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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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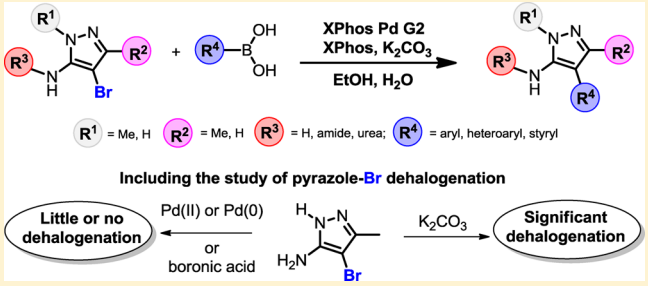
Supporting Information

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.[1,2] 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.[3,4] 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.[5−7] 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.[8−10]

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,[11,12] 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.[13] The first issue has been largely solved by the use of new advanced palladium (pre)catalysts and ligands,[14−18] while the development of alternative organoboron reagents, particularly MIDA esters[19] and trifluoroborates,[20] 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.[21,22]

We were interested in the synthesis of the 4-substituted aminopyrazoles, especially 4-styryl aminopyrazoles due to their structural similarity to 4-arylazo pyrazoles, which were found as the potent inhibitors of cyclin-dependent kinases.[23] 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.[24]

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

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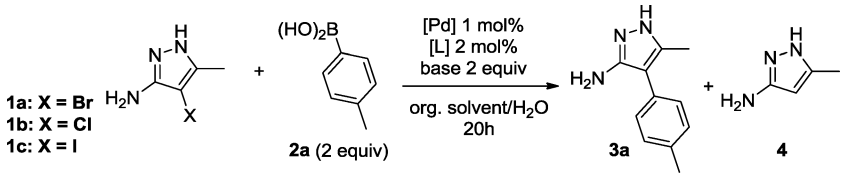
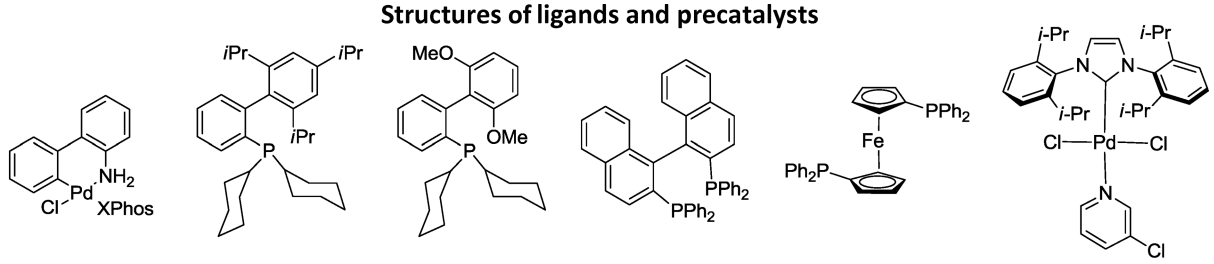
Table 1. Optimization of Reaction Conditions



entry	solvent	base	[Pd]	ligand	T (°C)	X	3a[a]	1[a]	4[a]
1	Dioxane	K_2CO_3	$Pd(OAc)_2$	XPhos	100	Br	2	1	89
2	Dioxane	K_2CO_3	XPhos Pd G2	XPhos	100	Br	16	18	60
3	EtOH	K_2CO_3	$Pd(OAc)_2$	XPhos	90	Br	57	11	24
4	MeCN	K_2CO_3	$Pd(OAc)_2$	XPhos	90	Br	20	8	62
5	DMF	K_2CO_3	$Pd(OAc)_2$	XPhos	100	Br	4	0	94
6	EtOH	Cs_2CO_3	$Pd(OAc)_2$	XPhos	90	Br	33	0	59
7	EtOH	CsF	$Pd(OAc)_2$	XPhos	90	Br	5	35	48
8	EtOH	K_3PO_4	$Pd(OAc)_2$	XPhos	90	Br	16	0	79
9	EtOH	K_2CO_3	$Pd(OAc)_2$	SPhos	90	Br	18	0	74
10	EtOH	K_2CO_3	$Pd(OAc)_2$	BINAP	90	Br	8	33	40
11	EtOH	K_2CO_3	$Pd(OAc)_2$	dppf	90	Br	9	16	65
12	EtOH	K_2CO_3	$Pd(OAc)_2$	PAd_2Bu	90	Br	50	0	41
13	EtOH	K_2CO_3	PEPPSI	IPr	90	Br	44	14	30
14	EtOH	K_2CO_3	XPhos Pd G2	XPhos	90	Br	89	0	8
15	EtOH	K_2CO_3	XPhos Pd G2	XPhos	90	Br	33[b]	0	59
16	EtOH	K_2CO_3	XPhos Pd G2	XPhos	90	Br	27[c]	0	63
17	EtOH	K_2CO_3	XPhos Pd G2	XPhos	70	Br	36	42	18
18	**EtOH**	**K_2CO_3**	**XPhos Pd G2**	**XPhos**	**135**	**Br**	**88[d]**	**0**	**7**
19	EtOH	K_2CO_3	XPhos Pd G2	XPhos	135	Cl	87[d]	0	6
20	EtOH	K_2CO_3	XPhos Pd G2	XPhos	135	I	11[d]	0	84

[a]HPLC yield (%) determined from the crude reaction mixture (see Supporting Information for more details). [b]3 equiv of K_2CO_3. [c]4 equiv of K_2CO_3. [d]Reaction was carried out in a microwave reactor for 20 min.

Structures of ligands and precatalysts



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 β-elimination of alkoxypalladium complexes,[25,26] this mechanism is not the predominant pathway in the case of NH containing heteroarenes.

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_2CO_3, and a catalytic amount of $Pd(OAc)_2$ and XPhos, only 2% of the product **3a** was detected by LCMS (Table 1, entry 1). The product was accompanied by 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 $Pd(OAc)_2$ increased the product formation to 16% (entry 2).[27] This can be further improved to 57% if the reaction is performed with $Pd(OAc)_2$/XPhos in a mixture of EtOH/H_2O (entry 3), while DMF and MeCN gave unsatisfactory results (entries 4 and 5). The use of various bases such as Cs_2CO_3, CsF, and K_3PO_4 resulted only in diminished conversion or increased dehalogenation (entries 6–8). The combination of $Pd(OAc)_2$ 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_2Bu 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 precatalyst (or Pd source) is of significance for the efficient cross-coupling, as it determines the formation and availability of the active $L_nPd(0)$ species.[28] If the active ligated Pd(0) is formed readily and under mild conditions, it can diminish unwanted side reactions of both

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coupling partners, such as protodeboronation and oxidative homocouping of boronic acids, and dehalogenation of aryl halides. When the XPhos derived precatalyst XPhos Pd G2 was used instead of $Pd(OAc)_2$ in $EtOH/H_2O$, the amount of the product **3a** considerably increased to 89% (entry 14). LCMS of the reaction mixture showed that the starting material **1a** was completely consumed and dehalogenated pyrazole **4** was formed in 8% after 20 h.[29] Increasing the amount of a base, or decreasing reaction temperature to 70 °C resulted in the increased dehalogenation (entries 15 and 16), or incomplete conversion of the starting material (entry 17). The reaction time was reduced to 20 min, when the reaction was heated in a microwave reactor at 135 °C (entry 18).[30] Subsequently, 88% of the product **3a** and 7% of dehalogenated pyrazole **4** were formed. The coupling product **3a** was then isolated in 78% yield from either entry 14 or entry 18.

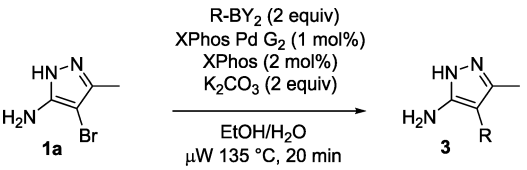
Finally, the reactivity of chloro **1b** and iodo **1c** pyrazoles was compared to bromo derivative **1a**. On heating in a microwave reactor at 135 °C for 20 min, chlorinated pyrazole **1b** displayed nearly the same reactivity as **1a**, providing 87% of the coupling product **3a** and 6% of dehalogenated pyrazole **4** (entry 19). On the other hand, iodo derivative **1c** showed the increased tendency to deiodination, furnishing 84% of dehalogenated pyrazole **4** (entry 20) and only 11% of product **3a**.

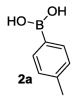
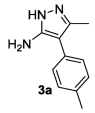
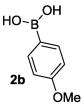
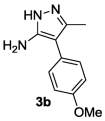
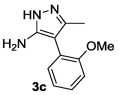
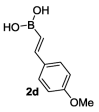
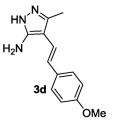
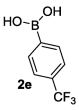
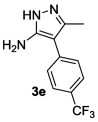
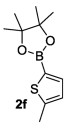
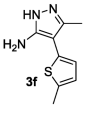
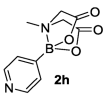
Under the optimized conditions (Table 1, entry 18), the scope of the Suzuki reaction between pyrazole **1a** and various aryl, heteroaryl, and styryl boronic acids was examined (Table 2). Boronic acids bearing electron-donating groups reacted smoothly furnishing biaryls **3b** and **3c** in high yields. Moreover, high yield of **3c** demonstrated that the reaction is somewhat tolerant to sterically hindered boronic acids. Note that pyrazole **1a** itself is "*ortho*" disubstituted. Likewise, the coupling of pyrazole **1a** with styrylboronic acid **2d** gave stilbene-like structure **3d** in 84% isolated yield. As expected, electron-poor boronic acid **2e** gave lower conversion, as well as a portion of unreacted starting material **1a** and dehalogenated pyrazole **4**. Thus, biaryl **3e** bearing strongly electron-withdrawing *p*-CF_3 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 $Cu(OAc)_2$, were employed in order to improve the product conversion; however, neither one improved the conversion of **3h** significantly.[31]

In the next step, we examined the Suzuki-Myiaura 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.[27] 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 ref 27). Initially, the optimized reaction conditions from ref 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_2O at 100 °C

Table 2. Scope of the Suzuki–Miyaura Reaction Using Pyrazole 1a



entry	nucleophile	product	yield (%)
1	 2a	 3a	78
2	 2b	 3b	87
3	 2c	 3c	82
4	 2d	 3d	84
5	 2e	 3e	30
6	 2f	 3f	57
7	 2g	 3g	74
8	 2h	 3h	NI[a]

[a]Not isolated.

(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 24 h. 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 $EtOH/H_2O$ (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 required for pyrazole **1a**. The full conversion of bromide **5b** was achieved after just 20 min, providing biaryl **6a** in 88% yield (entry 4).

In this context, iodinated pyrazole **5c** (method A) or brominated pyrazole **5a** (method B) were coupled with a set of representative boronic acids yielding biaryls **6a–e** (Table 3). In all cases, the reaction using bromide **5b**, higher temperature (120 °C), and a solvent system $EtOH/H_2O$ provided higher yields of the respective coupling products. This was applied for

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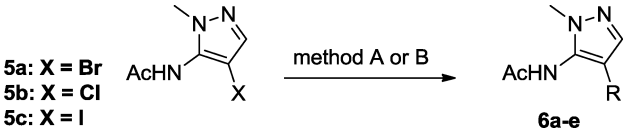
Table 3. Scope of the Suzuki−Miyaura Reaction Using Pyrazole 5[a]



entry	product	method	X	yield
1			Br	79
2		A	Cl	77
3			I	83
4	6a	B	Br	88
5		A	I	84
6	6b	B	Br	89
7		A	I	60
8	6c	B	Br	70
9		A	I	53
10	6d	B	Br	62
11		A	I	83
12	6e	B	Br	85

[a]Method A: pyrazole **5** (1 mmol), K_2CO_3 (2 mmol), boronic acid (2 mmol), Xphos Pd G2 (1 mol %), XPhos (2 mol %), dioxane/H_2O, 100 °C, 24 h. Method B: pyrazole **5a** (1 mmol), K_2CO_3 (2 mmol), boronic acid (2 mmol), Xphos Pd G2 (1 mol %), XPhos (2 mol %), EtOH/H_2O, μW 120 °C, 20 min.

the coupling of sterically hindered boronic acid (entries 5 vs 6), styrylboronic acid (entries 7 vs 8), and heteroarylboronic acid (entries 11 vs 12). The lower reactivity of the electron poor boronic acid resulted in the increased dehalogenation, therefore biaryl **6d** containing CF_3 group was isolated in 53% (method A, entry 9) and 62% yield (method B, entry 10), respectively.

Up to this point, we have explored the Suzuki coupling of aminopyrazoles featuring endocyclic N−Me vs N−H (Table 2 vs Table 3 and ref 24), exocyclic NH_2 vs NH−Ac (ref 27 and Table 2), and varying the C-3 substitution (Table 3 and ref 27). Finally, we wished to explore the effect of diverse substituents connected to the amino group on the cross-coupling reaction. Therefore, we synthesized 4-brominated aminopyrazoles **7a−h** and one chlorinated derivative **7i** bearing diverse *N*-amide substitution in two steps using readily available starting materials (Scheme 1). The cross-coupling of pyrazole amides **7a−d** and boronic acids (or esters in some cases) required just 20 min and 110 °C (Table 4), which was somewhat lower temperature compared to unsubstituted pyrazoles **1a−c** (see Tables 1 and 2 for comparison).[32]

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 **7e** with *p*-tolylboronic acid furnished only traces of the respective product **8s**, which precluded its isolation. To examine whether the catalyst inhibition, apparently caused by pyridine ring nitrogen, can be reversed, we synthesized *N*-oxide **7f** and employed it in the reaction with *p*-tolylboronic acid.[33] Even in this case, unfortunately, only traces of the respective biaryl **8t** were detected. Using both amides **7e** and **7f**, we tested the possibility of CuI and $Cu(OAc)_2$ cocatalysis, as well as a combination of solvents (DMF, *i*-PrOH) and additives (*N*,*N*-diethanolamine); however, none of these attempts increased the conversion of respective products **8s** and **8t** significantly.[31]

Scheme 1. Preparation and Structures of Pyrazoles 7a−i

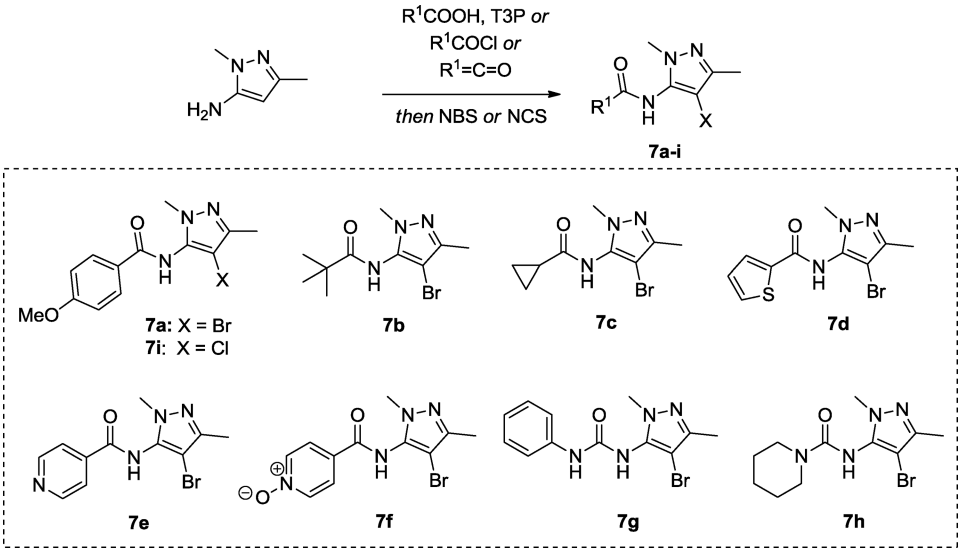


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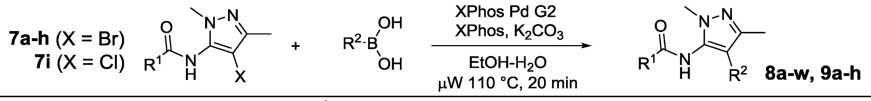
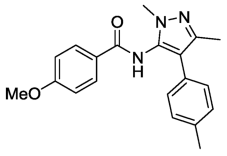
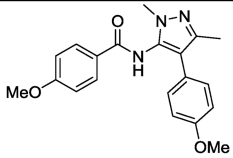
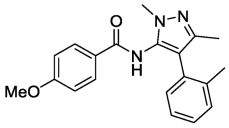
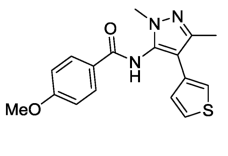
Table 4. Scope of the Suzuki–Miyaura Reaction Using Pyrazoles 7a–i

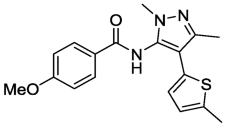


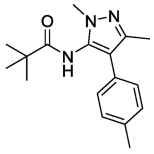

8a (80%) from **7a:** X = Br
8a (78%) from **7i**: X = Cl

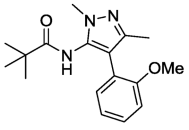

8b (83%) from **7a:** X = Br

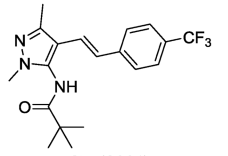

8c (79%) from **7a:** X = Br

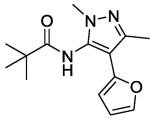

8d (78%) from **7a:** X = Br

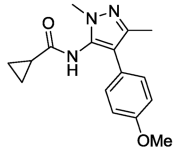

8e (76%)[a] from **7a:** X = Br

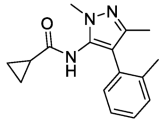

8f (82%) from **7b:** X = Br

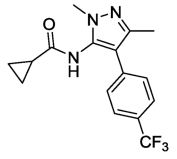

8g (75%) from **7b:** X = Br

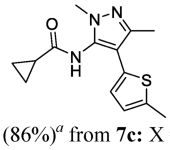

8h (83%) from **7b:** X = Br

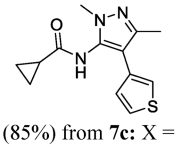

8i (80%)[b] from **7b:** X = Br

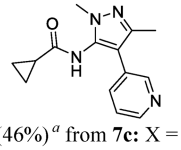

8j (88%) from **7c:** X = Br

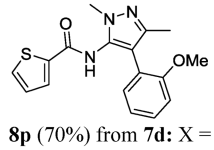

8k (87%) from **7c:** X = Br

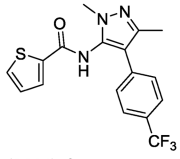

8l (87%) from **7c:** X = Br

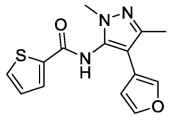

8m (86%)[a] from **7c:** X = Br

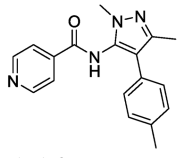

8n (85%) from **7c:** X = Br

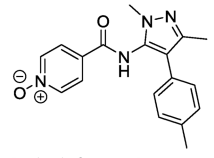

8o (46%)[a] from **7c:** X = Br

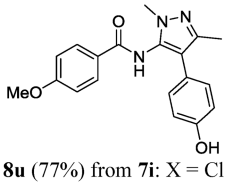

8p (70%) from **7d:** X = Br

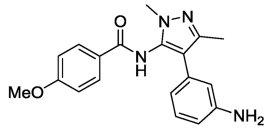

8q (28%) from **7d:** X = Br

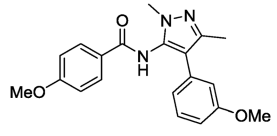

8r (59%) from **7d:** X = Br

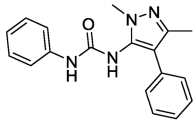

8s (NI) from **7e:** X = Br

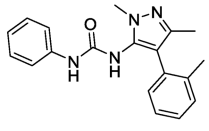

8t (NI) from **7f:** X = Br

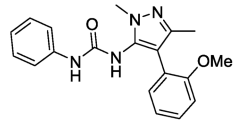

8u (77%) from **7i**: X = Cl

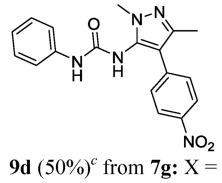

8v (85%) from **7i**: X = Cl

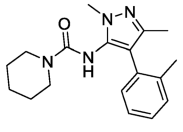

8w (NI)[e] from **7i**: X = Cl
8w (90%)[e] from **7a**: X = Br

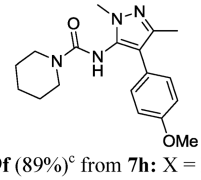

9a (77%)[c] from **7g:** X = Br

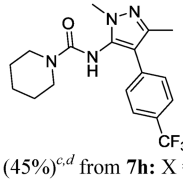

9b (44%)[c] from **7g:** X = Br

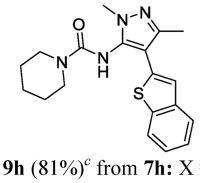

9c (76%)[c] from **7g:** X = Br


9d (50%)[c] from **7g:** X = Br


9e (63%)[c] from **7h:** X = Br


9f (89%)[c] from **7h:** X = Br


9g (45%)[c,d] from **7h:** X = Br


9h (81%)[c] from **7h:** X = Br

[a]Pinacol ester was used. [b]MIDA ester was used. [c]Reaction temperature 60 °C. [d]Reaction time 40 min. [e]Potassium 3-methoxyphenyltrifluoroborate was used.

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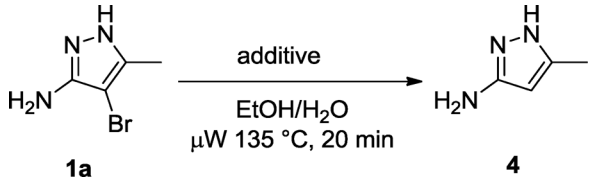
Chlorinated pyrazole **7i** gave upon coupling with *p*-tolylboronic acid biaryl **8a** in 78% yield, which is close to the yield achieved with its brominated analogue **7a** (80%). Chlorinated pyrazole **7i** proved to be efficient coupling partner with aryl boronic acids bearing sensitive functional groups, such as hydroxyl and amino group. Thus, biaryls **8u** and **8v** containing −OH and $-NH_2$ groups were obtained in 77 and 85% yield, respectively. The reaction of **7i** with potassium 3-methoxyphenyltrifluoroborate gave a mixture of dehalogenated compound, starting material and product **8w** in the ratio of 1:1:2. The chromatographic separation on silica gel did not allow to separate compound **7i** from **8w**. When brominated derivative **7a** was used instead of **7i**, the staring material was completely consumed and the major product detected in a crude mixture was **8w**, which was subsequently isolated in 90% yield.

Urea derivatives **7g** and **7h** were found unstable under the reaction condition (110 °C) resulting in partial hydrolysis of the carboxamide function. Consequently around 30−40% of the free amine product was observed. Hydrolytic instability of **7g** and **7h** at 110 °C stimulated us to explore, whether a lower reaction temperature preserves the carboxamide group and still maintains the effective coupling with various boronic acids. To our delight, the reaction of **7g** and **7h** with electron-neutral, electron-rich, and heterocyclic boronic acids went to completion in just 20 min even at 60 °C, giving biaryls **9a**, **9c**, **9e**−**f**, and **9h** in 77−89% yields. Under the same conditions, sterically hindered and electron-poor boronic acids gave an incomplete conversion of the starting material, leading to biaryls **9b**, **9d**, and **9g** in diminished yields (44−50%). Note that sterically hindered 2-methoxyphenyl boronic acid gave considerably higher yield than *o*-tolyl boronic acid, which could be explained by the beneficial electron-donating effect of the methoxy group.

During our study, a majority of cross-coupling reactions went to completion; nevertheless all of them were accompanied by undesired dehalogenation, ranging from ∼5 to 20% (and more with pyridylboronates). Unwanted dehalogenation of aryl halides affects Suzuki reaction, as well as other important cross-couplings; therefore, the recognition of factors causing this side reaction, as well as understanding its mechanism is of importance for the synthetic community.[34]

Cleavage of the C-halogen and forming of the C−H bond is obviously a reductive process; hence one can suspect that the palladium and/or boronic acid are involved in this transformation. In order to identify factors causing the dehalogenation, we performed experiments with brominated pyrazole **1a** (Table 5). The compound **1a** was heated with two equivalents of K_2CO_3 resulting in the formation of the dehaloganated pyrazole **4** in 90% (entry 1), and the staring material was completely consumed. The preliminary observation suggested that the dehalogenation can be a base promoted process and motivated us to further explore this phenomenon. The same situation occurred when strong base KOH was used (entry 2). In this case the detected amount of pyrazole **4** was slightly lower presumably due to a partial decomposition. On the other hand, weaker base KOAc led only to a partial dehalogenation, leaving 61% of staring material **1a** untouched (entry 3). In order to minimize the possibility that a low amount of palladium or other heavy metal in the inorganic base can distort the result,[35] 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%

Table 5. Evaluation of Factors Causing Dehalogenation



entry	additive	equiv	**4** (%)[a]	**1a** (%)[a]
1	K_2CO_3	2	90	0
2	KOH	2	82	0
3	KOAc	2	36	61
4	K_2CO_3[b]	2	89	0
5	**2a**	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

[a]HPLC yield (%) determined from the crude reaction mixture (see Supporting Information for more details). [b]Trace metal basis K_2CO_3 was used.

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).

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^+ 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^+ species from **12** generates the anion **13**, which after protonation gives dehalogenated pyrazole **4**. Likewise, *N*-methyl analogues (e.g., **5** or **7**) are expected to deprotonate the amidic NH bond.

When *N*-methyl pyrazole **14** was heated with two equivalents of K_2CO_3, 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.

In order to prove that mildly oxidizing Br^+ species are formed during dehalogenation of **1a**, we heated thoroughly degassed mixture of pyrazole **1a**, K_2CO_3, and thiophenol in EtOH/H_2O 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,

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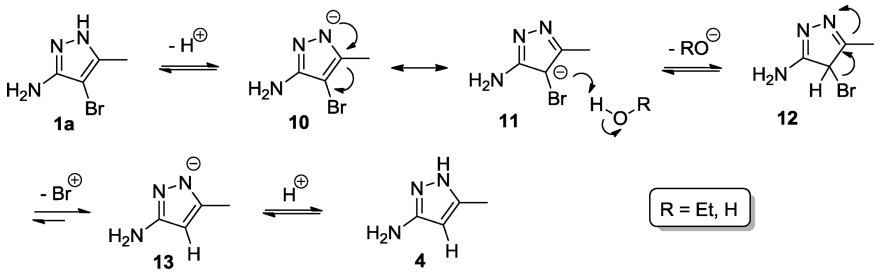
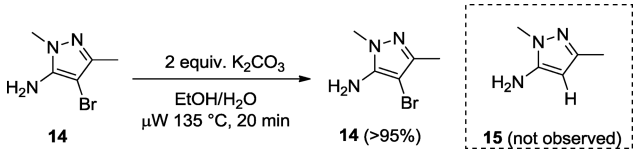
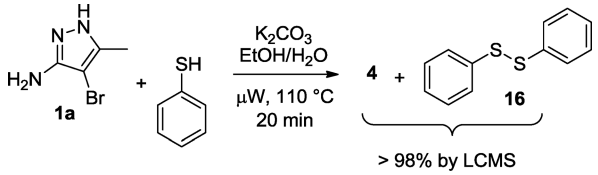
Scheme 2



Scheme 3



Scheme 4. Oxidation of Thiophenol by Released Br^+ Species



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 K_2CO_3 were also heated in a presence of 4-methoxystyrene, anisole, or phenol in order to trap suggested Br^+ species. However, any electrophilic addition or substitution was not observed.

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 observation of others. For instance, *N*-unprotected indoles were reported to suffer from unwanted dehalogenation, which was suppressed by the protection of indole nitrogen.[36]

CONCLUSION

Overall, we have developed the efficient Suzuki–Miyaura cross-coupling of various boronic acids/esters with 4-halogenated aminopyrazoles featuring the free endocyclic pyrazole–NH/amino group, N–Me/NH–acetyl, N–Me/NH–amides, and NH–ureas. The use of palladacylce XPhos Pd G2 in a combination with K_2CO_3 and user-friendly solvent system EtOH/H_2O afforded diverse (hetero)biaryls generally in high yields. Additionally, the presented method allowed the preparation of 4-styryl aminopyrazoles, which are otherwise difficult to access by standard methods. The reaction temperature is strongly dependent on the pyrazole substrate. While some pyrazoles bearing substituents on both pyrazole NH and amino group can be coupled almost quantitatively after 20 min at 60 °C, unsubstituted pyrazoles required 135 °C for the same reaction time. The cross-coupling reactions were accompanied by undesired dehalogenation, which was primarily caused by a base and its mechanism was proposed on the basis of our experimental observations.

EXPERIMENTAL SECTION

All reactions were carried out under inert atmosphere of nitrogen or argon. All starting materials, reagents and catalysts were purchased from commercial sources. Solvents were distilled, degassed, and stored under inert atmosphere. Reactions were monitored by LCMS using C-18 column and MeCN – 1 mM $AcONH_4$ buffer as a mobile phase. Product purifications were performed with silica gel (40–200 mesh). NMR spectra were recorded with 400 MHz spectrometer and chemical shifts are reported in ppm relative to a residual solvent peak. Accurate mass spectra were measured using ESI-TOF detector.

General Procedure for the Cross-Coupling of Pyrazole 1a (Table 2). A mixture of pyrazole **1a** (0.174 g, 1.0 mmol), boronic acid (2.0 mmol), and K_2CO_3 (0.276 g, 2.0 mmol) in EtOH (4 mL) and water (1 mL) was thoroughly degassed with a stream of nitrogen. Then, XPhos (0.009 g, 0.02 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added and the microwave vial containing the mixture was capped and inserted into microwave reactor. The reaction mixture was irradiated (setup: variable power, maximum of 300W, 135 °C) for 20 min. After that, the mixture was filtered through a Celite, washed with EtOAc, and concentrated under reduced pressure. Purification of the crude via column chromatography (MeOH–Et_3N–DCM 100:0.5:0 to 100:0.5:3) afforded desired pyrazole as an oil or solid, which was characterized by ^1H, ^{13}C NMR and HRMS. In some cases, a product was crystallized from appropriate solvents before measurement of a melting point.

*3-Methyl-4-(4-p-tolyl)-1H-pyrazol-5-amine (**3a**).* The compound **3a** is known; however, no analytical data were reported.[37] Title compound was prepared according the general procedure from pyrazole **1a** and 4-tolylboronic acid **2a**. Purification via column chromatography afforded title product as a white solid (0.146 g, 78%); mp 80–82 °C (DCM–hexanes); ^1H NMR (400 MHz, CD_3COOD) δ (ppm) = 7.28 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 2.37 (s, 3H), 2.3 (s, 3H); ^{13}C NMR (100 MHz, CD_3COOD) δ (ppm) = 149.8, 143.2, 138.4, 130.7, 129.9, 127.8, 106.2, 21.2, 10.5 ppm; HRMS (ESI) calcd for $C_{11}H_{13}N_3$ $[M + H]^+$ 188.1182, found 188.1183.

*4-(4-Methoxyphenyl)-3-methyl-1H-pyrazol-5-amine (**3b**).* Pyrazole **3b** is a known compound and its analytical data were in accordance with the literature.[38] Title compound was prepared according the general procedure from pyrazole **1a** and 4-methoxyphenylboronic acid **2b**. Purification via column chromatography afforded title product as a white solid (0.176 g, 87%); mp 139–141 °C (DCM–hexanes); ^1H NMR (400 MHz, DMSO-d_6) 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_2), 3.75 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 156.9, 152.1, 135.2, 129.1, 126.3, 114.0, 104.4, 55.0, 10.8; HRMS (ESI) calcd for $C_{11}H_{13}ON_3$ $[M + H]^+$ 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.[39] We were not able to crystallize the compound, albeit it was reported as a solid melting from 67 to 68 °C. Title

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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%); ^{1}H NMR (400 MHz, DMSO-d_6) 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); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{11}H_{13}ON_3$ [M + H]$^+$ 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); ^{1}H NMR (400 MHz, CD_3COOD) 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); ^{13}C NMR (100 MHz, CD_3COOD) 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 $C_{13}H_{15}ON_3$ [M + H]$^+$ 230.1288, found 230.1289.

*3-Methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-amine (**3e**).* The compound **3e** is known; however, no analytical data were reported.[40] Title compound was prepared according the general procedure from pyrazole **1a** and 4-(trifluoromethyl)phenylboronic acid **2e**. Purification via column chromatography afforded title product as a pale yellow solid (0.072 g, 30%); mp 114−119 °C (DCM−hexanes), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.68 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 151.1, 138.8, 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 (ESI) calcd for $C_{11}H_{10}N_3F_3$ [M + H]$^+$ 242.0900, found 242.0900.

*3-Methyl-4-(5-methylthiophen-2-yl)-1H-pyrazol-5-amine (**3f**).* Title compound was prepared according the general procedure from pyrazole **1a** and 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane **2f**. Purification via column chromatography afforded title product as a white solid (0.110 g, 57%); mp 118−122 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) 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, NH_2), 2.42 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 151.4, 137.2, 135.6, 133.5, 125.5, 122.6, 98.8, 14.8, 11.5; HRMS (ESI) calcd for $C_9H_{11}N_3S$ [M + H]$^+$ 194.0746, found 194.0748.

*4-(Furan-3-yl)-3-methyl-1H-pyrazol-5-amine (**3g**).* Title compound was prepared according the general procedure from pyrazole **1a** and furan-3-ylboronic acid **2g**. Purification via column chromatography afforded title product as a white solid (0.122 g, 74%); mp 93−96 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.31 (br.s, 1H, NH), 7.72 (dd, J = 1.6 Hz, 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, NH_2), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 151.1, 142.8, 137.5 (overlapped C-2 of furan and C-3 of pyrazole), 117.7, 109.7, 95.6, 11.5; HRMS (ESI) calcd for $C_8H_9ON_3$ [M + H]$^+$ 164.0818, found 164.0820.

General Procedure for the Cross-Coupling of Pyrazoles 5 (Table 3). *Method A.* A mixture of pyrazole **5c** (0.265 g, 1.0 mmol), boronic acid (2.0 mmol), and K_2CO_3 (0.276 g, 2.0 mmol) in dioxane (4 mL) and water (1 mL) was thoroughly degassed with a stream of nitrogen. Then, XPhos (0.009 g, 0.02 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added and the sealed tube inserted into a preheated oil bath to 100 °C. The reaction mixture was stirred at 100 °C for 24 h. After that, the mixture was filtered through a Celite, washed with EtOAc, and concentrated under reduced pressure. Purification of the crude via column chromatography (MeOH−DCM 100:0 to 100:3) afforded desired pyrazole as an oil or solid, which was characterized by ^{1}H, ^{13}C NMR and HRMS. In some cases, a product was crystallized from appropriate solvents before measurement of a melting point.

Method B. A mixture of pyrazole **5a** (0.174 g, 1.0 mmol), boronic acid (2.0 mmol), and K_2CO_3 (0.276 g, 2.0 mmol) in EtOH (4 mL) and water (1 mL) was thoroughly degassed with a stream of nitrogen. Then, XPhos (0.009 g, 0.02 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added and the microwave vial containing the mixture was capped and inserted into microwave reactor. The reaction mixture was irradiated (setup: variable power, maximum of 300 W, 120 °C) for 20 min. After that, the mixture processed the same way as in the Method A.

*N-(1-Methyl-4-(p-tolyl)-1H-pyrazol-5-yl)acetamide (**6a**).* Title compound was prepared from 4-tolylboronic acid **2a** and pyrazole **5c** (Method A, 0.190 g, 83%) or pyrazole **5a** (Method B, 0.201 g, 88%). Entry 3: white solid; mp 147−148 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) major conformer δ (ppm) = 9.88 (s, 1H), 7.71 (s, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 3.61 (s, 3H), 2.29 (s, 3H), 2.10 (s, 3H), minor conformer δ (ppm) = 9.36 (s, 1H), 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); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 170.0, 136.0, 135.3, 132.2, 129.4, 129.3, 125.9, 115.7, 35.5, 22.6, 20.7; HRMS (ESI) calcd for $C_{13}H_{15}ON_3$ [M + H]$^+$ 230.1288, found 230.1289.

*N-(1-Methyl-4-(o-tolyl)-1H-pyrazol-5-yl)acetamide (**6b**).* Title compound was prepared from 2-methylphenylboronic acid **2i** and pyrazole **5c** (Method A, 0.192 g, 84%) or pyrazole **5a** (Method B, 0.203 g, 89%), and obtained as a colorless oil. Entry 5: ^{1}H NMR (400 MHz, DMSO-d_6) major conformer δ (ppm) = 9.72 (s, 1H), 7.50 (s, 1H), 7.24−7.12 (m, 4H), 3.63 (s, 3H), 2.22 (s, 3H), 2.00 (s, 3H); minor conformer δ (ppm) = 9.81 (s, 1H), 9.30 (s, 1H), 7.58 (s, 1H), 3.73 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 169.9, 137.6, 135.9, 133.3, 131.6, 130.2, 129.7, 126.9, 125.7, 115.3, 35.7, 22.4, 20.2; HRMS (ESI) calcd for $C_{13}H_{15}ON_3$ [M + H]$^+$ 230.1288, found 230.1289.

*(E)-N-(1-Methyl-4-styryl-1H-pyrazol-5-yl)acetamide (**6c**).* Title compound was prepared from (*E*)-styrylboronic acid **2j** and pyrazole **5c** (Method A, 0.144 g, 60%) or pyrazole **5a** (Method B, 0.168 g, 70%). Entry 7: white solid; mp 107−109 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.91 (s, 1H), 7.77 (s, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.34 (t, J = 7.3 Hz, 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), 2.14 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 169.5, 137.5, 135.1, 133.9, 128.7, 126.9, 125.7, 125.4, 118.1, 113.4, 35.7, 22.7; HRMS (ESI) calcd for $C_{14}H_{15}N_3O$ [M + H]$^+$ 242.1288, found 242.1288.

*N-(1-Methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-acetamide (**6d**).* Title compound was prepared from 4-(trifluoromethyl)phenylboronic acid **2e** and pyrazole **5c** (Method A, 0.150 g, 53%) or pyrazole **5a** (Method B, 0.175 g, 62%). Entry 9: white solid; mp 141−142 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.02 (s, 1H), 7.89 (s, 1H), 7.73 (d, J = 9.3 Hz, 2H), 7.70 (d, J = 9.3 Hz, 2H), 3.65 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (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)-1H-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); ^{1}H NMR (400 MHz, DMSO-d_6) major conformer δ (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) δ (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-1H-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 h. After that, *N*-bromosuccinimide (3.91 g, 22.0 mmol) was added in one portion

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and the mixture was stirred for another 4 h. Then the mixture was diluted with water and extracted with EtOAc (3 × 60 mL). After removing solvents under reduced pressure the residue was crystallized first from DCM−hexanes, then from MeOH−H_2O yielding title product as white needles (4.46 g, 69%); mp 174−176 °C (MeOH−H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (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) δ (ppm) = 165.8, 163.0, 144.7, 135.6, 130.4, 125.3, 114.4, 90.9, 56.0, 36.6, 12.9; HMRS (ESI) calcd for $C_{13}H_{14}BrN_3O_2$ $[M + H]^+$ 324.0342 and 326.0322, found 324.0344 and 326.0319.

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

*N-(4-Bromo-1,3-dimethyl-1H-pyrazol-5-yl)-cyclopropanecarboxamide (**7c**).* Compound **7c** was prepared from cyclopropanecarboxylic acid using the same procedure as for compound **7a**. Purification via a column chromatography (SiO_2, 0−4% MeOH in DCM) and subsequent crystallization from MeOH−H_2O (charcoal) yielded title product as a white solid (3.92 g, 76%); mp 161−163 °C (MeOH−H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.10 (s, 1H), 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 MHz, DMSO-d_6) δ (ppm) = 172.8, 144.0, 134.8, 89.3, 36.2, 13.5, 12.3, 7.6; HRMS (ESI) calcd for $C_9H_{12}BrN_3O$ $[M + H]^+$ 258.0237 and 260.0216, found 258.0240 and 260.0215.

*N-(4-Bromo-1,3-dimethyl-1H-pyrazol-5-yl)thiophene-2-carboxamide (**7d**).* Pyrazole **7d** is commercially available; however, no reference exists for this compound. Pyrazole **7d** was prepared from thiophene-2-carboxylic acid using the same procedure as for compound **7a**. Purification via a column chromatography (SiO_2, 0−4% MeOH in DCM) and subsequent crystallization from DCM−hexanes yielded title product as a white solid (3.70 g, 62%); mp 152−153 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.38 (s, 1H), 8.02 (d, J = 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, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{10}H_{10}BrN_3OS$ $[M + H]^+$ 299.9801 and 301.9780, found 299.9802 and 301.9776.

*N-(4-Bromo-1,3-dimethyl-1H-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_2O yielding title product as a pale yellow crystalline solid (3.35 g, 57%); mp 80−82 °C (MeOH−H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (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}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 164.5, 150.6, 144.5, 139.7, 134.1, 121.6, 90.4, 36.2, 12.4; HRMS (ESI) calcd. for $C_{11}H_{11}BrN_4O$ $[M + H]^+$ 295.0189 and 297.0169, found 295.0190 and 297.0165.

*4-((4-Bromo-1,3-dimethyl-1H-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}H NMR (400 MHz, DMSO-d_6) δ (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}C NMR (100 MHz, DMSO-d_6) δ = 162.7, 144.5, 139.2, 134.2, 127.7, 125.4, 90.3, 36.2, 12.4; HRMS (ESI) calcd for $C_{11}H_{11}BrN_4O_2$ $[M + H]^+$ 311.0138 and 313.0118, found 311.0139 and 313.0114.

*1-(4-Bromo-1,3-dimethyl-1H-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 24 h under nitrogen atmosphere. Then the mixture was cooled to ambient temperature and *N*-bromosuccinimide (1.96 g, 11.0 mmol) was added. After stirring for 4 h at ∼20 °C, the mixture was diluted with water and extracted to EtOAc (3 × 40 mL). The crude product was purified via crystallization from DCM−hexanes, then from MeOH−H_2O, yielding white crystalline solid (2.15 g, 70%); mp 278−280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.99 (s, 1H), 8.21 (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), 2.11 (s,3 H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) = 153.1, 144.4, 139.9, 135.7, 129.3, 122.7, 119.0, 90.6, 36.6, 12.9; HMRS (ESI) calcd for $C_{12}H_{13}BrN_4O$ $[M + H]^+$ 309.0351 and 311.0331, found 309.0347 and 311.0322.

*N-(4-Bromo-1,3-dimethyl-1H-pyrazol-5-yl)piperidine-1-carboxamide (**7h**).* To the mixture of 1,3-dimethyl-1*H*-pyrazol-5-amine (2.22 g, 20.0 mmol) and DABCO (4.39 g, 36.0 mmol) in DCM (80 mL) was added the solution of piperidine-1-carbonyl chloride (4.48 mL, 36 mmol) in DCM (40 mL) dropwise over 45 min. The mixture was stirred at ambient temperature for 14 h. Then it was washed with water (3 × 50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was crystallized from DCM−hexanes yielding a white crystalline solid (2.48 g, 11.2 mmol, 56%), which was then dissolved in acetonitrile (60 mL). To the solution intermediate urea was added *N*-bromosuccinimide (2.09 g, 11.76 mmol) and the mixture was stirred at ambient temperature for 3 h. Then the mixture was diluted with water and extracted to EtOAc (3 × 50 mL). Combined organic extracts were washed with 10% $NaHCO_3$ (2 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was crystallized from EtOAc−hexanes to yield title product as a white crystalline solid (2.78 g, 83%, 46% over two steps); mp 150−152 °C (EtOAc−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.38 (s, 1H), 3.53 (s, 3H), 3.44−3.37 (m, 4H), 2.09 (s, 3H), 1.63−1.56 (m, 2H), 1.53−1.45 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 154.5, 143.6, 136.4, 90.3, 44.9, 35.7, 25.4, 24.0, 12.4; HRMS (ESI) calcd for $C_{11}H_{17}BrN_4O$ $[M + H]^+$ 301.0659 and 303.0638, found 301.0659 and 303.0634.

*N-(4-Chloro-1,3-dimethyl-1H-pyrazol-5-yl)-4-methoxybenzamide (**7i**).* To a mixture of 1,3-dimethyl-1*H*-pyrazol-5-amine (1.11 g, 10.0 mmol) in acetonitrile (20 mL), 4-methoxybenzoic acid (1.67 g, 11.0 mmol), DMAP (0.12 g, 1.0 mmol), and DIPEA (3.5 mL, 20.0 mmol) were added. The solution was cooled in an ice water bath and T3P (50% in EtOAc, 7.2 mL, 12.0 mmol) was added dropwise. Resulting mixture was stirred at room temperature for 18 h. After that, *N*-chlorosuccinimide (1.47 g, 11.0 mmol) was added in one portion and the mixture was stirred for another 4 h. Then the mixture was diluted with water and extracted with EtOAc (3 × 60 mL). After removing solvents under reduced pressure, the residue was purified via a column chromatography (silica gel, DMC−MeOH 100:2). Then the compound was crystallized from MeOH−H_2O in order to remove any residual succinimide. Title product **7i** was obtained as a white crystalline solid (1.60 g, 57% over two steps); mp 180−181 °C (MeOH−H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.19 (s, 1H), 7.99 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 3.85 (s, 3H), 3.59 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (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) calcd for $C_{13}H_{14}N_3O_2$ $[M + H]^+$ 280.0847, found 280.0844.

General Procedure for the Cross-Coupling of Pyrazoles 7a−i (Table 4). A mixture of respective pyrazole **7** (1.0 mmol), boronic acid **2** (2.0 mmol), and K_2CO_3 (0.276 g, 2.0 mmol) in EtOH (4 mL) and water (1 mL) was thoroughly degassed with a stream of nitrogen. Then, XPhos (0.009 g, 0.02 mmol) and XPhos Pd G2 (0.008 g, 0.01 mmol) were added and the microwave vial was inserted into microwave reactor. The reaction mixture was irradiated (setup: variable power, a maximum of 300W, 110 or 60 °C) for 20 min. After that, the mixture was filtered through a Celite, washed with EtOAc, and concentrated under reduced pressure. Purification of the

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crude via column chromatography (MeOH−DCM 100:0 to 100:3) afforded the desired pyrazole as an oil or solid, which was characterized by ^{1}H, ^{13}C NMR and HRMS. In some cases, a product was crystallized from appropriate solvents before measurement of a melting point.

*N-(1,3-Dimethyl-4-(p-tolyl)-1H-pyrazol-5-yl)-4-methoxybenzamide (**8a**).* Title compound was prepared according the general procedure using pyrazole **7a** and 4-tolylboronic acid **2a** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.268 g, 80%). Title compound was also prepared from chloro derivative **7i** in 78% yield. Reported analytical data belong to the sample prepared from **7a**: mp 209−210 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.06 (s, 1H), 7.96 (d, J = 8.8 Hz, 2H), 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, 3H), 2.26 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 166.2, 162.4, 143.4, 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 $C_{20}H_{21}N_3O_2$ $[M + H]^+$ 336.1705, found 336.1707.

*4-Methoxy-N-(4-(4-methoxyphenyl)-1,3-dimethyl-1H-pyrazol-5-yl)benzamide (**8b**).* Title compound was prepared from pyrazole **7a** 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 (0.291 g, 83%); mp 175−177 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 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, J = 8.3 Hz, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 3.59 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 166.2, 162.4, 157.7, 143.3, 133.0, 129.8, 129.2, 125.1, 124.9, 114.9, 114.0, 113.8, 55.5, 55.0, 35.0, 13.2; HRMS (ESI) calcd for $C_{20}H_{21}N_3O_3$ $[M + H]^+$ 352.1654, found 352.1656.

*N-(1,3-Dimethyl-4-(o-tolyl)-1H-pyrazol-5-yl)-4-methoxybenzamide (**8c**).* Title compound was prepared according the general procedure using pyrazole **7a** 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 (0.265 g, 79%); mp 89−91 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (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, 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, 2H), 3.81−3.78 (m, 3H), 3.61 (s, 3H), 2.11 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (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, 115.0, 113.7, 55.4, 35.2, 19.6, 12.7; HRMS (ESI) calcd for $C_{20}H_{21}N_3O_2$ $[M + H]^+$ 336.1707, found 336.1706.

*N-(1,3-Dimethyl-4-(thiophen-3-yl)-1H-pyrazol-5-yl)-4-methoxybenzamide (**8d**).* Title compound was prepared according the general procedure using pyrazole **7a** and thiophen-3-ylboronic acid **2k** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.255 g, 78%); mp 204−206 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (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 (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), 3.55 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 165.9, 162.4, 143.5, 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) calcd for $C_{17}H_{17}N_3O_2S$ $[M + H]^+$ 328.1114, found 328.1114.

*N-(1,3-Dimethyl-4-(5-methylthiophen-2-yl)-1H-pyrazol-5-yl)-4-methoxybenzamide (**8e**).* Title compound was prepared according the general procedure using pyrazole **7a** and 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane **2f** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.259 g, 76%); mp 210−211 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.15 (s, 1H), 8.01 (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, 1H), 3.85 (s, 3H), 3.58 (s, 3H), 2.37 (d, J = 0.9 Hz, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 165.9, 162.4, 143.0, 137.1, 133.0, 131.8, 129.9, 125.5, 125.1, 123.4, 113.9, 109.6, 55.5, 35.1, 14.8, 13.9; HRMS (ESI) calcd for $C_{18}H_{19}N_3O_2S$ $[M + H]^+$ 342.1271, found 342.1270.

*N-(1,3-Dimethyl-4-(p-tolyl)-1H-pyrazol-5-yl)pivalamide (**8f**).* Title compound was prepared according the general procedure using pyrazole **7b** and 4-tolylboronic acid **2a** at 110 °C. The crude material was purified via a column chromatography to yield title product as white solid (0.233 g, 82%); mp 201−202 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 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); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 178.3, 143.2, 133.3, 129.7, 128.9, 127.9, 114.7, 38.6, 34.6, 27.1, 20.7, 13.3; HRMS (ESI) calcd for $C_{17}H_{23}N_3O$ $[M + H]^+$ 286.1914, found 286.1911.

*N-(4-(2-Methoxyphenyl)-1,3-dimethyl-1H-pyrazol-5-yl)-pivalamide (**8g**).* Title compound was prepared according the general procedure using pyrazole **7b** and 2-methoxyphenylboronic acid **2c** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.225 g, 75%); mp 131−132 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) 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, 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 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 178.1, 156.4, 144.5, 134.0, 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 $C_{17}H_{23}N_3O_2$ $[M + H]^+$ 302.1863, found 302.1860.

*(E)-N-(1,3-Dimethyl-4-(4-(trifluoromethyl)styryl)-1H-pyrazol-5-yl)-pivalamide (**8h**).* Compound was prepared according the general procedure using pyrazole **7b** and (*E*)-(4-(trifluoromethyl)styryl)-boronic acid **2m** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.303 g, 83%); mp 152−156 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.53 (s, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.64 (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, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{19}H_{22}F_3N_3O$ $[M + H]^+$ 366.1788, found 366.1786.

*N-(4-(Furan-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)pivalamide (**8i**).* Title compound was prepared according the general procedure using pyrazole **7b** and 2-furanylboronic acid MIDA ester **2l** 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_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (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}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{14}H_{19}N_3O_2$ $[M + H]^+$ 262.1550, found 262.1552.

*N-(4-(4-Methoxyphenyl)-1,3-dimethyl-1H-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}H NMR (400 MHz, DMSO-d_6) δ (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}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{16}H_{19}N_3O_2$ $[M + H]^+$ 286.1550, found 286.1545.

*N-(1,3-Dimethyl-4-(o-tolyl)-1H-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}H NMR (400 MHz, DMSO-d_6) major conformer δ (ppm) = 9.79 (s, 1H), 7.26 (td, J = 7.3, 1.6 Hz, 1H), 7.21 (dd, J = 7.3, 1.6 Hz, 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 (s, 3H), 1.73−1.66 (m, 1H), 0.77−0.70 (m, 4H); minor conformer δ = 9.26 (s, NH), 3.67 (s, CH_3), 2.10 (s, CH_3), 1.98 (s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 173.2, 143.7,

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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) calcd for $C_{16}H_{19}N_3O$ $[M + H]^+$ 270.1601, found 270.1604.

*N-(1,3-Dimethyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-cyclopropanecarboxamide (**8l**).* Title compound was prepared according the general procedure using pyrazole **7c** and 4-(trifluoromethyl)phenylboronic acid **2e** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.281 g, 87%); mp 190−194 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.04 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 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, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 144.2, 137.6, 135.2, 134.3, 129.1, 127.0 (q, J = 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) calcd for $C_{16}H_{16}F_3N_3O$ $[M + H]^+$ 324.1318, found 324.1317.

*N-(1,3-Dimethyl-4-(5-methylthiophen-2-yl)-1H-pyrazol-5-yl)-cyclopropanecarboxamide (**8m**).* Title compound was prepared according the general procedure using pyrazole **7c** and 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane **2f** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.236 g, 86%); mp 111−113 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.08 (s, 1H), 6.83 (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, 3H), 1.86 (ddd, J = 9.6, 7.6, 5.3 Hz, 1H), 0.87−0.79 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (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; HRMS (ESI) calcd for $C_{14}H_{17}N_3OS$ $[M + H]^+$ 276.1165, found 276.1170.

*N-(1,3-Dimethyl-4-(thiophen-3-yl)-1H-pyrazol-5-yl)-cyclopropanecarboxamide (**8n**).* Title compound was prepared according the general procedure using pyrazole **7c** and 3-thienylboronic acid **2k** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.221 g, 85%); mp 171−173 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.04 (s, 1H), 7.60 (dd, J = 4.9, 2.9 Hz, 1H), 7.37 (dd, J = 2.9, 1.2 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), 0.87−0.79 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 173.4, 143.3, 132.9, 132.7, 127.1, 125.9, 120.4, 109.9, 35.0, 13.6, 13.5, 7.3; HRMS (ESI) calcd for $C_{13}H_{15}N_3OS$ $[M + H]^+$ 262.1009, found 262.1009.

*N-(1,3-Dimethyl-4-(pyridin-3-yl)-1H-pyrazol-5-yl)-cyclopropanecarboxamide (**8o**).* Title compound was prepared according the general procedure using pyrazole **7c** and 3-pyridylboronic acid pinacol ester **2n** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.117 g, 46%); mp 166−168 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.07 (s, 1H), 8.51 (d, J = 1.6 Hz, 1H), 8.46 (dd, J = 4.8, 1.6 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), 2.21 (s, 3H), 1.78 (tt, J = 7.7, 4.8 Hz, 1H), 0.85−0.78 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) 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; HRMS (ESI) calcd for $C_{14}H_{16}N_4O$ $[M + H]^+$ 257.1397, found 257.1398.

*N-(4-(2-Methoxyphenyl)-1,3-dimethyl-1H-pyrazol-5-yl)-thiophene-2-carboxamide (**8p**).* Title compound was prepared according the general procedure using pyrazole **7d** and 2-methoxyphenylboronic acid **2c** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.228 g, 70%); 88−90 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.01 (s, 1H), 7.88 (d, J = 3.5 Hz, 1H), 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, 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; ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 161.2, 156.6, 144.7, 138.2, 133.1, 132.3, 130.8, 129.9, 128.4, 128.2, 120.9, 120.2, 112.1, 111.2, 55.0, 35.2, 13.2; HRMS (ESI) calcd for $C_{17}H_{17}N_3O_2S$ $[M + H]^+$ 328.1114, found 328.1114.

*N-(1,3-Dimethyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-5-yl)-thiophene-2-carboxamide (**8q**).* Title compound was prepared according the general procedure using pyrazole **7d** and (4-(trifluoromethyl)phenyl)boronic acid **2e** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.102 g, 28%); mp 206−208 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.39 (s, 1H), 7.97 (dd, J = 3.8, 1.1 Hz, 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 = 5.0, 3.8 Hz, 1H), 3.64 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 161.3, 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), 124.4 (q, J = 271 Hz), 113.9, 35.2, 13.2; HRMS (ESI) calcd for $C_{17}H_{14}F_3N_3OS$ $[M + H]^+$ 366.0882, found 366.0883.

*N-(4-(Furan-3-yl)-1,3-dimethyl-1H-pyrazol-5-yl)thiophene-2-carboxamide (**8r**).* Title compound was prepared according the general procedure using pyrazole **7d** and furan-3-ylboronic acid **2g** at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.169 g, 59%); mp 189−190 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (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 = 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 Hz, 1H), 3.60 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 161.0, 143.5, 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) calcd for $C_{14}H_{13}N_3O_2S$ $[M + H]^+$ 288.0801, found 288.0798.

*N-(4-(4-Hydroxyphenyl)-1,3-dimethyl-1H-pyrazol-5-yl)-4-methoxybenzamide (**8u**).* Title compound was prepared according the general procedure using pyrazole **7i** and 4-hydroxyphenylboronic acid at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.26 g, 77%); mp 272−274 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.00 (s, 1H), 9.34 (s, 1H), 7.94 (d, J = 8.2 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), 3.57 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 166.2, 162.3, 155.9, 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) calcd for $C_{19}H_{19}N_3O_3$ $[M + H]^+$ 338.1499, found 338.1498.

*N-(4-(3-Aminophenyl)-1,3-dimethyl-1H-pyrazol-5-yl)-4-methoxybenzamide (**8v**).* Title compound was prepared according the general procedure using pyrazole **7i** and 3-aminophenylboronic acid at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.29 g, 85%); mp 159−160 °C (MeOH−H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (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), 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 (s, 3H), 3.57 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 166.2, 162.3, 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, 13.4; HRMS (ESI) calcd for $C_{19}H_{20}N_4O_2$ $[M + H]^+$ 337.1659, found 338.1663.

*4-Methoxy-N-(4-(3-methoxyphenyl)-1,3-dimethyl-1H-pyrazol-5-yl)benzamide (**8w**).* Title compound was prepared according the general procedure using pyrazole **7a** and potassium 3-methoxyphenyltrifluoroborate at 110 °C. The crude material was purified via a column chromatography to yield title product as a white solid (0.29 g, 85%); mp 157−159 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.11 (s, 1H), 7.96 (d, J = 8.6 Hz, 2H), 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 (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}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{20}H_{21}N_3O_3$ $[M + H]^+$ 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 date 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}H NMR (400 MHz,

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DMSO-d_6) δ (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}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{18}H_{18}N_4O$ $[M + H]^+$ 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}H NMR (400 MHz, DMSO-d_6) δ (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}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{19}H_{20}N_4O$ $[M + H]^+$ 321.1710, found 321.1709.

*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); ^{1}H NMR (400 MHz, DMSO-d_6) 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); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{19}H_{20}N_4O_2$ $[M + H]^+$ 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); ^{1}H NMR (400 MHz, DMSO-d_6) 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); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{18}H_{17}N_5O_3$ $[M + H]^+$ 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); ^{1}H NMR (400 MHz, DMSO-d_6) 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}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{18}H_{24}N_4O$ $[M + H]^+$ 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}H NMR (400 MHz, $CDCl_3$) δ (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}C NMR (100 MHz, $CDCl_3$) δ (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 $C_{18}H_{24}N_4O_2$ $[M + H]^+$ 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 min. 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}H NMR (400 MHz, DMSO-d_6) δ (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}C NMR (100 MHz, DMSO-d_6) δ (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 $C_{18}H_{21}F_3N_4O$ $[M + H]^+$ 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 chromatography to yield title product as a white solid (0.286 g, 81%); mp >350 °C (DCM−hexanes); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.54 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.79 (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), 3.50−3.46 (m, 4H), 2.40 (s, 3H), 1.66−1.60 (m, 2H), 1.57−1.51 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 154.8, 143.4, 139.8, 138.1, 135.7, 135.3, 124.4, 123.7, 122.9, 121.9, 119.1, 109.1, 44.9, 34.8, 25.7, 24.1, 14.3; HRMS (ESI) calcd. for $C_{19}H_{22}N_4OS$ $[M + H]^+$ 355.1587, found 355.1587.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02306.

Copies of ^{1}H and ^{13}C NMR spectra, representative HPLC chromatograms for the optimization and dehalogenation experiments (PDF)

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Notes

The authors declare no competing financial interest.

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(31) Various conditions utilizing copper cocatalysis, including those reported in references 31a and 31b, were tried in order to improve the reaction with pyridylboronates; however, none of these attempts gave satisfactory result. Mostly dehalogenated pyrazoles were formed as well as pyridine (from protodeboronation). (a) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345. (b) Dick, G. R.; Woerly, E. M.; Burke, M. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 2667.
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