** with *p*-tolylboronic acid furnished only traces of the respective product **8s**, which precluded its  
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5 isolation. To examine whether the catalyst inhibition, apparently caused by pyridine ring  
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7 nitrogen, can be reversed, we synthesized *N*-oxide **7f** and employed it in the reaction with *p*-  
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9 tolylboronic acid.<sup>33</sup> Even in this case, unfortunately, only traces of the respective biaryl **8t** were  
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11 detected. Using both amides **7e** and **7f**, we tested the possibility of CuI and Cu(OAc)<sub>2</sub> co-  
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13 catalysis, as well as a combination of solvents (DMF, *i*-PrOH) and additives (*N,N*-  
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15 diethanolamine); however, none of these attempts increased the conversion of respective products  
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17 **8s** and **8t** significantly.<sup>31</sup>

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22 Chlorinated pyrazole **7i** gave upon coupling with *p*-tolylboronic acid biaryl **8a** in 78% yield,  
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24 which is close to the yield achieved with its brominated analog **7a** (80%). Chlorinated pyrazole **7i**  
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26 proved to be efficient coupling partner with aryl boronic acids bearing sensitive functional  
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28 groups, such as hydroxyl and amino group. Thus, biaryls **8u** and **8v** containing –OH and –NH<sub>2</sub>  
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30 groups were obtained in 77 and 85% yield, respectively. The reaction of **7i** with potassium 3-  
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32 methoxyphenyltrifluoroborate gave a mixture of dehalogenated compound, starting material and  
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34 product **8w** in the ratio of 1:1:2. The chromatographic separation on silica gel did not allow to  
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36 separate compound **7i** from **8w**. When brominated derivative **7a** was used instead of **7i**, the  
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38 starting material was completely consumed and the major product detected in a crude mixture was  
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40 **8w**, which was subsequently isolated in 90% yield.

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47 Urea derivatives **7g** and **7h** were found unstable under the reaction condition (110 °C) resulting  
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49 in partial hydrolysis of the carboxamide function. Consequently around 30 – 40% of the free  
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51 amine product was observed. Hydrolytic instability of **7g** and **7h** at 110 °C stimulated us to  
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53 explore, whether a lower reaction temperature preserves the carboxamide group and still  
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55 maintains the effective coupling with various boronic acids. To our delight, the reaction of **7g** and  
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3 **7h** with electron-neutral, electron-rich, and heterocyclic boronic acids went to completion in just  
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5 20 minutes even at 60 °C, giving biaryls **9a**, **9c**, **9e-f**, and **9h** in 77 – 89% yields. Under the same  
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7 conditions, sterically hindered and electron-poor boronic acids gave an incomplete conversion of  
8  
9 the starting material, leading to biaryls **9b**, **9d**, and **9g** in diminished yields (44 – 50%). Note that  
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11 sterically hindered 2-methoxyphenyl boronic acid gave considerably higher yield than *o*-tolyl  
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13 boronic acid, which could be explained by the beneficial electron-donating effect of the methoxy  
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15 group.  
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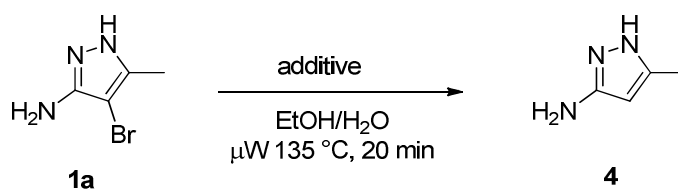
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21 During our study, a majority of cross-coupling reactions went to completion; nevertheless all of  
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23 them were accompanied with undesired dehalogenation, ranging from ~ 5 to 20% (and more with  
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25 pyridylboronates). Unwanted dehalogenation of aryl halides affects Suzuki reaction, as well as  
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27 other important cross-couplings; therefore, the recognition of factors causing this side reaction, as  
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29 well as understanding its mechanism is of importance for the synthetic community.<sup>34</sup>  
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34 Cleavage of the C-halogen and forming of the C-H bond is obviously a reductive process; hence  
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36 one can suspect that the palladium and/or boronic acid are involved in this transformation. In  
37  
38 order to identify factors causing the dehalogenation, we performed experiments with brominated  
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40 pyrazole **1a** (Table 5). The compound **1a** was heated with two equivalents of K<sub>2</sub>CO<sub>3</sub> resulting in  
41  
42 the formation of the dehalogenated pyrazole **4** in 90% (entry 1), and the starting material was  
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44 completely consumed. The preliminary observation suggested that the dehalogenation can be a  
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46 base promoted process and motivated us to further explore this phenomenon. The same situation  
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48 occurred when strong base KOH was used (entry 2). In this case the detected amount of pyrazole  
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50 **4** was slightly lower presumably due to a partial decomposition. On the other hand, weaker base  
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52 KOAc led only to a partial dehalogenation, leaving 61% of starting material **1a** untouched (entry  
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54 3). In order to minimize the possibility that a low amount of palladium or other heavy metal in  
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the inorganic base can distort the result,<sup>35</sup> we repeated the experiment with trace metal basis  $K_2CO_3$  (entry 4). Complete consumption of the pyrazole **1a** occurred and the dehalogenated pyrazole **4** was formed in 89% even with  $K_2CO_3$  of 99.995% purity. These findings also explained why the higher amount of  $K_2CO_3$  during optimization resulted in the increased dehalogenation (Table 1, entries 15 and 16).

The influence of other reaction components on the dehalogenation was also investigated. When pyrazole **1a** was heated with two equivalents of boronic acid **2a**, only traces of the dehalogenated pyrazole **4** were detected together with 95% of the starting material (entry 5). The catalytic amount of palladium, either Pd(0) or Pd(II), had a little effect on the dehalogenation (entries 6 and 7). In the control experiment, when compound **1a** was heated without any additive, no detectable dehalogenation occurred (entry 8).

**Table 5. The evaluation of factors causing dehalogenation**



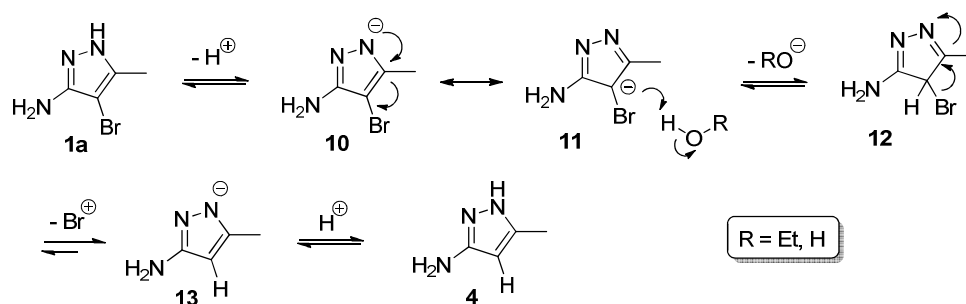
entry	Additive	equivalents	<b>4</b> (%) <sup>a</sup>	<b>1a</b> (%) <sup>a</sup>
1	$K_2CO_3$	2	90	0
2	KOH	2	82	0
3	KOAc	2	36	61
4	$K_2CO_3$ <sup>b</sup>	2	89	0
5	<b>2a</b>	2	traces	95
6	XPhos Pd G2	0.01	1	95
7	$Pd_2dba_3$ /XPhos	0.01/0.02	6	91
8	none	none	0	>95



<sup>a</sup> HPLC yield (%) determined from the crude reaction mixture (see Supporting Information for more details). <sup>b</sup> Trace metal basis K<sub>2</sub>CO<sub>3</sub> was used.

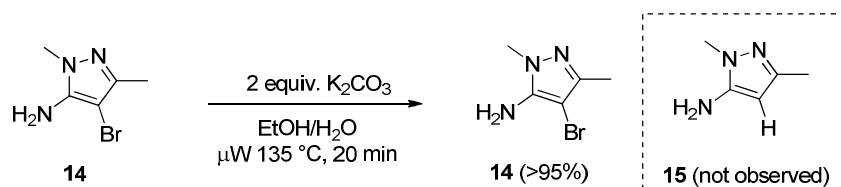
Generally, cleavage of the C-Br bond can release the bromine atom as a cation, anion, or radical. Considering that the dehalogenation is promoted by a base, Br<sup>+</sup> seems to be a reasonable leaving group, while the formation of bromine radical and anion is unlikely. The plausible mechanism of the base-promoted dehalogenation leading to pyrazole **4** is depicted in Scheme 2. Deprotonation of **1a** leads to the anion **10** and its resonance contributor **11** that can accept a proton from a solvent to form 4-*H* tautomer **12**. Rearomatization by releasing of Br<sup>+</sup> species from **12** generates the anion **13**, which after protonation gives dehalogenated pyrazole **4**. Likewise, *N*-methyl analogs (e.g. **5** or **7**) are expected to deprotonate the amidic NH bond.

### Scheme 2.



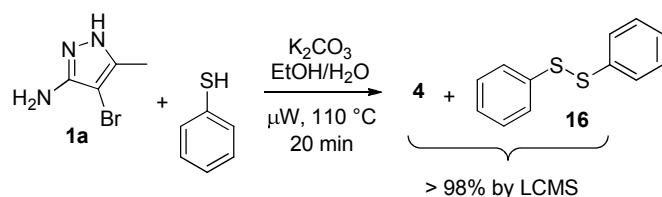
When *N*-methyl pyrazole **14** was heated with two equivalents of K<sub>2</sub>CO<sub>3</sub>, no dehalogenation product **15** was observed (Scheme 3). Consequently, >95% of starting material **14** remained unchanged, as was revealed by the HPLC analysis of a crude reaction mixture. The propensity of **14** toward base promoted dehalogenation suggested that the presence of more acidic azole N-H or amide N-H is required for the proposed mechanism to be operative.

### Scheme 3.



In order to prove that mildly oxidizing  $\text{Br}^+$  species are formed during dehalogenation of **1a**, we heated thoroughly degassed mixture of pyrazole **1a**,  $\text{K}_2\text{CO}_3$ , and thiophenol in EtOH/ $\text{H}_2\text{O}$  to 110 °C under microwave irradiation. As a result, dehalogenated pyrazole **4** and disulfide **16** were formed quantitatively (Scheme 4). When the same experiment was repeated without pyrazole **1a**, more than 98% of thiophenol remained unchanged. Traces of disulfide **16** were detected, presumably as a consequence of the presence of residual oxygen. The same experiment was repeated in the presence of pyrazole **4**, in order to prove that it cannot act as an oxidizing agent, and thiophenol remained practically unchanged (see Supporting Information for more details). Pyrazole **1a** and  $\text{K}_2\text{CO}_3$  were also heated in a presence of 4-methoxystyrene, anisole, or phenol in order to trap suggested  $\text{Br}^+$  species. However, any electrophilic addition or substitution was not observed.

**Scheme 4.** Oxidation of thiophenol by released  $\text{Br}^+$  species



The proposed mechanism corresponds to the observed ratio of pyrazoles **1**, **3a**, and **4** (Table 1, entries 18-20), where iodopyrazole **1c** predominantly underwent dehalogenation. This can be explained by the increased iodine susceptibility to oxidation. Our explanation, that deprotonation of mildly acidic NH is involved in a mechanism leading to the dehalogenation, agrees with the

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3 observation of others. For instance, *N*-unprotected indoles were reported to suffer from unwanted  
4 dehalogenation, which was suppressed by the protection of indole nitrogen.<sup>36</sup>  
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## 8 9 **CONCLUSION**

10 Overall, we have developed the efficient Suzuki-Miyaura cross-coupling of various boronic  
11 acids/esters with 4-halogenated aminopyrazoles featuring the free endocyclic pyrazole-NH/amino  
12 group, *N*-Me/NH-acetyl, *N*-Me/NH-amides, and NH-ureas. The use of palladacycle XPhos Pd G2  
13 in a combination with K<sub>2</sub>CO<sub>3</sub> and user friendly solvent system EtOH/H<sub>2</sub>O afforded diverse  
14 (hetero)biaryls generally in high yields. Additionally, the presented method allowed the  
15 preparation of 4-styryl aminopyrazoles, which are otherwise difficult to access by standard  
16 methods. The reaction temperature is strongly dependent on the pyrazole substrate. While some  
17 pyrazoles bearing substituents on both pyrazole NH and amino group can be coupled almost  
18 quantitatively after 20 minutes at 60 °C, unsubstituted pyrazoles required 135 °C for the same  
19 reaction time. The cross-coupling reactions were accompanied with undesired dehalogenation,  
20 which was primarily caused by a base and its mechanism was proposed on the basis of our  
21 experimental observations.  
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## 40 **EXPERIMENTAL SECTION**

41 All reactions were carried out under inert atmosphere of nitrogen or argon. All starting materials,  
42 reagents and catalysts were purchased from commercial sources. Solvents were distilled,  
43 degassed, and stored under inert atmosphere. Reactions were monitored by LCMS using C-18  
44 column and MeCN – 1 mM AcONH<sub>4</sub> buffer as a mobile phase. Product purifications were  
45 performed with silica gel (40 -200 mesh). NMR spectra were recorded with 400 MHz  
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3 spectrometer and chemical shifts are reported in ppm relative to a residual solvent peak. Accurate  
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5 mass spectra were measured using ESI-TOF detector.  
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9 **General procedure for the cross-coupling of pyrazole 1a (Table 2).** A mixture of pyrazole **1a**  
10 (0.174 g, 1.0 mmol), boronic acid (2.0 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.276 g, 2.0 mmol) in EtOH (4 mL)  
11 and water (1 mL) was thoroughly degassed with a stream of nitrogen. Then, XPhos (0.009 g, 0.02  
12 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added and the microwave vial containing the  
13 mixture was capped and inserted into microwave reactor. The reaction mixture was irradiated  
14 (setup: variable power, maximum of 300W, 135 °C) for 20 min. After that, the mixture was  
15 filtered through a Celite, washed with EtOAc, and concentrated under reduced pressure.  
16 Purification of the crude via column chromatography (MeOH-Et<sub>3</sub>N-DCM 100:0.5:0 to 100:0.5:3)  
17 afforded desired pyrazole as an oil or solid, which was characterized by <sup>1</sup>H, <sup>13</sup>C NMR and  
18 HRMS. In some cases, a product was crystallized from appropriate solvents before measurement  
19 of a melting point.  
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35 *3-methyl-4-(4-p-tolyl)-1H-pyrazol-5-amine (3a).* The compound **3a** is known; however no  
36 analytical data were reported.<sup>37</sup> Title compound was prepared according the general procedure  
37 from pyrazole **1a** and 4-tolylboronic acid **2a**. Purification via column chromatography afforded  
38 title product as a white solid (0.146 g, 78%); mp 80 – 82 °C (DCM – hexanes); <sup>1</sup>H NMR (400  
39 MHz, CD<sub>3</sub>COOD) δ (ppm) = 7.28 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 2.37 (s, 3H), 2.3  
40 (s, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COOD) δ (ppm) = 149.8, 143.2, 138.4, 130.7, 129.9, 127.8,  
41 106.2, 21.2, 10.5 ppm; HRMS (ESI): calcd for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub> [M + H]<sup>+</sup> 188.1182, found 188.1183.  
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52 *4-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5-amine (3b).* Pyrazole **3b** is a known compound and  
53 its analytical data were in accordance with the literature.<sup>38</sup> Title compound was prepared  
54 according the general procedure from pyrazole **1a** and 4-methoxyphenylboronic acid **2b**.  
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Purification via column chromatography afforded title product as a white solid (0.176 g, 87%); mp 139 – 141 °C (DCM – hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 11.32 (br.s, 1H, NH), 7.25 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.32 (br.s, 2H, NH<sub>2</sub>), 3.75 (s, 3H), 2.13 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 156.9, 152.1, 135.2, 129.1, 126.3, 114.0, 104.4, 55.0, 10.8; HRMS (ESI): calcd for C<sub>11</sub>H<sub>13</sub>ON<sub>3</sub> [M + H]<sup>+</sup> 204.1131, found 204.1131.

*4-(2-methoxyphenyl)-3-methyl-1H-pyrazol-5-amine (3c)*. Pyrazole **3c** is a known compound and its NMR data were in accordance with the literature.<sup>39</sup> We were not able to crystallize the compound, albeit it was reported as a solid melting from 67 to 68 °C. Title compound was prepared according the general procedure from pyrazole **1a** and 2-methoxyphenylboronic acid **2c**. Purification via column chromatography afforded title product as a pale brown oil (0.166 g, 82%); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 7.24 (td, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.95 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 3.76 (s, 3H), 2.02 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 156.3, 151.4, 138.3, 130.9, 127.4, 122.2, 120.4, 111.3, 101.5, 55.1, 10.9; HRMS (ESI): calcd for C<sub>11</sub>H<sub>13</sub>ON<sub>3</sub> [M + H]<sup>+</sup> 204.1131, found 204.1132.

*(E)-4-(4-methoxystyryl)-3-methyl-1H-pyrazol-5-amine (3d)*. Title compound was prepared according the general procedure from pyrazole **1a** and (*E*)-(4-methoxystyryl)boronic acid **2d**. Purification via column chromatography afforded title product as a beige solid (0.192 g, 84%); mp 171 – 175 °C (DCM – hexanes); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>COOD) δ (ppm) = 7.44 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 16.6 Hz, 1H), 6.74 (d, *J* = 17.1 Hz, 1H), 3.80 (s, 3H), 2.41 (s, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COOD) δ (ppm) = 159.3, 149.0, 142.1, 130.4, 128.4, 127.2, 114.0, 113.8, 102.6, 54.6, 10.1; HRMS (ESI): calcd for C<sub>13</sub>H<sub>15</sub>ON<sub>3</sub> [M + H]<sup>+</sup> 230.1288, found 230.1289.

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3 *3-methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-amine (3e)*. The compound **3e** is known;  
4  
5 however no analytical data were reported.<sup>40</sup> Title compound was prepared according the general  
6  
7 procedure from pyrazole **1a** and 4-(trifluoromethyl)phenylboronic acid **2e**. Purification via  
8  
9 column chromatography afforded title product as a pale yellow solid (0.072 g, 30%); mp 114 –  
10  
11 119 °C (DCM – hexanes), <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 7.68 (d, *J* = 8.2 Hz, 2H),  
12  
13 7.57 (d, *J* = 8.2 Hz, 2H), 2.21 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 151.1, 138.8,  
14  
15 138.0, 127.9, 125.3 (q, *J* = 4 Hz), 124.9 (q, *J* = 32 Hz), 124.6 (q, *J* = 272 Hz), 102.8, 11.5; HRMS  
16  
17 (ESI): calcd for C<sub>11</sub>H<sub>10</sub>N<sub>3</sub>F<sub>3</sub> [M + H]<sup>+</sup> 242.0900, found 242.0900.  
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22 *3-methyl-4-(5-methylthiophen-2-yl)-1H-pyrazol-5-amine (3f)*. Title compound was prepared  
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24 according the general procedure from pyrazole **1a** and 4,4,5,5-tetramethyl-2-(5-methylthiophen-  
25  
26 2-yl)-1,3,2-dioxaborolane **2f**. Purification via column chromatography afforded title product as a  
27  
28 white solid (0.110 g, 57%); mp 118 – 122 °C (DCM – hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  
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30 δ (ppm) = 11.45 (br.s, 1H, NH), 6.77 (d, *J* = 3.1 Hz, 1H), 6.73 (d, *J* = 3.1 Hz, 1H) 4.56 (br.s, 2H,  
31  
32 NH<sub>2</sub>), 2.42 (s, 3H), 2.20 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 151.4, 137.2, 135.6,  
33  
34 133.5, 125.5, 122.6, 98.8, 14.8, 11.5; HRMS (ESI): calcd for C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>S [M + H]<sup>+</sup> 194.0746,  
35  
36 found 194.0748.  
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41 *4-(furan-3-yl)-3-methyl-1H-pyrazol-5-amine (3g)*. Title compound was prepared according the  
42  
43 general procedure from pyrazole **1a** and furan-3-ylboronic acid **2g**. Purification via column  
44  
45 chromatography afforded title product as a white solid (0.122 g, 74%); mp 93 – 96 °C (DCM –  
46  
47 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 11.31 (br.s, 1H, NH), 7.72 (dd, *J* = 1.6 Hz,  
48  
49 0.8 Hz, 1H), 7.67 (dd, *J* = 1.8 Hz, 1.6 Hz, 1H), 6.68 (dd, *J* = 1.8 Hz, 0.8 Hz, 1H), 4.45 (br.s, 2H,  
50  
51 NH<sub>2</sub>), 2.18 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 151.1, 142.8, 137.5 (overlapped  
52  
53 C-2 of furan and C-3 of pyrazole), 117.7, 109.7, 95.6, 11.5; HRMS (ESI): calcd for C<sub>8</sub>H<sub>9</sub>ON<sub>3</sub> [M  
54  
55 + H]<sup>+</sup> 164.0818, found 164.0820.  
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3 **General procedure for the cross-coupling of pyrazoles 5 (Table 3).** *Method A:* A mixture of  
4 pyrazole **5c** (0.265 g, 1.0 mmol), boronic acid (2.0 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.276 g, 2.0 mmol) in  
5 dioxane (4 mL) and water (1 mL) was thoroughly degassed with a stream of nitrogen. Then,  
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10 XPhos (0.009 g, 0.02 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added and the sealed  
11  
12 tube inserted into a preheated oil bath to 100 °C. The reaction mixture was stirred at 100 °C for  
13  
14  
15 24h. After that, the mixture was filtered through a Celite, washed with EtOAc, and concentrated  
16  
17 under reduced pressure. Purification of the crude via column chromatography (MeOH-DCM  
18  
19 100:0 to 100:3) afforded desired pyrazole as an oil or solid, which was characterized by <sup>1</sup>H, <sup>13</sup>C  
20  
21 NMR and HRMS. In some cases, a product was crystallized from appropriate solvents before  
22  
23 measurement of a melting point.  
24  
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26  
27 *Method B:* A mixture of pyrazole **5a** (0.174 g, 1.0 mmol), boronic acid (2.0 mmol), and K<sub>2</sub>CO<sub>3</sub>  
28  
29 (0.276 g, 2.0 mmol) in EtOH (4 mL) and water (1 mL) was thoroughly degassed with a stream of  
30  
31 nitrogen. Then, XPhos (0.009 g, 0.02 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added  
32  
33 and the microwave vial containing the mixture was capped and inserted into microwave reactor.  
34  
35 The reaction mixture was irradiated (setup: variable power, maximum of 300W, 120 °C) for 20  
36  
37 min. After that, the mixture processed the same way as in the method A.  
38  
39

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41 *N*-(1-methyl-4-(*p*-tolyl)-1*H*-pyrazol-5-yl)acetamide (**6a**). Title compound was prepared from 4-  
42  
43 tolylboronic acid **2a** and pyrazole **5c** (Method A, 0.190 g, 83%) or pyrazole **5a** (Method B, 0.201  
44  
45 g, 88%). Entry 3: white solid; mp 147 - 148 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-  
46  
47 *d*<sub>6</sub>) major conformer  $\delta$  (ppm) = 9.88 (s, 1H), 7.71 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* =  
48  
49 8.1 Hz, 2H), 3.61 (s, 3H), 2.29 (s, 3H), 2.10 (s, 3H), minor conformer  $\delta$  (ppm) = 9.36 (s, 1H),  
50  
51 7.82 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 3.71 (s, 3H), 1.55 (s, 3H); <sup>13</sup>C  
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3 NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 170.0, 136.0, 135.3, 132.2, 129.4, 129.3, 125.9, 115.7,  
4  
5 35.5, 22.6, 20.7; HRMS (ESI): calcd for C<sub>13</sub>H<sub>15</sub>ON<sub>3</sub> [M + H]<sup>+</sup> 230.1288, found 230.1289.  
6  
7

8 *N*-(1-methyl-4-(*o*-tolyl)-1*H*-pyrazol-5-yl)acetamide (**6b**). Title compound was prepared from 2-  
9 methylphenylboronic acid **2i** and pyrazole **5c** (Method A, 0.192 g, 84%) or pyrazole **5a** (Method  
10 B, 0.203 g, 89%), and obtained as a colourless oil. Entry 5: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  
11 major conformer  $\delta$  (ppm) = 9.72 (s, 1H), 7.50 (s, 1H), 7.24 - 7.12 (m, 4H), 3.63 (s, 3H), 2.22 (s,  
12 3H), 2.00 (s, 3H); minor conformer  $\delta$  (ppm) = 9.81 (s, 1H), 9.30 (s, 1H), 7.58 (s, 1H), 3.73 (s,  
13 3H), 1.46 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 169.9, 137.6, 135.9, 133.3, 131.6,  
14 130.2, 129.7, 126.9, 125.7, 115.3, 35.7, 22.4, 20.2; HRMS (ESI): calcd for C<sub>13</sub>H<sub>15</sub>ON<sub>3</sub> [M + H]<sup>+</sup>  
15 230.1288, found 230.1289.  
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27 *(E)*-*N*-(1-methyl-4-styryl-1*H*-pyrazol-5-yl)acetamide (**6c**). Title compound was prepared from  
28 *(E)*-styrylboronic acid **2j** and pyrazole **5c** (Method A, 0.144 g, 60%) or pyrazole **5a** (Method B,  
29 0.168 g, 70%). Entry 7: white solid; mp 107 - 109 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz,  
30 DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 9.91 (s, 1H), 7.77 (s, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.3 Hz,  
31 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 16.5 Hz, 1H), 6.82 (d, *J* = 16.5 Hz, 1H), 3.60 (s, 3H),  
32 2.14 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 169.5, 137.5, 135.1, 133.9, 128.7,  
33 126.9, 125.7, 125.4, 118.1, 113.4, 35.7, 22.7; HRMS (ESI): calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O [M + H]<sup>+</sup>  
34 242.1288, found 242.1288.  
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46 *N*-(1-methyl-4-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)acetamide (**6d**). Title compound was  
47 prepared from 4-(trifluoromethyl)phenylboronic acid **2e** and pyrazole **5c** (Method A, 0.150 g,  
48 53%) or pyrazole **5a** (Method B, 0.175 g, 62%). Entry 9: white solid; mp 141 - 142 °C (DCM -  
49 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 10.02 (s, 1H), 7.89 (s, 1H), 7.73 (d, *J* = 9.3  
50 Hz, 2H), 7.70 (d, *J* = 9.3 Hz, 2H), 3.65 (s, 3H), 2.13 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$   
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(ppm) = 169.9, 136.6, 136.5, 133.2, 126.4 (q,  $J = 32$  Hz), 126.2, 125.6 (q,  $J = 4$  Hz), 124.5 (q,  $J = 271$  Hz), 114.3, 35.5, 22.6; HRMS (ESI): calcd for  $C_{13}H_{12}F_3N_3O$   $[M + H]^+$  284.1005, found 284.1004.

*N*-(1-methyl-4-(thiophen-3-yl)-1*H*-pyrazol-5-yl)acetamide (**6e**). Title compound was prepared from thiophen-3-ylboronic acid **2k** and pyrazole **5c** (Method A, 0.183 g, 83%) or pyrazole **5a** (Method B, 0.187 g, 85%). Entry 11: white solid; mp 111 - 113 °C (DCM - hexanes);  $^1H$  NMR (400 MHz, DMSO- $d_6$ ) major conformer:  $\delta$  (ppm) = 9.90 (s, 1H), 7.75 (s, 1H), 7.56 (dd,  $J = 5.0$ , 3.0 Hz, 1H), 7.48 (dd,  $J = 3.0$ , 1.3 Hz, 1H), 7.32 (dd,  $J = 5.0$ , 1.3 Hz, 1H), 3.61 (s, 3H), 2.13 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 169.8, 136.1, 132.4, 132.1, 126.2, 126.1, 118.7, 111.8, 35.5, 22.6; HRMS (ESI): calcd for  $C_{10}H_{11}OSN_3$   $[M + H]^+$  222.0696, found 222.0696.

### Synthesis of halogenated pyrazoles **7a-h** (Scheme 1)

*N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**7a**). DIPEA (6.97 mL, 40.0 mmol) was added to the mixture of 1,3-dimethyl-1*H*-pyrazol-5-amine (2.22 g, 20.0 mmol), 4-methoxybenzoic acid (3.34 g, 22.0 mmol), and DMAP (0.25 g, 2.0 mmol) in acetonitrile (20 mL). The solution was cooled in an ice water bath and T3P (50% in EtOAc, 14.3 mL, 24.0 mmol) was added dropwise. Resulting mixture was stirred at room temperature for 18 hours. After that, *N*-bromosuccinimide (3.91 g, 22.0 mmol) was added in one portion and the mixture was stirred for another 4 hours. Then the mixture was diluted with water and extracted with EtOAc (3x60 mL). After removing solvents under reduced pressure the residue was crystallized first from DCM - hexanes, then from MeOH - H<sub>2</sub>O yielding title product as white needles (4.46 g, 69%); mp 174 - 176 °C (MeOH - H<sub>2</sub>O);  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 10.16 (s, 1H), 7.99 (d,  $J = 8.8$  Hz, 2H), 7.09 (d,  $J = 9.0$  Hz, 2H), 3.85 (s, 3H), 3.62 - 3.59 (m, 3H), 2.13 (s, 3H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 165.8, 163.0, 144.7, 135.6, 130.4, 125.3, 114.4, 90.9, 56.0, 36.6,

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3 12.9; HMRS (ESI): calcd for  $C_{13}H_{14}BrN_3O_2$   $[M + H]^+$  324.0342 and 326.0322, found 324.0344  
4  
5 and 326.0319.  
6

7  
8 *N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)pivalamide (**7b**). Compound **7b** was prepared from  
9  
10 pivalic acid using the same procedure as for compound **7a**. Purification via a column  
11  
12 chromatography ( $SiO_2$ , 0 – 4 % MeOH in DCM) and subsequent crystallization from MeOH -  
13  
14  $H_2O$  yielded title product as a white solid (3.22 g, 59%); mp 104 - 106 °C (MeOH -  $H_2O$ );  $^1H$   
15  
16 NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  (ppm) = 9.36 (s, 1H), 3.52 (s, 3H), 2.10 (s, 3H), 1.24 (s, 9H);  $^{13}C$   
17  
18 NMR (100 MHz,  $DMSO-d_6$ ):  $\delta$  (ppm) = 177.7, 144.0, 135.1, 90.2, 38.7, 35.7, 27.1. HRMS (ESI):  
19  
20 calcd for  $C_{10}H_{16}BrN_3O$   $[M + H]^+$  274.0555 and 276.0535, found 274.0554 and 276.0534.  
21  
22  
23

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25 *N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)cyclopropanecarboxamide (**7c**). Compound **7c** was  
26  
27 prepared from cyclopropanecarboxylic acid using the same procedure as for compound **7a**.  
28  
29 Purification via a column chromatography ( $SiO_2$ , 0 – 4 % MeOH in DCM) and subsequent  
30  
31 crystallization from MeOH -  $H_2O$  (charcoal) yielded title product as a white solid (3.92 g, 76%);  
32  
33 mp 161 – 163 °C (MeOH –  $H_2O$ );  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  (ppm) = 10.10 (s, 1H),  
34  
35 3.53 (s, 3H), 2.09 (s, 3H), 1.82 (tt,  $J = 4.7, 7.9$  Hz, 1H), 0.89 - 0.78 (m, 4H);  $^{13}C$  NMR (100  
36  
37 MHz,  $DMSO-d_6$ ):  $\delta$  (ppm) = 172.8, 144.0, 134.8, 89.3, 36.2, 13.5, 12.3, 7.6; HRMS (ESI): calcd  
38  
39 for  $C_9H_{12}BrN_3O$   $[M + H]^+$  258.0237 and 260.0216, found 258.0240 and 260.0215.  
40  
41  
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44 *N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)thiophene-2-carboxamide (**7d**). Pyrazole **7d** is  
45  
46 commercially available; however no reference exists for this compound. Pyrazole **7d** was  
47  
48 prepared from thiophene-2-carboxylic acid using the same procedure as for compound **7a**.  
49  
50 Purification via a column chromatography ( $SiO_2$ , 0 – 4 % MeOH in DCM) and subsequent  
51  
52 crystallization from DCM - hexanes yielded title product as a white solid (3.70 g, 62%); mp 152  
53  
54 – 153 °C (DCM – hexanes);  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  (ppm) = 10.38 (s, 1H), 8.02 (d,  $J$   
55  
56 = 3.4 Hz, 1H), 7.93 (dd,  $J = 4.9, 1.0$  Hz, 1H), 7.26 (dd,  $J = 4.9, 3.8$  Hz, 1H), 3.62 (s, 3H), 2.14 (s,  
57  
58 = 3.4 Hz, 1H), 7.93 (dd,  $J = 4.9, 1.0$  Hz, 1H), 7.26 (dd,  $J = 4.9, 3.8$  Hz, 1H), 3.62 (s, 3H), 2.14 (s,  
59  
60

3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 160.4, 144.4, 137.7, 134.3, 132.9, 130.4, 128.4, 90.5, 36.2, 12.4; HRMS (ESI): calcd for  $\text{C}_{10}\text{H}_{10}\text{BrN}_3\text{OS}$   $[\text{M} + \text{H}]^+$  299.9801 and 301.9780, found 299.9802 and 301.9776.

*N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)isonicotinamide (**7e**). Compound **7e** was prepared from isonicotinic acid using the same procedure as for compound **7a**. The crude product was crystallized first from EtOAc - toluene, then from MeOH - H<sub>2</sub>O yielding title product as a pale yellow crystalline solid (3.35 g, 57%); mp 80 – 82 °C (MeOH - H<sub>2</sub>O);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 10.68 (s, 1H), 8.83 (dd,  $J$  = 4.4, 1.6 Hz, 2H), 7.90 (dd,  $J$  = 4.4, 1.6 Hz, 2H), 3.64 (s, 3H), 2.14 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 164.5, 150.6, 144.5, 139.7, 134.1, 121.6, 90.4, 36.2, 12.4; HRMS (ESI): calcd. for  $\text{C}_{11}\text{H}_{11}\text{BrN}_4\text{O}$   $[\text{M} + \text{H}]^+$  295.0189 and 297.0169, found 295.0190 and 297.0165.

4-((4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)carbamoyl)pyridine 1-oxide (**7f**). Compound **7f** was prepared from 4-carboxypyridine 1-oxide using the same procedure as for compound **7a**. The crude product was purified via crystallization from EtOAc – hexanes yielding pale yellow solid (1.79 g, 29%); mp 129 – 131 °C (EtOAc – hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 10.56 (s, 1H), 8.39 (d,  $J$  = 7.3 Hz, 2H), 7.97 (d,  $J$  = 7.3 Hz, 2H), 3.62 (s, 3H), 2.13 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 162.7, 144.5, 139.2, 134.2, 127.7, 125.4, 90.3, 36.2, 12.4; HRMS (ESI): calcd for  $\text{C}_{11}\text{H}_{11}\text{BrN}_4\text{O}_2$   $[\text{M} + \text{H}]^+$  311.0138 and 313.0118, found 311.0139 and 313.0114.

1-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)-3-phenylurea (**7g**). The compound **7g** is known from a patent literature; however no synthetic procedure and analytical data were reported. To the solution of 1,3-dimethyl-1*H*-pyrazol-5-amine (1.11 g, 10.0 mmol) in THF (10 mL) was added phenyl isocyanate (1.19 mL, 11.0 mmol), and the mixture was heated at ~ 66 °C for 24h under nitrogen atmosphere. Then the mixture was cooled to ambient temperature and *N*-

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2  
3 bromosuccinimide (1.96 g, 11.0 mmol) was added. After stirring for 4h at ~ 20 °C, the mixture  
4  
5 was diluted with water and extracted to EtOAc (3x40 mL). The crude product was purified via  
6  
7 crystallization from DCM – hexanes, then from MeOH – H<sub>2</sub>O, yielding white crystalline solid  
8  
9 (2.15 g, 70%); mp 278 – 280 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 8.99 (s, 1H), 8.21  
10  
11 (s, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.28 (t, *J* = 8,6 Hz, 2H), 6.98 (t, *J* = 8.6 Hz, 1H), 3.62 (s, 3H),  
12  
13 2.11 (s,3 H); <sup>13</sup>C NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 153.1, 144.4, 139.9, 135.7, 129.3,  
14  
15 122.7, 119.0, 90.6, 36.6, 12.9; HMRS (ESI): calcd for C<sub>12</sub>H<sub>13</sub>BrN<sub>4</sub>O [M + H]<sup>+</sup> 309.0351 and  
16  
17 311.0331, found 309.0347 and 311.0322.

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21 *N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)piperidine-1-carboxamide (**7h**). To the mixture of 1,3-  
22  
23 dimethyl-1*H*-pyrazol-5-amine (2.22 g, 20.0 mmol) and DABCO (4.39 g, 36.0 mmol) in DCM (80  
24  
25 mL) was added the solution of piperidine-1-carbonyl chloride (4.48 mL, 36 mmol) in DCM (40  
26  
27 mL) dropwise over 45 minutes. The mixture was stirred at ambient temperature for 14h. Then it  
28  
29 was washed with water (3x50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure.  
30  
31 The residue was crystallized from DCM – hexanes yielding a white crystalline solid (2.48 g, 11.2  
32  
33 mmol, 56%), which was then dissolved in acetonitrile (60 mL). To the solution intermediate urea  
34  
35 was added *N*-bromosuccinimide (2.09 g, 11.76 mmol) and the mixture was stirred at ambient  
36  
37 temperature for 3h. Then the mixture was diluted with water and extracted to EtOAc (3x50 mL).  
38  
39 Combined organic extracts were washed with 10% NaHCO<sub>3</sub> (2x20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and  
40  
41 concentrated under reduced pressure. The residue was crystallized from EtOAc – hexanes to  
42  
43 yield title product as a white crystalline solid (2.78 g, 83%, 46% over two steps); mp 150 – 152  
44  
45 °C (EtOAc – hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 8.38 (s, 1H), 3.53 (s, 3H),  
46  
47 3.44 - 3.37 (m, 4H), 2.09 (s, 3H), 1.63 - 1.56 (m, 2H), 1.53 - 1.45 (m, 4H); <sup>13</sup>C NMR (100 MHz,  
48  
49 DMSO-*d*<sub>6</sub>): δ (ppm) = 154.5, 143.6, 136.4, 90.3, 44.9, 35.7, 25.4, 24.0, 12.4; HRMS (ESI): calcd  
50  
51 for C<sub>11</sub>H<sub>17</sub>BrN<sub>4</sub>O [M + H]<sup>+</sup> 301.0659 and 303.0638, found 301.0659 and 303.0634.  
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3 *N*-(4-chloro-1,3-dimethyl-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**7i**). To a mixture of 1,3-  
4 dimethyl-1*H*-pyrazol-5-amine (1.11 g, 10.0 mmol) in acetonitrile (20 mL), 4-methoxybenzoic  
5 acid (1.67 g, 11.0 mmol), DMAP (0.12 g, 1.0 mmol), and DIPEA (3.5 mL, 20.0 mmol) were  
6 added. The solution was cooled in an ice water bath and T3P (50% in EtOAc, 7.2 mL, 12.0  
7 mmol) was added dropwise. Resulting mixture was stirred at room temperature for 18 hours.  
8 After that, *N*-chlorosuccinimide (1.47 g, 11.0 mmol) was added in one portion and the mixture  
9 was stirred for another 4 hours. Then the mixture was diluted with water and extracted with  
10 EtOAc (3x60 mL). After removing solvents under reduced pressure, the residue was purified via  
11 a column chromatography (silica gel, DMC – MeOH 100:2). Then the compound was  
12 crystallized from MeOH – H<sub>2</sub>O in order to remove any residual succinimide. Title product **7i** was  
13 obtained as a white crystalline solid (1.60 g, 57% over two steps); mp 180 – 181 °C (MeOH -  
14 H<sub>2</sub>O); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 10.19 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.08 (d,  
15 *J* = 8.6 Hz, 2H), 3.85 (s, 3H), 3.59 (s, 3H), 2.14 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ  
16 (ppm) = 165.3, 162.5, 142.6, 133.3, 129.9, 124.7, 113.9, 103.5, 55.5, 36.1, 11.5; HRMS (ESI):  
17 calcd for C<sub>13</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 280.0847, found 280.0844.  
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39 **General procedure for the cross-coupling of pyrazoles 7a-i (Table 4).** A mixture of respective  
40 pyrazole **7** (1.0 mmol), boronic acid **2** (2.0 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.276 g, 2.0 mmol) in EtOH (4  
41 mL) and water (1 mL) was thoroughly degassed with a stream of nitrogen. Then, XPhos (0.009 g,  
42 0.02 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added and the microwave vial was  
43 inserted into microwave reactor. The reaction mixture was irradiated (setup: variable power, a  
44 maximum of 300W, 110 or 60 °C) for 20 min. After that, the mixture was filtered through a  
45 Celite, washed with EtOAc, and concentrated under reduced pressure. Purification of the crude  
46 via column chromatography (MeOH-DCM 100:0 to 100:3) afforded the desired pyrazole as an oil  
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3 or solid, which was characterized by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and HRMS. In some cases, a product was  
4  
5 crystallized from appropriate solvents before measurement of a melting point.  
6

7  
8 *N*-(1,3-dimethyl-4-(*p*-tolyl)-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**8a**). Title compound was  
9  
10 prepared according the general procedure using pyrazole **7a** and 4-tolylboronic acid **2a** at 110 °C.  
11  
12 The crude material was purified via a column chromatography to yield title product as a white  
13  
14 solid (0.268 g, 80%). Title compound was also prepared from chloro derivative **7i** in 78% yield.  
15  
16 Reported analytical data belong to the sample prepared from **7a**: mp 209 – 210 °C (DCM -  
17  
18 hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 10.06 (s, 1H), 7.96 (d,  $J$  = 8.8 Hz, 2H),  
19  
20 7.23 (d,  $J$  = 8.3 Hz, 2H), 7.15 (d,  $J$  = 8.3 Hz, 2H), 7.06 (d,  $J$  = 8.8 Hz, 2H), 3.83 (s, 3H), 3.60 (s,  
21  
22 3H), 2.26 (s, 3H), 2.23 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 166.2, 162.4, 143.4,  
23  
24 135.3, 133.2, 129.8, 129.7, 128.0, 125.1, 115.0, 113.8, 55.5, 20.7, 13.2; HRMS (ESI): calcd for  
25  
26  $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2$   $[\text{M} + \text{H}]^+$  336.1705, found 336.1707.  
27  
28

29  
30  
31 *4*-methoxy-*N*-(4-(4-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)benzamide (**8b**). Title  
32  
33 compound was prepared from pyrazole **7a** and 4-methoxyphenylboronic acid **2b** at 110 °C. The  
34  
35 crude material was purified via a column chromatography to yield title product as a white solid  
36  
37 (0.291 g, 83%); mp 175 - 177 °C (DCM - hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) =  
38  
39 10.05 (s, 1H), 7.96 (d,  $J$  = 8.6 Hz, 2H), 7.26 (d,  $J$  = 8.3 Hz, 2H), 7.06 (d,  $J$  = 8.6 Hz, 2H), 6.93 (d,  
40  
41  $J$  = 8.3 Hz, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 3.59 (s, 3H), 2.22 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  
42  
43 DMSO- $d_6$ ):  $\delta$  (ppm) = 166.2, 162.4, 157.7, 143.3, 133.0, 129.8, 129.2, 125.1, 124.9, 114.9, 114.0,  
44  
45 113.8, 55.5, 55.0, 35.0, 13.2; HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3$   $[\text{M} + \text{H}]^+$  352.1654, found  
46  
47 352.1656.  
48  
49  
50

51  
52  
53 *N*-(1,3-dimethyl-4-(*o*-tolyl)-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**8c**). Title compound was  
54  
55 prepared according the general procedure using pyrazole **7a** and 2-methylphenylboronic acid **2i**  
56  
57 at 110 °C. The crude material was purified via a column chromatography to yield title product as  
58  
59  
60

1  
2  
3 a white solid (0.265 g, 79%); mp 89 – 91 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  
4  
5  $\delta$  (ppm) = 9.89 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.22 (dd, *J* = 1.6, 7.4 Hz, 1H), 7.18 (dd, *J* = 1.8,  
6  
7 7.3 Hz, 1H), 7.14 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.09 (dt, *J* = 1.6, 7.7 Hz, 1H), 7.01 (d, *J* = 8.8 Hz,  
8  
9 2H), 3.81 - 3.78 (m, 3H), 3.61 (s, 3H), 2.11 (s, 3H), 1.99 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-  
10  
11 *d*<sub>6</sub>):  $\delta$  (ppm) = 165.8, 162.3, 143.9, 137.0, 133.8, 132.0, 130.8, 129.8, 129.8, 127.1, 125.4, 125.2,  
12  
13 115.0, 113.7, 55.4, 35.2, 19.6, 12.7; HRMS (ESI): calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 336.1707,  
14  
15 found 336.1706.  
16  
17

18  
19  
20 *N*-(1,3-dimethyl-4-(thiophen-3-yl)-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**8d**). Title compound  
21  
22 was prepared according the general procedure using pyrazole **7a** and thiophen-3-ylboronic acid  
23  
24 **2k** at 110 °C. The crude material was purified via a column chromatography to yield title product  
25  
26 as a white solid (0.255 g, 78%); mp 204 – 206 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz,  
27  
28 DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 10.11 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.50 (dd, *J* = 3.0, 5.1 Hz, 1H), 7.37  
29  
30 (dd, *J* = 1.2, 2.9 Hz, 1H), 7.18 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H),  
31  
32 3.55 (s, 3H), 2.25 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 165.9, 162.4, 143.5,  
33  
34 133.1, 132.7, 129.8, 127.0, 125.9, 125.0, 120.4, 113.9, 110.7, 55.5, 35.0, 13.7; HRMS (ESI):  
35  
36 calcd for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 328.1114, found 328.1114.  
37  
38

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40  
41 *N*-(1,3-dimethyl-4-(5-methylthiophen-2-yl)-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**8e**). Title  
42  
43 compound was prepared according the general procedure using pyrazole **7a** and 4,4,5,5-  
44  
45 tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane **2f** at 110 °C. The crude material was  
46  
47 purified via a column chromatography to yield title product as a white solid (0.259 g, 76%); mp  
48  
49 210 – 211 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 10.15 (s, 1H), 8.01  
50  
51 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 3.5 Hz, 1H), 6.72 (dd, *J* = 1.1, 3.4 Hz,  
52  
53 1H), 3.85 (s, 3H), 3.58 (s, 3H), 2.37 (d, *J* = 0.9 Hz, 3H), 2.30 (s, 3H); <sup>13</sup>C NMR (100 MHz,  
54  
55 DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 165.9, 162.4, 143.0, 137.1, 133.0, 131.8, 129.9, 125.5, 125.1, 123.4, 113.9,  
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3 109.6, 55.5, 35.1, 14.8, 13.9; HRMS (ESI): calcd for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>S [M + H]<sup>+</sup> 342.1271, found  
4  
5 342.1270.

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7  
8 *N*-(1,3-dimethyl-4-(*p*-tolyl)-1*H*-pyrazol-5-yl)pivalamide (**8f**). Title compound was prepared  
9  
10 according the general procedure using pyrazole **7b** and 4-tolylboronic acid **2a** at 110 °C. The  
11  
12 crude material was purified via a column chromatography to yield title product as white solid  
13  
14 (0.233 g, 82%); mp 201 – 202 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) =  
15  
16 9.28 (s, 1H), 7.14 – 7.20 (m, 4H), 3.50 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 1.19 (s, 9H); <sup>13</sup>C NMR  
17  
18 (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 178.3, 143.2, 133.3, 129.7, 128.9, 127.9, 114.7, 38.6, 34.6,  
19  
20 27.1, 20.7, 13.3; HRMS (ESI): calcd for C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O [M + H]<sup>+</sup> 286.1914, found 286.1911.

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23  
24 *N*-(4-(2-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)pivalamide (**8g**). Title compound was  
25  
26 prepared according the general procedure using pyrazole **7b** and 2-methoxyphenylboronic acid **2c**  
27  
28 at 110 °C. The crude material was purified via a column chromatography to yield title product as  
29  
30 a white solid (0.225 g, 75%); mp 131 – 132 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-  
31  
32 *d*<sub>6</sub>): δ (ppm) = 9.01 (s, 1H), 7.29 - 7.23 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1H), 7.05 (dd, *J* = 7.5, 1.8 Hz,  
33  
34 1H), 7.02 (dd, *J* = 8.3, 0.5 Hz, 1H), 6.91 (dt, *J* = 7.4, 1.0 Hz, 1H), 3.74 (s, 3H), 3.50 (s, 3H), 2.03  
35  
36 (s, 3H), 1.13 (s, 9H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 178.1, 156.4, 144.5, 134.0,  
37  
38 130.8, 128.3, 121.0, 120.0, 111.8, 111.0, 55.0, 38.6, 34.8, 27.1, 13.3; HRMS (ESI): calcd for  
39  
40 C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 302.1863, found 302.1860.

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46 (*E*)-*N*-(1,3-dimethyl-4-(4-(trifluoromethyl)styryl)-1*H*-pyrazol-5-yl)pivalamide (**8h**). Compound  
47  
48 was prepared according the general procedure using pyrazole **7b** and (*E*)-(4-  
49  
50 (trifluoromethyl)styryl)boronic acid **2m** at 110 °C. The crude material was purified via a column  
51  
52 chromatography to yield title product as a white solid (0.303 g, 83%); mp 152 – 156 °C (DCM –  
53  
54 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 9.53 (s, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.64  
55  
56 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 16.6 Hz, 1H), 6.79 (d, *J* = 16.6 Hz, 1H), 3.50 (s, 3 H), 2.31 (s,  
57  
58  
59  
60



3H), 1.29 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 177.8, 144.7, 142.1, 134.8, 126.7 (q,  $J$  = 32 Hz), 125.9, 125.6 (q,  $J$  = 4 Hz), 124.4 (q,  $J$  = 271 Hz), 123.7, 121.9, 110.8, 38.8, 34.9, 27.1, 13.5; HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{22}\text{F}_3\text{N}_3\text{O}$  [ $\text{M} + \text{H}$ ] $^+$  366.1788, found 366.1786.

*N*-(4-(furan-2-yl)-1,3-dimethyl-1*H*-pyrazol-5-yl)pivalamide (**8i**). Title compound was prepared according the general procedure using pyrazole **7b** and 2-furanylboronic acid MIDA ester **2i** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.208 g, 80%); mp 90 - 92 °C (MeOH - H<sub>2</sub>O);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 9.42 (s, 1H), 7.60 – 7.62 (m, 1H), 6.50 – 6.52 (m, 1H), 6.29 (d,  $J$  = 2.6 Hz, 1H), 3.50 (s, 3H), 2.29 (s, 3H), 1.26 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 177.8, 147.5, 142.7, 140.9, 133.2, 111.1, 106.3, 104.5, 38.7, 34.7, 27.1, 13.9; HRMS (ESI): calcd for  $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  262.1550, found 262.1552.

*N*-(4-(4-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)cyclopropanecarboxamide (**8j**). Title compound was prepared according the general procedure using pyrazole **7c** and 4-methoxyphenylboronic acid **2b** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.250 g, 88%); mp 157 – 158 °C (DCM - hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 9.91 (s, 1H), 7.19 (d,  $J$  = 8.8 Hz, 2H), 6.97 (d,  $J$  = 8.8 Hz, 2H), 3.76 (s, 3H), 3.51 (s, 3H), 2.16 (s, 3H), 1.77 (tt,  $J$  = 7.0, 5.4 Hz, 1H), 0.87 - 0.71 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 173.6, 157.8, 143.1, 132.8, 129.3, 124.9, 114.1, 114.0, 55.1, 35.0, 13.5, 13.1, 7.2; HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  286.1550, found 286.1545.

*N*-(1,3-dimethyl-4-(*o*-tolyl)-1*H*-pyrazol-5-yl)cyclopropanecarboxamide (**8k**). Title compound was prepared according the general procedure using pyrazole **7c** and 2-methylphenylboronic acid **2i** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.234 g, 87%); mp 148 – 150 °C (DCM - hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )

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3 major conformer:  $\delta$  (ppm) = 9.79 (s, 1H), 7.26 (td,  $J = 7.3, 1.6$  Hz, 1H), 7.21 (dd,  $J = 7.3, 1.6$  Hz,  
4 1H), 7.19 (td,  $J = 7.3, 1.6$  Hz, 1H), 7.03 (dd,  $J = 7.3, 1.6$  Hz, 1H), 3.53 (s, 3H), 2.07 (s, 3H), 1.94  
5 (s, 3H), 1.73 – 1.66 (m, 1H), 0.77 – 0.70 (m, 4H); minor conformer:  $\delta = 9.26$  (s, NH), 3.67 (s,  
6 CH<sub>3</sub>), 2.10 (s, CH<sub>3</sub>), 1.98 (s, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 173.2, 143.7,  
7 137.0, 133.8, 131.8, 130.9, 129.9, 127.3, 125.6, 114.0, 35.3, 19.6, 13.5, 12.6, 7.3; HRMS (ESI):  
8 calcd for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O [M + H]<sup>+</sup> 270.1601, found 270.1604.  
9

10  
11 *N*-(1,3-dimethyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)cyclopropanecarboxamide (**8l**).  
12

13 Title compound was prepared according the general procedure using pyrazole **7c** and 4-  
14 (trifluoromethyl)phenylboronic acid **2e** at 110 °C. The crude material was purified via a column  
15 chromatography to yield title product as a white solid (0.281 g, 87%); mp 190 – 194 °C (DCM –  
16 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 10.04 (s, 1H), 7.72 (d,  $J = 8.2$  Hz, 2H),  
17 7.47 (d,  $J = 8.2$  Hz, 2H), 3.51 (s, 3H), 2.18 (s, 3H), 1.74 (tt,  $J = 7.2, 5.2$  Hz, 1H), 0.81 – 0.74 (m,  
18 4H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 144.2, 137.6, 135.2, 134.3, 129.1, 127.0 (q,  $J =$   
19 32 Hz), 125.9 (q,  $J = 4$  Hz), 124.9 (q,  $J = 272$  Hz), 113.6, 35.6, 14.1, 13.7, 7.8; HRMS (ESI):  
20 calcd for C<sub>16</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O [M + H]<sup>+</sup> 324.1318, found 324.1317.  
21

22  
23 *N*-(1,3-dimethyl-4-(5-methylthiophen-2-yl)-1H-pyrazol-5-yl)cyclopropanecarboxamide (**8m**).  
24

25 Title compound was prepared according the general procedure using pyrazole **7c** and 4,4,5,5-  
26 tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane **2f** at 110 °C. The crude material was  
27 purified via a column chromatography to yield title product as a white solid (0.236 g, 86%); mp  
28 111 – 113 °C (DCM – hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 10.08 (s, 1H), 6.83  
29 (d,  $J = 3.4$  Hz, 1H), 6.76 (dd,  $J = 3.4, 0.9$  Hz, 1H), 3.50 (s, 3H), 2.43 (d,  $J = 0.9$  Hz, 3H), 2.24 (s,  
30 3H), 1.86 (ddd,  $J = 9.6, 7.6, 5.3$  Hz, 1H), 0.87 – 0.79 (m, 4H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  
31  $\delta$  (ppm) = 173.4, 142.9, 137.2, 132.9, 131.7, 125.5, 123.7, 108.8, 35.1, 14.8, 13.8, 13.6, 7.2;  
32 HRMS (ESI): calcd for C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>OS [M + H]<sup>+</sup> 276.1165, found 276.1170.  
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3 *N*-(1,3-dimethyl-4-(thiophen-3-yl)-1*H*-pyrazol-5-yl)cyclopropanecarboxamide (**8n**). Title  
4  
5 compound was prepared according the general procedure using pyrazole **7c** and 3-thienylboronic  
6  
7 acid **2k** at 110 °C. The crude material was purified via a column chromatography to yield title  
8  
9 product as a white solid (0.221 g, 85%); mp 171 – 173 °C (DCM – hexanes); <sup>1</sup>H NMR (400  
10  
11 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 10.04 (s, 1H), 7.60 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.37 (dd, *J* = 2.9, 1.2  
12  
13 Hz, 1H), 7.20 (dd, *J* = 4.9, 1.2 Hz, 1H), 3.52 (s, 3H), 2.24 (s, 3H), 1.82 (tt, *J* = 7.5, 5.1 Hz, 1H),  
14  
15 0.87 – 0.79 (m, 4H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 173.4, 143.3, 132.9, 132.7,  
16  
17 127.1, 125.9, 120.4, 109.9, 35.0, 13.6, 13.5, 7.3; HRMS (ESI): calcd for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>OS [M + H]<sup>+</sup>  
18  
19 262.1009, found 262.1009.  
20  
21  
22  
23

24 *N*-(1,3-dimethyl-4-(pyridin-3-yl)-1*H*-pyrazol-5-yl)cyclopropanecarboxamide (**8o**). Title  
25  
26 compound was prepared according the general procedure using pyrazole **7c** and 3-pyridylboronic  
27  
28 acid pinacol ester **2n** at 110 °C. The crude material was purified via a column chromatography to  
29  
30 yield title product as a white solid (0.117 g, 46%); mp 166 – 168 °C (DCM – hexanes); <sup>1</sup>H NMR  
31  
32 (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 10.07 (s, 1H), 8.51 (d, *J* = 1.6 Hz, 1H), 8.46 (dd, *J* = 4.8, 1.6  
33  
34 Hz, 1H), 7.68 (ddd, *J* = 7.9, 2.2, 1.6 Hz, 1H), 7.43 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 3.55 (s, 3H),  
35  
36 2.21 (s, 3H), 1.78 (tt, *J* = 7.7, 4.8 Hz, 1H), 0.85 – 0.78 (m, 4H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  
37  
38 δ (ppm) = 173.6, 148.7, 147.2, 143.7, 135.2, 133.7, 128.6, 123.6, 111.2, 35.1, 13.6, 13.0, 7.3;  
39  
40 HRMS (ESI): calcd for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O [M + H]<sup>+</sup> 257.1397, found 257.1398.  
41  
42  
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45 *N*-(4-(2-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)thiophene-2-carboxamide (**8p**). Title  
46  
47 compound was prepared according the general procedure using pyrazole **7d** and 2-  
48  
49 methoxyphenylboronic acid **2c** at 110 °C. The crude material was purified via a column  
50  
51 chromatography to yield title product as a white solid (0.228 g, 70%); 88 – 90 °C (DCM –  
52  
53 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 10.01 (s, 1H), 7.88 (d, *J* = 3.5 Hz, 1H),  
54  
55 7.86 (d, *J* = 5.0 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.18 (t, *J* = 4.3 Hz, 1H), 7.14 (dd, *J* = 7.0, 1.0 Hz,  
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3 1H), 7.02 (d,  $J = 8.2$  Hz, 1H), 6.91 (t,  $J = 7.2$  Hz, 1H), 3.69 (s,H), 3.60 (s, 3H), 2.05 (s, 3H) ppm;  
4  
5  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 161.2, 156.6, 144.7, 138.2, 133.1, 132.3, 130.8,  
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7 129.9, 128.4, 128.2, 120.9, 120.2, 112.1, 111.2, 55.0, 35.2, 13.2; HRMS (ESI): calcd for  
8  
9  $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$   $[\text{M} + \text{H}]^+$  328.1114, found 328.1114.

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12 *N*-(1,3-dimethyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)thiophene-2-carboxamide (**8q**).

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14 Title compound was prepared according the general procedure using pyrazole **7d** and (4-  
15  
16 (trifluoromethyl)phenyl)boronic acid **2e** at 110 °C. The crude material was purified via a column  
17  
18 chromatography to yield title product as a white solid (0.102 g, 28%); mp 206 – 208 °C (DCM –  
19  
20 hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 10.39 (s, 1H), 7.97 (dd,  $J = 3.8, 1.1$  Hz,  
21  
22 1H), 7.91 (dd,  $J = 5.0, 1.1$  Hz, 1H), 7.74 (d,  $J = 8.0$  Hz, 2H), 7.57 (d,  $J = 8.0$  Hz, 2H), 7.24 (dd,  $J$   
23  
24 = 5.0, 3.8 Hz, 1H), 3.64 (s, 3H), 2.28 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 161.3,  
25  
26 144.0, 137.8, 137.0, 133.1, 132.8, 130.3, 128.5, 128.4, 126.6 (q,  $J = 32$  Hz), 125.5 (q,  $J = 4$  Hz),  
27  
28 124.4 (q,  $J = 271$  Hz), 113.9, 35.2, 13.2; HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{OS}$   $[\text{M} + \text{H}]^+$   
29  
30 366.0882, found 366.0883.

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36 *N*-(4-(furan-3-yl)-1,3-dimethyl-1H-pyrazol-5-yl)thiophene-2-carboxamide (**8r**). Title compound  
37  
38 was prepared according the general procedure using pyrazole **7d** and furan-3-ylboronic acid **2g** at  
39  
40 110 °C. The crude material was purified via a column chromatography to yield title product as a  
41  
42 white solid (0.169 g, 59%); mp 189 – 190 °C (DCM – hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  
43  
44  $\delta$  (ppm) = 10.03 (s, 1H), 8.04 (dd,  $J = 3.8, 1.0$  Hz, 1H), 7.92 (dd,  $J = 5.0, 1.0$  Hz, 1H), 7.74 (dd,  $J$   
45  
46 = 1.5, 0.8 Hz, 1H), 7.67 (t,  $J = 1.6$  Hz, 1H), 7.26 (dd,  $J = 5.0, 3.8$  Hz, 1H), 6.61 (dd,  $J = 1.9, 0.8$   
47  
48 Hz, 1H), 3.60 (s, 3H), 2.25 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 161.0, 143.5,  
49  
50 143.4, 138.5, 138.1, 132.7, 132.4, 130.1, 128.4, 116.6, 109.4, 106.6, 35.1, 13.7; HRMS (ESI):  
51  
52 calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$   $[\text{M} + \text{H}]^+$  288.0801, found 288.0798.  
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3 *N*-(4-(4-hydroxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**8u**). Title  
4  
5 compound was prepared according the general procedure using pyrazole **7i** and 4-  
6  
7 hydroxyphenylboronic acid at 110 °C. The crude material was purified via a column  
8  
9 chromatography to yield title product as a white solid (0.26 g, 77%); mp 272 – 274 °C (DCM –  
10  
11 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 10.00 (s, 1H), 9.34 (s, 1H), 7.94 (d, *J* = 8.2  
12  
13 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 3.83 (s, 3H),  
14  
15 3.57 (s, 3H), 2.20 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 166.2, 162.3, 155.9,  
16  
17 143.2, 132.8, 129.8, 129.3, 125.2, 123.2, 115.3, 115.2, 113.8, 55.5, 35.0, 13.2; HRMS (ESI):  
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19 calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 338.1499, found 338.1498.  
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24 *N*-(4-(3-aminophenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**8v**). Title compound  
25  
26 was prepared according the general procedure using pyrazole **7i** and 3-aminophenylboronic acid  
27  
28 at 110 °C. The crude material was purified via a column chromatography to yield title product as  
29  
30 a white solid (0.29 g, 85%); mp 159 – 160 °C (MeOH – H<sub>2</sub>O); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ  
31  
32 (ppm) = 10.01 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.96 (t, *J* = 7.8 Hz, 2H),  
33  
34 6.58 – 6.55 (m, 1H), 6.50 – 6.46 (m, 1H), 6.43 (ddd, *J* = 7.8, 2.2, 1.0 Hz, 1H), 4.99 (s, 2H), 3.83  
35  
36 (s, 3H), 3.57 (s, 3H), 2.22 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 166.2, 162.3,  
37  
38 148.7, 143.3, 133.2, 133.1, 129.9, 128.8, 125.3, 116.0, 115.7, 113.9, 113.8, 112.0, 55.5, 35.0,  
39  
40 13.4; HRMS (ESI): calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 337.1659, found 338.1663.  
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45 *4*-methoxy-*N*-(4-(3-methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-yl)benzamide (**8w**). Title  
46  
47 compound was prepared according the general procedure using pyrazole **7a** and potassium 3-  
48  
49 methoxyphenyltrifluoroborate at 110 °C. The crude material was purified via a column  
50  
51 chromatography to yield title product as a white solid (0.29 g, 85%); mp 157 – 159 °C (DCM –  
52  
53 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 10.11 (s, 1H), 7.96 (d, *J* = 8.6 Hz, 2H),  
54  
55 7.27 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.95 – 6.92 (m, 1H), 6.92 – 6.89 (m, 1H), 6.79  
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(dd,  $J = 8.2, 2.5$  Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H), 2.25 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 166.2, 162.4, 159.3, 143.5, 134.1, 133.4, 129.8, 129.5, 125.0, 120.4, 115.0, 113.9, 113.5, 111.8, 55.5, 54.9, 35.0, 13.4; HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3$   $[\text{M} + \text{H}]^+$  352.1656, found 338.1655.

*1-(1,3-dimethyl-4-phenyl-1H-pyrazol-5-yl)-3-phenylurea (9a)*. The compound **9a** is known from a patent literature; however no synthetic procedure and analytical data were reported. Title compound was prepared according the general procedure using pyrazole **7g** and phenylboronic acid **2o** at 60 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.235 g, 77%); mp 196 – 198 °C (DCM – hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 8.88 (s, 1H), 8.14 (s, 1H), 7.43 (dd,  $J = 8.7, 1.0$  Hz, 2H), 7.38 (d,  $J = 7.4$  Hz, 2H), 7.36 – 7.32 (m, 2H), 7.28 – 7.23 (m, 3H), 6.96 (td,  $J = 7.4, 1.1$  Hz, 1H), 3.63 (s, 3H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 153.5, 143.2, 139.5, 133.5, 132.8, 128.7, 128.4, 128.3, 126.1, 122.0, 118.3, 114.8, 35.0, 13.2; HRMS (ESI): calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}$   $[\text{M} + \text{H}]^+$  307.1553, found 307.1551.

*1-(1,3-dimethyl-4-(o-tolyl)-1H-pyrazol-5-yl)-3-phenylurea (9b)*. Title compound was prepared according the general procedure using pyrazole **7g** and 2-methylphenylboronic acid **2i** at 60 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.140 g, 44%); mp 207 – 209 °C (DCM – hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 8.70 (s, 1H), 7.95 (s, 1H), 7.37 (dd,  $J = 8.6, 1.2$  Hz, 2H), 7.27 – 7.16 (m, 5H), 7.10 (dd,  $J = 7.2, 1.6$  Hz, 1H), 6.94 (tt,  $J = 7.4, 0.9$  Hz, 1H), 3.64 (s, 3H), 2.11 (s, 3H), 1.96 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 153.1, 143.6, 139.4, 137.1, 133.8, 132.0, 130.9, 129.9, 128.7, 127.2, 125.5, 122.0, 118.2, 114.2, 35.3, 19.5, 12.6; HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}$   $[\text{M} + \text{H}]^+$  321.1710, found 321.1709.

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*1-(4-(2-methoxyphenyl)-1,3-dimethyl-1H-pyrazol-5-yl)-3-phenylurea (9c)*. Title compound was prepared according the general procedure using pyrazole **7g** and 2-methoxyphenylboronic acid **2c** at 60 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.255 g, 76%); mp 190 – 192 °C (DCM – hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 8.91 (s, 1H), 7.75 (s, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.31 – 7.22 (m, 3H), 7.16 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.99 – 6.93 (m, 2H), 3.72 (s, 3H), 3.62 (s, 3H), 2.03 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 156.6, 153.3, 144.0, 139.5, 134.2, 131.1, 128.8, 128.3, 122.0, 121.1, 120.4, 118.2, 111.3, 110.7, 55.3, 35.4, 13.0; HRMS (ESI): calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 337.1659, found 337.1657.

*1-(1,3-dimethyl-4-(4-nitrophenyl)-1H-pyrazol-5-yl)-3-phenylurea (9d)*. Title compound was prepared according the general procedure using pyrazole **7g** and 4-nitrophenylboronic acid **2p** at 60 °C. The crude material was purified via a column chromatography to yield title product as a yellow solid (0.175 g, 50%); mp 321 – 323 °C (EtOAc – hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 9.02 (s, 1H), 8.34 (s, 1H), 8.26 (d, *J* = 9.2 Hz, 2H), 7.63 (d, *J* = 9.2 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.25 (dd, *J* = 8.1, 7.6 Hz, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 3.66 (s, 3H), 2.27 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 153.7, 145.8, 144.4, 140.8, 139.9, 135.1, 129.2, 124.3, 122.7, 119.0, 113.7, 35.7, 14.0; HRMS (ESI): calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub> [M + H]<sup>+</sup> 352.1404, found 352.1403.

*N-(1,3-dimethyl-4-(o-tolyl)-1H-pyrazol-5-yl)piperidine-1-carboxamide (9e)*. Title compound was prepared according the general procedure using pyrazole **7h** and 2-methylphenylboronic acid **2i** at 60 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.196 g, 63%); mp 178 - 180 °C (DCM - hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 8.07 (s, 1H), 7.26 – 7.22 (m, 1H), 7.19 (td, *J* = 7.0, 1.6 Hz, 1H), 7.15 (td, *J* = 7.2, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.2, 1.6 Hz, 1H), 3.54 (s, 3H), 3.31 – 3.27 (m, 4H), 2.11 (s, 3H), 1.94 (s,

3H), 1.55 – 1.49 (m, 2H), 1.38 – 1.32 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 155.3, 143.4, 137.0, 135.2, 132.4, 131.0, 129.7, 126.9, 125.3, 114.7, 44.9, 34.8, 25.3, 24.1, 19.7, 12.8; HRMS (ESI): calcd. for  $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}$   $[\text{M} + \text{H}]^+$  313.2023, found 313.2023.

*N*-(4-(4-methoxyphenyl)-1,3-dimethyl-1H-pyrazol-5-yl)piperidine-1-carboxamide (**9f**). Title compound was prepared according the general procedure using pyrazole **7h** and 4-methoxyphenylboronic acid **2b** at 60 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.291 g, 89%); mp 190 – 192 °C (DCM - hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 7.15 (d,  $J$  = 8.8 Hz, 2H), 6.89 (d,  $J$  = 8.8 Hz, 2H), 6.19 (br. s, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.36 – 3.30 (m, 4H), 2.22 (s, 3H), 1.64 – 1.46 (m, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 158.3, 155.6, 144.5, 133.9, 129.9, 125.3, 114.6, 114.1, 55.4, 45.6, 35.3, 25.8, 24.4, 13.2; HRM (ESI): calcd for  $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_2$   $[\text{M} + \text{H}]^+$  329.1972; found 329.1973.

*N*-(1,3-dimethyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)piperidine-1-carboxamide (**9g**). Title compound was prepared according the general procedure using pyrazole **7h** and (4-(trifluoromethyl)phenyl)boronic acid **2e** at 60 °C for 40 minutes. The crude material was purified via a column chromatography to yield title product as a white solid (0.164 g, 45%); mp 205 – 208 °C (DCM - hexanes);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 8.38 (s, 1H), 7.74 (d,  $J$  = 8.2 Hz, 2H), 7.54 (d,  $J$  = 8.2 Hz, 2H), 3.56 (s, 3H), 3.41 – 3.37 (m, 4H), 2.24 (s, 3H), 1.61 – 1.55 (m, 2H), 1.48 – 1.42 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) = 155.3, 143.4, 137.6, 135.5, 128.5, 126.2 (q,  $J$  = 32 Hz), 125.5 (q,  $J$  = 4 Hz), 124.5 (q,  $J$  = 272 Hz), 113.5, 44.9, 34.7, 25.5, 24.1, 13.4; HRMS (ESI): calcd. for  $\text{C}_{18}\text{H}_{21}\text{F}_3\text{N}_4\text{O}$   $[\text{M} + \text{H}]^+$  367.1740, found 367.1740.

*N*-(4-(benzo[*b*]thiophen-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)piperidine-1-carboxamide (**9h**). Title compound was prepared according the general procedure using pyrazole **7h** and benzo[*b*]thiophen-2-ylboronic acid **2q** at 60 °C. The crude material was purified via a column



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2  
3 chromatography to yield title product as a white solid (0.286 g, 81%); mp > 350 °C (DCM -  
4 hexanes); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ (ppm) = 8.54 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.79  
5 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.37 – 7.33 (m, 1H), 7.31 – 7.27 (m, 1H), 3.58 (s, 3H), 3.50 –  
6 3.46 (m, 4H), 2.40 (s, 3H), 1.66 – 1.60 (m, 2H), 1.57 – 1.51 (m, 4H); <sup>13</sup>C NMR (100 MHz,  
7 DMSO-*d*<sub>6</sub>): δ (ppm) = 154.8, 143.4, 139.8, 138.1, 135.7, 135.3, 124.4, 123.7, 122.9, 121.9, 119.1,  
8 109.1, 44.9, 34.8, 25.7, 24.1, 14.3; HRMS (ESI): calcd. for C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>OS [M + H]<sup>+</sup> 355.1587,  
9 found 355.1587.  
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### 19 **Associated content**

20 Supporting Information. Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra, representative HPLC  
21 chromatograms for the optimization and dehalogenation experiments.  
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34 Notes: The authors declare no competing financial interest  
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31 (29) Later we have found that the reaction time can be reduced to 4 hours with similar result (data  
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35 (30) Even though the reaction and all subsequent reactions marked  $\mu$ W were conducted in a  
36  
37 microwave reactor for safety and convenience reasons, they were not accelerated by microwaves,  
38  
39 but purely the thermal effect was involved. This was proved by performing a few representative  
40  
41 reactions in a sealed tube inserted into a preheated oil bath.  
42  
43 (31) Various conditions utilizing copper co-catalysis, including those reported in references 31a  
44  
45 and 31b, were tried in order to improve the reaction with pyridylboronates; however, none of  
46  
47 these attempts gave satisfactory result. Mostly dehalogenated pyrazoles were formed as well as  
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