Conditions for Palladium-Catalyzed Direct Arylations of 4-Bromo and 4-Iodo N-Substituted Pyrazoles without C–Br or C–I Bond Cleavage

Journal:	*Organic Chemistry Frontiers*
Manuscript ID:	QO-RES-03-2015-000093.R1
Article Type:	Research Article
Date Submitted by the Author:	04-May-2015

Complete List of Authors:	Ibrahim, Mariem; Univ. de monastir, Smari, Imen; Univ. de monastir, Ben Ammar, Hamed; Univ. de monastir, Ben Hassine, Béchir; Univ. de monastir, ; Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, Faculté des Sciences de Monastir Soule, J.-F.; CNRS UMR6226, Chemistry Doucet, Henri; Universite de Rennes,

ORGANIC CHEMISTRY FRONTIERS RSCPublishing

ARTICLE

Conditions for Palladium-Catalyzed Direct Arylations of 4-Bromo and 4-Iodo *N*-Substituted Pyrazoles without C–Br or C–I Bond Cleavage

Mariem Brahim,[a,b] Imen Smari,[a,b] Hamed Ben Ammar,*[b] Bechir Ben Hassine,[b] Jean-Fran çois Soul é[a] and Henri Doucet*[a]

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

The Pd-catalyzed arylation at C5 position of *N*-protected pyrazole derivatives bearing bromo or iodo substituents at C4 position is described. Simple phosphine-free catalytic system was used, namely, 1 mol% $Pd(OAc)_2$ in DMA in the presence of KOAc as base. A wide aryl bromide scope as coupling partners has been coupled with pyrazole derivatives. The reaction was very chemoselective as the C-halogen bonds of the pyrazole units were not involved in the C–H arylation process. Some examples demonstrating the synthetic potential of the bromo and iodo pyrazole substituents for chemical transformations are reported.

Pyrazole derivatives including molecules containing a 5-arylpyrazole motif are well represented in pharmaceutical drugs. For example, Deracoxib (Deramaxx® drug developed by Novartis) is employed in veterinary medicine as a non-steroidal anti-inflammatory drug of the coxib class. Temonagrel is an inverse agonist of the serotonin 2A receptor in phase II. Nelotanserin is an inverse agonist on the serotonin receptor subtype 5-HT_{2A} developed by Arena Pharmaceuticals (Figure 1).

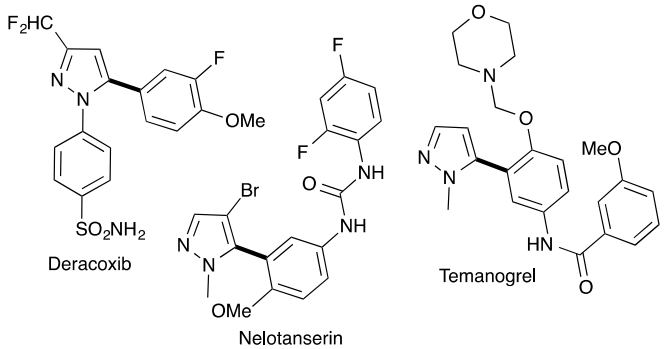


Figure 1. Examples of bioactive molecules containing a 5-arylpyrazole unit.

Traditionally, 5-arylpyrazole derivatives have been synthetized using cross-coupling reactions between an aryl halide with an organometallic pyrazole derivative,[1] or a halopyrazole with an organometallic aryl derivative using palladium catalysts.[2] More recently, metal-catalyzed direct C–H bond arylation has appeared as one of the most suitable alternative to such traditional cross-coupling reactions for the C–C bond formation with respect of the environment.[3] This strategy has been employed for the functionalization of large number of different heteroarenes, however examples with pyrazole remain scarce. Indeed, using pyrazoles the reaction generally suffers from regioselectivity issue. As examples, in 2009, Sames reported that the palladium-catalyzed direct arylation of *N*-protected pyrazole led to a mixture of C4 and C5 arylated pyrazoles with also the formation of large amount of C4,C5-diarylated pyrazole (Figure 2a).[4] Latter, Doucet and co-workers reported $Pd(OAc)_2$ phosphine-free conditions for the direct arylation of 1-methylpyrazole.[5] Again, the reaction was not regioselective and a mixture of C5, C4 arylated and diarylated products was obtained in 78:16:6 ratio. Moreover, a large excess of 1-methylpyrrazole (4 equiv.) was employed (Figure 2a). In 2013, Bellina obtained a higher C5:C4 ratio (i.e., 86:14) without formation of diarylated product, using Bu_4NOAc as base (Figure 2a).[6] According to Gorelsky calculations, in the concerted metallation deprotonation (CMD) process, this regioselectivity issue can be explained by similar energies of activation of C4 and C5 protons (28.5 *vs* 27.3).[7] In 2014, Kumpulainen and co-workers reported that $Pd(OAc)_2$ associated to PPh_3 catalyzes highly regioselective C5 arylation of *N*-dimethylaminosulfamoyl-protected pyrazole; whereas, other *N*-protected pyrazoles such as 1-methyl or 1-benzylpyrazoles lead to mixtures of C5 and C4 arylated

products and also to diarylated pyrazoles.[8] In 2010, Mateos and Mendiola, after a large screening of the reaction conditions, successfully arylated 4-chloro-1-methylpyrazole at the C5 position in good yield (Figure 1c).[9] However, chloro function is generally not appropriate for further transformations. 4-Bromo-1-methylpyrazole had also been tested under similar reaction conditions; albeit a poor yield was obtained and diarylated pyrazole was also formed (Figure 1c). Similar strategies, in which the C4 or C5 position was blocked by a substituent, were reported using chloro,[10] formyl,[11] nitro substituents,[12] or using indazole as starting materials.[13] The diarylation of pyrazole derivatives at C4 and C5 positions has also been reported using an excess of arylbromides.[14] Similar approaches, namely, regioselective Pd-catalyzed direct arylations of halo-heteroarenes have also been reported.[15]

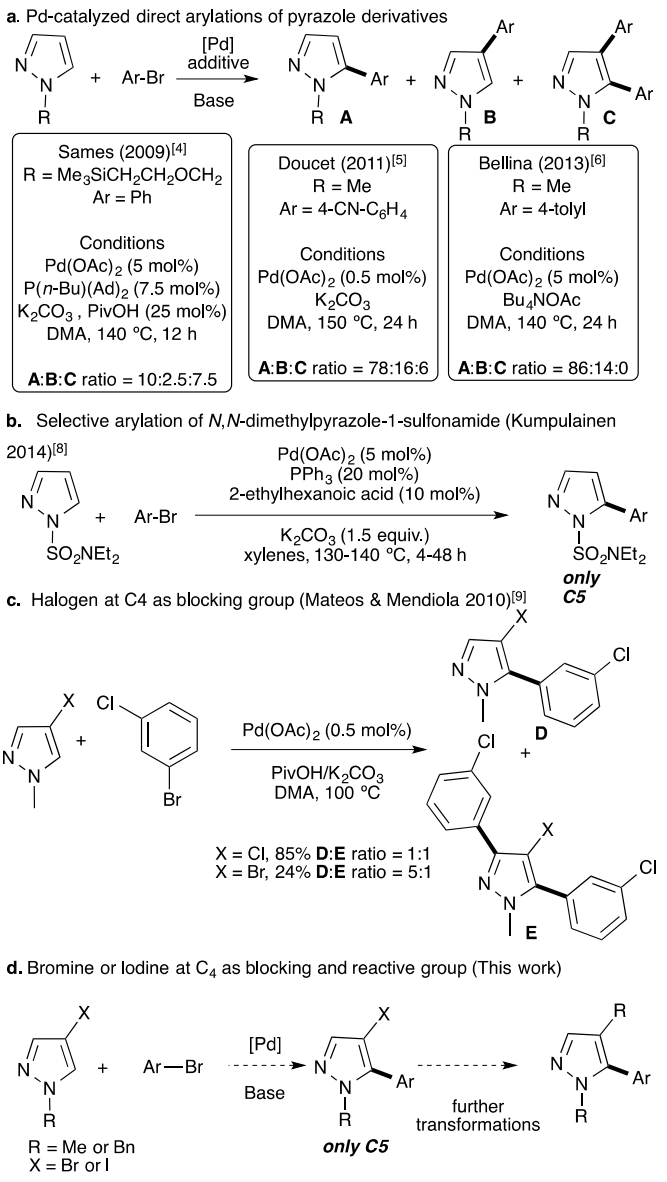
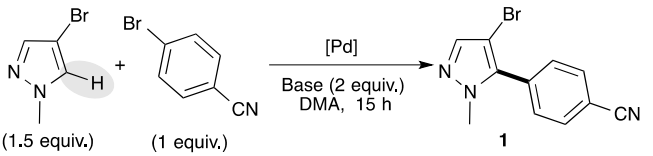


Figure 2. Previous examples of Pd-catalyzed direct arylations of pyrazoles using aryl bromides.

Here, we investigated the direct arylation of 4-bromo-1-(protected)pyrazole derivatives using simple catalytic system based on palladium and also extended this reaction to more challenging 4-iodo-1-(protected)pyrazole derivatives.

We selected 4-bromobenzonitrile and 3-bromo-1-methylpyrazole as model substrates for this reaction and used a small excess of pyrazole derivative in order to prevent the side diarylation reaction. Based on our previous results,[16] we firstly started our optimization using palladium-diphosphine complex catalyst, namely $PdCl(C_3H_5)$(dppb), in the presence of KOAc as base in DMA at 150 °C. Under these reaction conditions, the desired C5-arylated pyrazole **1** was obtained in excellent 85% yield (Table 1, entry 1). Using lower reaction temperature (130 °C), the reaction was not complete and the pyrazole **1** was obtained in only 65% yield (Table 2, entry 2). Interestingly, using 1 mol% of $Pd(OAc)_2$ without phosphine instead of $PdCl(C_3H_5)$(dppb) catalyst allowed a full conversion and **1** was isolated in 89% yield (Table 1, entry 3). Potassium pivalate (PivOK) instead of KOAc did not significantly affected the reaction, whereas when the reaction was performed in the presence of K_2CO_3 as base, lower conversion and yield of **1** were observed (Table 1, entries 4 and 5). Using a lower catalyst loading (i.e., 0.5 mol% of $Pd(OAc)_2$), the reaction was not complete and **1** was obtained in only 56% yield (Table 1, entry 6). The same result was observed when the reaction was performed at only 100 °C, whatever the catalyst (Table 1, entries 7 and 8). Finally, the reaction can also be performed using only 1.1 equivalent of the pyrazole derivative without influence on the reaction yield (Table 1, entry 9).

Table 1. Optimization of the reaction conditions

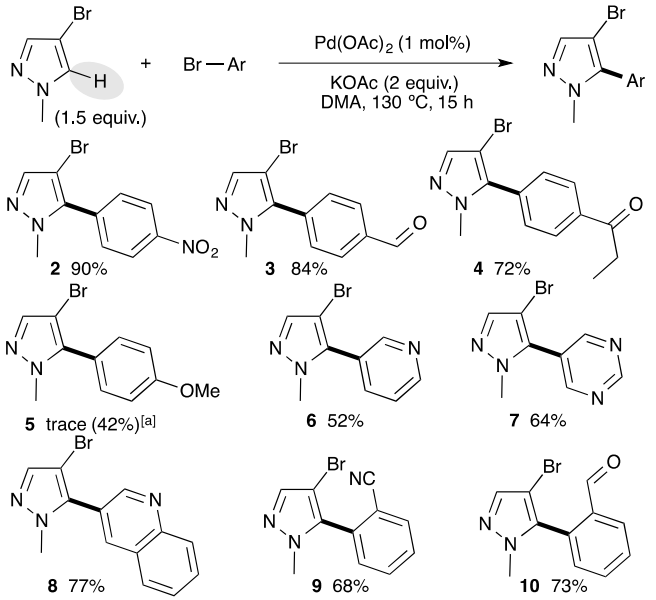


Entry	Cat . (x mol%)	Base	Temp. (°C)	Conv. (%)[a]	Yield in **1** (%)[b]
1	$PdCl(C_3H_5)$(dppb) (1)	KOAc	150	100	85
2	$PdCl(C_3H_5)$(dppb) (1)	KOAc	130	92	65
3	$Pd(OAc)_2$ (1)	KOAc	130	100	95 (89)
4	$Pd(OAc)_2$ (1)	KOPiv	130	100	95
5	$Pd(OAc)_2$ (1)	K_2CO_3	130	73	68
6	$Pd(OAc)_2$ (0.5)	KOAc	130	58	56
7	$Pd(OAc)_2$ (1)	KOAc	100	67	66
8	$PdCl(C_3H_5)$(dppb) (1)	KOAc	100	85	83
9[c]	$Pd(OAc)_2$ (1)	KOAc	130	100	95

[a] Based on the consumption of 4-bromobenzonitrile. [b] Determined using crude ^{1}H-NMR, the number in parentheses shows the isolated yield. [c] The reaction was performed using 1.1 equiv. of 4-bromo-1-methylpyrazole.

With the best reaction conditions in hands, we decided to turn our attention to the scope and limitation of the direct arylation of 4-bromo-1-methylpyrazole using a range of aryl bromides (Scheme 1). We started by a set of *para*-substituted aryl bromides. Electron-withdrawing substituents such as nitro, formyl, and propionyl on the aryl bromide partner allowed the formation of the C5 arylated pyrazoles **2**-**4** in 90%, 84% and

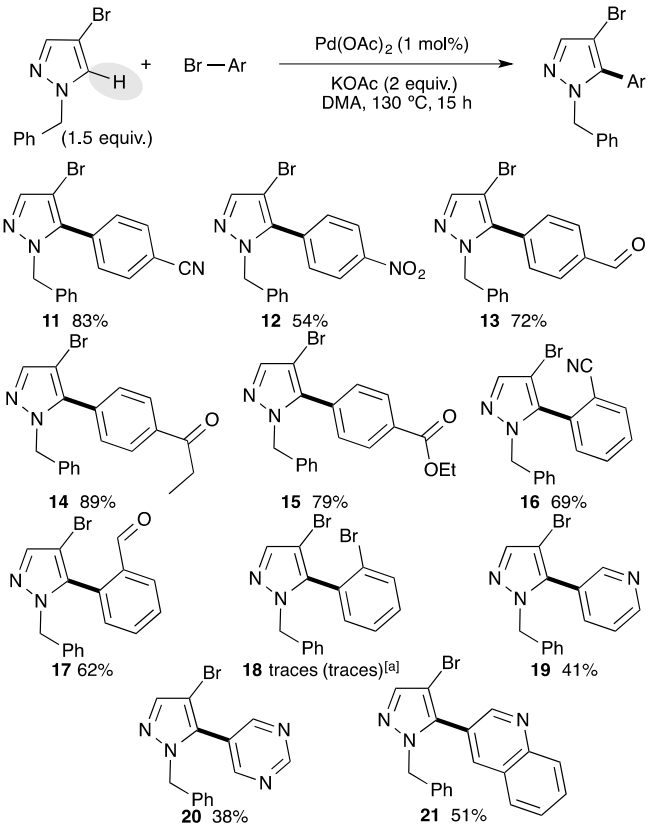
72% yields, respectively. Using an electron-donating group such as 4-methoxy, $Pd(OAc)_2$ was ineffective, while the use of 1 mol% $PdCl(C_3H_5)(dppb)$ catalyst afforded the desired arylated product **5** in 42% yield. The reaction also tolerates heteroaryl bromides as coupling partners. For examples, from 3-bromopyridine, 5-bromopyrimidine, or 3-bromoquinoline the C5 arylpyrazoles **6**-**8** were isolated in 52%, 64%, and 77% yields, respectively. Finally, the reaction was found to be slightly sensitive to the steric hindrance of the aryl bromide partners, as the use of 2-bromobenzonitrile or 2-bromobenzaldehyde gave the arylated pyrazoles **9** and **10** in lower yields than their *para*-substituted homologues.



[a] Reaction performed using 1 mol% $PdCl(C_3H_5)(dppb)$ instead of $Pd(OAc)_2$

Scheme 1. Pd-Catalyzed Direct Arylation of 4-bromo-1-methylpyrazole.

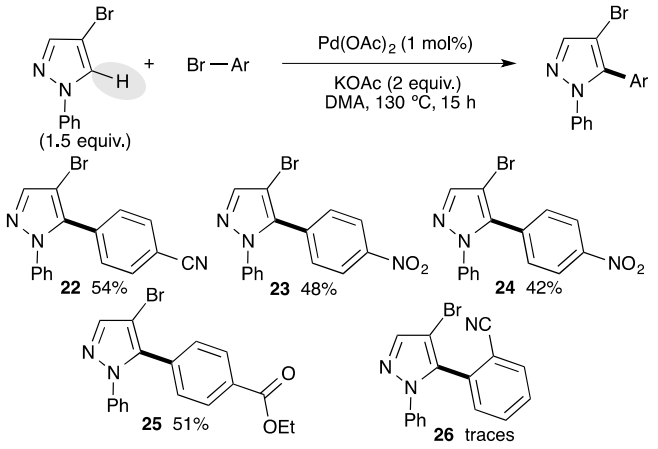
After having successfully arylated 4-bromo-1-methylpyrazole at the C5 position, we investigated the reactivity of 4-bromopyrazole without *N*H substituent. Unfortunately the reaction was completely inhibited. This lack of reactivity might be explained by the coordination of *N*H to palladium resulting into a catalyst poisoning. Next, we examined the reactivity of 4-bromo-1-benzylpyrazole with a set of bromobenzene derivatives using our optimized reaction conditions (Scheme 2). Again, using bromobenzenes bearing electron-withdrawing groups at the *para* position, the desired C5 arylated 4-bromo-1-benzylpyrazoles were isolated as single regioisomer in high yields, albeit using 4-bromonitrobenzene the arylated product **12** was obtained in only 54% yield. Under these reaction conditions, we never observed debenzylation side-reaction. *Ortho*-substituted bromobenzenes, such as 2-bromobenzonitrile or 2-bromobenzaldehyde, also allowed the formation of C5 arylated products **16** and **17** in 69% and 62% yields, respectively. However, a more bulky substituent such as bromo at the *ortho*-position inhibited the reaction and only trace amount of coupling product **18** was detected. Even a reverse stoichiometry did not afford the desired coupling product **18** or dipyrazole. affore Bromoheteroarenes, such as 3-bromopyridine, 5-bromopyrimidine and 3-bromoquinoline were coupled with 4-bromo-1-benzylpyrazole to afford the C5 arylated products **19**-**21** in moderate yields.



[a] Reaction performed using 1 equiv. of pyrazole and 2 equiv of 1,2-dibromobenzene

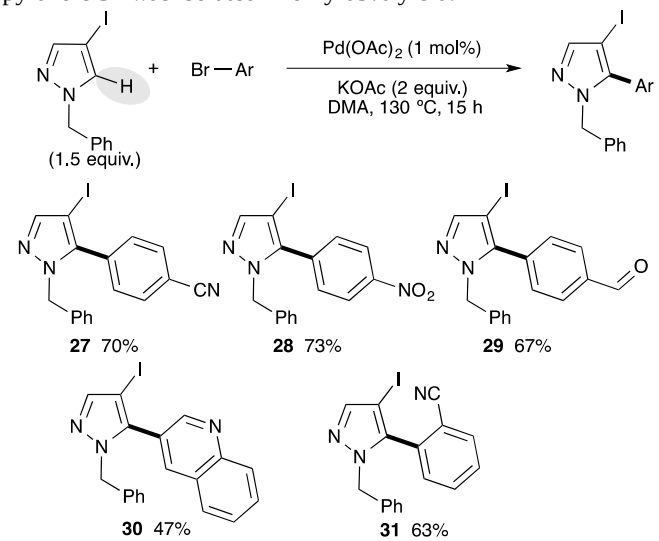
Scheme 2. Pd-Catalyzed Direct Arylation of 4-bromo-1-benzylpyrazole.

Then, 4-bromo-1-phenylpyrazole was used as starting material. It displayed a lower reactivity than its 1-methyl or 1-benzyl substituted analogues (Scheme 3). Indeed, using the same bromobenzene derivatives, only moderate yields of the desired cross-coupling products **22**-**25** were obtained. This lower reactivity might be explained by the steric hindrance of the phenyl group, which might partially block the C5 position of the pyrazole. An electronic influence, which modifies the nucleophilicity of such *N*-arylated pyrazole due to delocalization of lone pair on nitrogen to aryl group, might also explain this lower reactivity. The poor reactivity of 2-bromobenzonitrile seems to confirm this trend.



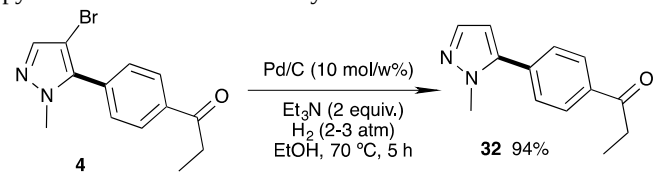
Scheme 3. Pd-Catalyzed Direct Arylation of 4-bromo-1-phenylpyrazole.

After having successfully arylated pyrazoles bearing a bromo substituent at C4 position, we investigated the reactivity of more challenging pyrazole bearing an iodo substituent at C4 position (Scheme 4). We used 1-benzyl-4-iodopyrazole as model substrate, which was easily prepared from pyrazole *via* iodation using I_2/CAN system followed by a benzylation.[17] Using electron-deficient *para*-substituted bromoarenes as cyano, ethyl ester, of formyl, the C5 arylated pyrazole derivatives **27**-**29** were isolated in good yields. The reaction is highly chemoselective and the C–I bond was not involved, allowing further transformations. 3-Bromoquinoline has also been coupled with 1-benzyl-4-iodopyrazole to give the desired product **30** in 47% yield. The reaction is slightly sensitive the steric hindrance, as from 2-bromobenzonitrile the 5-arylated pyrazole **31** was isolated in only 63% yield.



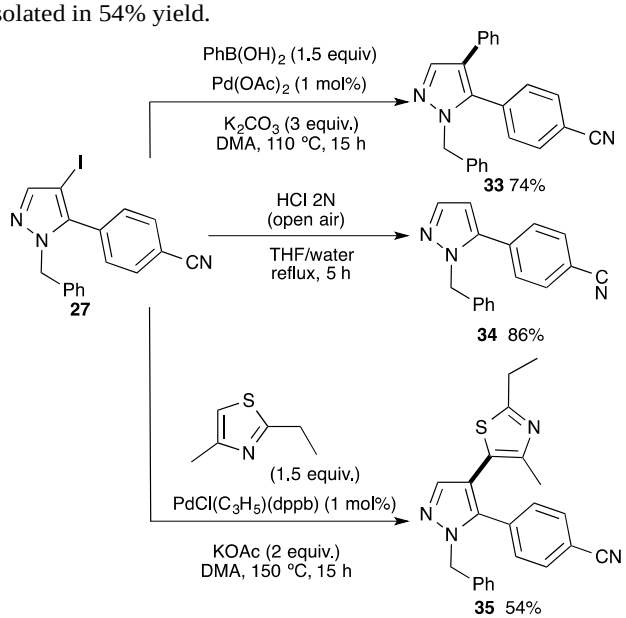
Scheme 4. Pd-Catalyzed Direct Arylation of 4-iodo-1-benzylpyrazole.

The debromination of a C5-arylated pyrazole was then studied (Scheme 5). In the presence of Pd/C (10 mass % of the starting materials) in ethanol and triethylamine under 3-5 bar of hydrogen atmosphere at 70 °C during 5 h, the 4-bromo-pyrazole **4** was debrominated to afford the 5-mono-arylated pyrazole **32** in excellent 94% yield.[18]



Scheme 5. Cleavage of the C–Br bond

Then, we investigated the reactivity of the C–I bond of the previously synthetized C5 arylated pyrazole derivative **27** (Scheme 6). Firstly, the 4-iodopyrazole **27** was arylated *via* a Suzuki-Miyaura reaction.[19] Using phenylboronic acid in the presence of 2 mol % $Pd(OAc)_2$ without phosphine and 3 equiv. of K_2CO_3 in DMA, the unsymmetrical C5,C4-diarylpyrazole **33** was isolated in 74% yield. Using the conditions described by Janin,[20] namely, HCl at conditions under air atmosphere, selective deiodination of **27** could be performed without the cleavage of the *N*-benzyl group to afford the 5-arylated pyrazole **34** in 86% yield. Finally, we also performed a C–H bond heteroarylation of this iodopyrrole with 2-ethyl-4-methylthiazole. Using 1 mol% $PdCl(C_3H_5)(dppb)$ in the presence of KOAc as base in DMA at 150 °C, 4-(1-benzyl-4-(2-ethyl-4-methylthiazol-5-yl)pyrazol-5-yl)benzonitrile (**35**) was isolated in 54% yield.



Scheme 6. Transformation of C-I bond of the pyrazole unit.

Conclusions

In summary, we have demonstrated that using appropriate reaction conditions, C4 halosubstituted *N*-protected pyrazole derivatives were regioselectively arylated at C5 position using aryl bromides as coupling partners. The reaction is very chemoselective as the C–X bonds (X = Br and I) on the pyrazole unit were never involved during the C–H arylation process. The reaction proceeds in moderate to very high yields

in the presence of electron-deficient aryl bromides or heteroaryl bromides using 1 mol % of $Pd(OAc)_2$ as the catalyst precursor. Electron-rich aryl bromides could also be employed with a high chemoselectivity using 1 mol% of $PdCl(C_3H_5)(dppb)$ as catalyst. We also showed that bromo or iodo substituents could be used as traceless protecting groups for the formation of selective C5-arylated pyrazoles. Moreover, using 4-iodopyrazole derivatives, orthogonal arylations were performed to allow the formation of C4,C5-diarylated pyrazoles bearing two different aryl units in high yields.

Experimental Section

All reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA (*N*,*N*-dimethylacetamide) (99%) was purchased from Acros. KOAc (99%), and $Pd(OAc)_2$ (98%) were purchased from Alfa Aesar. These compounds were not purified before use. ^{1}H NMR spectra were recorded on Bruker GPX (400 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

General procedure: As a typical experiment, the reaction of the aryl bromide (1 mmol), 4-bromo-1-methylpyrazole, 1-benzyl-4-bromopyrazole, 4-bromo-1-phenylpyrazole, or 1-benzyl-4-iodopyrazole (1.5 mmol) and KOAc (0.196 g, 2 mmol) at 130 °C during 16 h in DMA (2 mL) in the presence of $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol) (see tables or schemes) under argon affords the arylation product after evaporation of the solvent and filtration on silica gel.

4-(4-Bromo-1-methylpyrazol-5-yl)benzonitrile 1 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 4-bromobenzonitrile (0.182 g, 1 mmol), **1** was obtained in 89% (0.233 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 7.80 (d, J = 8.3 Hz, 2H), 7.56-7.53 (m, 3H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 139.5, 139.2, 132.9, 132.4, 130.4, 118.1, 113.0, 94.1, 38.5.

Elemental analysis: calcd (%) $C_{11}H_8BrN_3$ for (262.11): C 50.41, H 3.08; found: C 50.56, H 3.21.

4-Bromo-1-methyl-5-(4-nitrophenyl)pyrazole 2 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 4-bromonitrobenzene (0.202 g, 1 mmol), **2** was obtained in 80% (0.226 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 8.36 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.57 (s, 1H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 148.0, 139.6, 138.9, 134.7, 130.7, 123.9, 94.3, 38.6.

Elemental analysis: calcd (%) $C_{10}H_8BrN_3O_2$ for (282.10): C 42.58, H 2.86; found: C 42.74, H 3.12.

4-(4-Bromo-1-methylpyrazol-5-yl)benzaldehyde 3 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 4-bromobenzaldehyde (0.185 g, 1 mmol), **3** was obtained in 84% (0.223 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 10.10 (s, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.57 (s, 1H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 191.4, 139.9, 139.6, 136.4, 134.3, 130.4, 129.9, 94.1, 38.6.

Elemental analysis: calcd (%) $C_{11}H_9BrN_2O$ for (265.11): C 49.84, H 3.42; found: C 50.11, H 3.75.

1-(4-(4-Bromo-1-methylpyrazol-5-yl)phenyl)propan-1-one 4 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 4-bromopropiophenone (0.213 g, 1 mmol), **4** was obtained in 72% (0.211 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 8.09 (d, J = 8.3 Hz, 2H), 7.56-7.51 (m, 3H), 3.84 (s, 3H), 3.05 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 200.0, 140.2, 139.5, 137.2, 132.7, 130.0, 128.3, 93.8, 38.5, 31.9, 8.2.

Elemental analysis: calcd (%) $C_{13}H_{13}BrN_2O$ for (293.16): C 53.26, H 4.47; found: C 53.58, H 4.71.

4-Bromo-5-(4-methoxyphenyl)-1-methylpyrazole 5 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 4-bromoanisole (0.187 g, 1 mmol), **5** was obtained in 42% (0.112 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 7.51 (s, 1H), 7.33 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 160.2, 141.1, 139.1, 131.1, 120.5, 114.2, 93.3, 55.3, 38.2.

Elemental analysis: calcd (%) $C_{11}H_{11}BrN_2O$ for (267.13): C 49.46, H 4.15; found: C 49.85, H 4.01.

3-(4-Bromo-1-methylpyrazol-5-yl)pyridine 6 : 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 3-bromopyridine (0.158 g, 1 mmol), **6** was obtained in 52% (0.124 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 8.71 (brs, 1H), 8.68 (brs, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 7.45 (dd, J = 4.8 and 7.9 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ (ppm) = 150.2, 139.5, 138.0, 137.3, 137.1, 124.8, 123.5, 94.4, 38.4.

Elemental analysis: calcd (%) $C_9H_8BrN_3$ for (238.09): C 45.40, H 3.39; found: C 45.67, H 3.31.

5-(4-Bromo-1-methyl-1*H*-pyrazol-5-yl)pyrimidine 7 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 5-bromopyrimidine (0.159 g, 1 mmol), **7** was obtained in 64% (0.153 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 9.31 (s, 1H), 8.85 (s, 2H), 7.60 (s, 1H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 158.8, 157.2, 139.8, 134.8, 123.5, 95.2, 38.6.

Elemental analysis: calcd (%) $C_8H_7BrN_4$ for (239.08): C 40.19, H 2.95; found: C 40.33, H 3.18.

3-(4-Bromo-1-methylpyrazol-5-yl)quinoline 8 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 3-bromoquinoline (0.208 g, 1 mmol), **8** was obtained in 77% (0.222 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 8.94 (d, J = 2.3 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.81 (ddd, J = 1.8, 6.9 and 8.4 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.60 (s, 1H), 3.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 150.2, 147.8, 139.5, 138.1, 137.2, 130.7, 129.4, 128.1, 127.5, 127.2, 121.7, 94.6, 38.5.

Elemental analysis: calcd (%) $C_{13}H_{10}BrN_3$ for (288.15): C 54.19, H 3.50; found: C 54.36, H 3.32.

2-(4-Bromo-1-methylpyrazol-5-yl)benzonitrile 9 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 2-bromobenzonitrile (0.182 g, 1 mmol), **9** was obtained in 68% (0.178 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) = 7.85 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 139.4, 137.8, 133.5, 133.0, 132.1, 131.8, 130.0, 116.9, 113.9, 95.3, 38.3.

Elemental analysis: calcd (%) $C_{11}H_8BrN_3$ for (262.11): C 50.41, H 3.08; found: C 50.29, H 3.33.

2-(4-Bromo-1-methylpyrazol-5-yl)benzaldehyde 10 : From 4-bromo-1-methylpyrazole (0.241 g, 1.5 mmol) and 2-bromobenzaldehyde (0.185 g, 1 mmol), **10** was obtained in 73% (0.193 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 9.81 (s, 1H), 8.11 (dd, J = 1.6 and 7.7 Hz, 1H), 7.75 (dt, J = 1.8 and 7.5 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.60 (s, 1H), 7.39 (dd, J = 1.4 and 7.7 Hz, 1H), 3.72 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 190.4, 139.2, 137.9, 134.8, 134.1, 131.6, 131.1, 130.3, 128.8, 95.8, 38.2.

Elemental analysis: calcd (%) $C_{11}H_9BrN_2O$ for (265.11): C 49.84, H 3.42; found: C 59.99, H 3.27.

4-(1-Benzyl-4-bromopyrazol-5-yl)benzonitrile 11 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 4-bromobenzonitrile (0.182 g, 1 mmol), **11** was obtained in 83% (0.281 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 7.72 (d, J = 8.1 Hz, 2H), 7.65 (s, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.29-7.24 (m, 3H), 6.99-6.95 (m, 2H), 5.27 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 140.1, 139.7, 136.2, 133.1, 132.4, 130.6, 128.8, 128.1, 126.8, 118.1, 113.2, 94.8, 54.8.

Elemental analysis: calcd (%) $C_{17}H_{12}BrN_3$ for (338.21): C 60.37, H 3.58; found: C 60.84, H 3.71.

1-Benzyl-4-bromo-5-(4-nitrophenyl)pyrazole 12 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 4-bromonitrobenzene (0.202 g, 1 mmol), **12** was obtained in 54% (0.193 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.29 (d, J = 8.6 Hz, 2H), 7.66 (s, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.29-7.25 (m, 3H), 7.00-6.96 (m, 2H), 5.29 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 148.1, 140.2, 139.4, 136.2, 134.8, 130.9, 128.8, 128.1, 126.8, 123.9, 95.0, 54.8.

Elemental analysis: calcd (%) $C_{16}H_{12}BrN_3O_2$ for (358.20): C 53.65, H 3.38; found: C 53.89, H 3.11.

4-(1-Benzyl-4-bromopyrazol-5-yl)benzaldehyde 13 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 4-bromobenzaldehyde (0.185 g, 1 mmol), **13** was obtained in 72% (0.246 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 10.01 (s, 1H), 7.95 (d, J = 7.8 Hz, 2H), 7.65 (s, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.28-7.23 (m, 3H), 7.01-6.97 (m, 2H), 5.28 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 191.3, 140.4, 140.1, 136.6, 136.4, 134.4, 130.6, 129.8, 128.8, 128.0, 127.0, 94.7, 54.7.

Elemental analysis: calcd (%) $C_{17}H_{13}BrN_2O$ for (341.21): C 59.84, H 3.84; found: C 60.17, H 4.02.

1-(4-(1-Benzyl-4-bromopyrazol-5-yl)phenyl)propan-1-one 14 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 4-bromopropiophenone (0.213 g, 1 mmol), **14** was obtained in 89% (0.329g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.02 (d, J = 8.2 Hz, 2H), 7.64 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.27-7.24 (m, 3H), 7.02-6.98 (m, 2H), 5.27 (s, 2H), 3.03 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 200.0, 140.6, 140.0, 137.2, 136.4, 132.7, 130.1, 128.7, 128.2, 127.9, 126.9, 94.4, 54.5, 31.9, 8.1.

Elemental analysis: calcd (%) $C_{19}H_{17}BrN_2O$ for (369.26): C 61.80, H 4.64; found: C 62.17, H 4.46.

Ethyl 4-(1-benzyl-4-bromopyrazol-5-yl)benzoate 15 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and ethyl 4-bromobenzoate (0.229 g, 1 mmol), **15** was obtained in 79% (0.304 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.13 (d, J = 8.2 Hz, 2H), 7.65 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.29-7.25 (m, 3H), 7.03-6.98 (m, 2H), 5.29 (s, 2H), 4.43 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 165.9, 140.7, 140.0, 136.5, 132.8, 131.3, 129.9, 129.8, 128.7, 127.9, 127.0, 94.4, 61.2, 54.6, 14.3.

Elemental analysis: calcd (%) $C_{19}H_{17}BrN_2O_2$ for (385.26): C 59.23, H 4.45; found: C 59.48, H 4.11.

2-(1-Benzyl-4-bromopyrazol-5-yl)benzonitrile 16 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 2-bromobenzonitrile (0.182 g, 1 mmol), **16** was obtained in 69% (0.234 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 7.77 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.28-7.26 (m, 1H), 7.23-7.19 (m, 3H), 6.92-6.88 (m, 2H), 5.32 (d, J = 15.4 Hz, 1H), 5.18 (d, J = 15.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 139.9, 138.0, 135.9, 133.4, 132.8, 132.2, 131.7, 130.0, 128.7, 128.1, 127.2, 116.7, 114.3, 96.3, 55.2.

Elemental analysis: calcd (%) $C_{17}H_{12}BrN_3$ for (338.21): C 60.37, H 3.58; found: C 60.12, H 3.18.

2-(1-Benzyl-4-bromopyrazol-5-yl)benzaldehyde 17 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 2-bromobenzaldehyde (0.185 g, 1 mmol), **19** was obtained in 62% (0.212 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 9.52 (s, 1H), 8.02 (dd, J = 1.9 and 7.5 Hz, 1H), 7.72-7.60 (m, 3H), 7.28-7.18 (m, 4H), 6.91-6.86 (m, 2H), 5.20 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 189.9, 139.4, 137.8, 135.8, 134.7, 133.9, 131.4, 131.2, 130.3, 128.7, 128.3, 128.1, 127.3, 96.8, 55.1.

Elemental analysis: calcd (%) $C_{17}H_{13}BrN_2O$ for (341.21): C 59.84, H 3.84; found: C 60.08, H 3.49.

3-(1-Benzyl-4-bromopyrazol-5-yl)pyridine 19 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 3-bromopyridine (0.158 g, 1 mmol), **19** was obtained in 41% (0.129 g) yield.

^{1}H NMR (400 MHz, DMSO-d_6, 25 ℃): δ (ppm) = 8.66 (d, J = 4.8 Hz, 1H), 8.53 (s, 1H), 7.82 (s, 1H), 7.80 (t, J = 2.1 Hz, 1H), 7.53 (dd, J = 4.8 and 7.9 Hz, 1H), 7.28-7.21 (m, 3H), 6.91 (dd, J = 1.8 and 7.5 Hz, 2H), 5.33 (s, 2H).

^{13}C NMR (75 MHz, DMSO-d_6, 25 ℃): δ (ppm) = 150.3, 149.8, 139.4, 138.2, 137.3, 136.7, 128.5, 127.6, 126.8, 124.2, 123.8, 94.2, 54.0.

Elemental analysis: calcd (%) $C_{15}H_{12}BrN_3$ for (314.19): C 57.34, H 3.85; found: C 57.69, H 4.10.

5-(1-Benzyl-4-bromopyrazol-5-yl)pyrimidine 20 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 5-bromopyrimidine (0.159 g, 1 mmol), **20** was obtained in 38% (0.120 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 9.25 (s, 1H), 8.62 (s, 2H), 7.69 (s, 1H), 7.29-7.25 (m, 3H), 7.00-6.96 (m, 2H), 5.30 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 158.9, 157.3, 140.2, 135.9, 135.1, 129.0, 128.4, 126.8, 123.6, 96.0, 55.1.

Elemental analysis: calcd (%) $C_{14}H_{11}BrN_4$ for (315.17): C 53.35, H 3.52; found: C 53.56, H 3.17.

3-(1-Benzyl-4-bromopyrazol-5-yl)quinoline 21 : From 1-benzyl-4-bromopyrazole (0.356 g, 1.5 mmol) and 3-bromoquinoline (0.208 g, 1 mmol), **21** was obtained in 52% (0.189 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.82 (br, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 2.3 Hz, 1H), 7.81 (ddd, J = 1.5, 8.4 and 16.6 Hz, 2H), 7.71 (s, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.29-7.24 (m, 3H), 7.04-7.00 (m, 2H), 5.32 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 149.6, 146.9, 140.1, 138.3, 138.1, 136.3, 131.2, 128.9, 128.8, 128.1, 127.8, 127.2, 126.9, 121.8, 95.5, 54.9.

Elemental analysis: calcd (%) $C_{19}H_{14}BrN_3$ for (364.25): C 62.65, H 3.87; found: C 62.96, H 3.61.

4-(4-Bromo-1-phenylpyrazol-5-yl)benzonitrile 22 : From 4-bromo-1-phenylpyrazole (0.334 g, 1.5 mmol) and 4-bromobenzonitrile (0.182 g, 1 mmol), **22** was obtained in 54% (0.175 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 7.78 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.35-7.33 (m, 3H), 7.20-7.17 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 141.4, 139.4, 138.4, 133.1, 132.2, 130.6, 129.2, 128.3, 124.9, 118.1, 112.7, 96.6.

Elemental analysis: calcd (%) $C_{16}H_{10}BrN_3$ for (324.18): C 59.28, H 3.11; found: C 59.10, H 3.32.

4-Bromo-5-(4-nitrophenyl)-1-phenylpyrazole 23 : From 4-bromo-1-phenylpyrazole (0.334 g, 1.5 mmol) and 4-bromonitrobenzene (0.202 g, 1 mmol), **23** was obtained in 48% (0.165 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.22 (d, J = 8.7 Hz, 2H), 7.80 (s, 1H), 7.47 (d, J = 8.7 Hz, 2H), 7.37-7.33 (m, 3H), 7.22-7.18 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 147.7, 141.4, 139.2, 138.0, 134.9, 130.8, 129.3, 128.3, 124.9, 123.7, 96.7.

Elemental analysis: calcd (%) $C_{15}H_{10}BrN_3O_2$ for (344.17): C 52.35, H 2.93; found: C 52.71, H 2.98.

4-(4-Bromo-1-phenylpyrazol-5-yl)benzaldehyde 24 : From 4-bromo-1-phenylpyrazole (0.334 g, 1.5 mmol) and 4-bromobenzaldehyde (0.185 g, 1 mmol), **24** was obtained in 42% (0.145 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 10.03 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.79 (s, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.34-7.30 (m, 3H), 7.23-7.18 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 191.5, 141.4, 139.5, 139.0, 136.1, 134.4, 130.6, 129.6, 129.1, 128.1, 124.9, 96.5.

Elemental analysis: calcd (%) $C_{16}H_{11}BrN_2O$ for (327.18): C 58.74, H 3.39; found: C 58.59, H 3.47.

Ethyl 4-(4-bromo-1-phenylpyrazol-5-yl)benzoate 25 : From 4-bromo-1-phenylpyrazole (0.334 g, 1.5 mmol) and ethyl 4-bromobenzoate (0.229 g, 1 mmol), **25** was obtained in 51% (0.189 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.03 (d, J = 8.4 Hz, 2H), 7.77 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.32-7.28 (m, 3H), 7.23-7.17 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 166.2, 141.5, 139.9, 139.7, 133.1, 131.0, 130.2, 129.8, 129.3, 128.2, 125.1, 96.5, 61.4, 14.5.

Elemental analysis: calcd (%)$C_{18}H_{15}BrN_2O_2$ for (371.23): C 58.24, H 4.07; found: C 58.46, H 4.25.

4-(1-Benzyl-4-iodopyrazol-5-yl)benzonitrile 27 : From 1-benzyl-4-iodopyrazole (0.426 g, 1.5 mmol) and 4-bromobenzonitrile (0.182 g, 1 mmol), **27** was obtained in 70% (0.270 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 7.74 (d, J = 8.3 Hz, 2H), 7.70 (s, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.30-7.26 (m, 3H), 6.99-6.96 (m 2H), 5.30 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 144.6, 142.9, 136.3, 134.1, 132.4, 130.9, 128.8, 128.1, 126.9, 118.2, 113.3, 54.8.

Elemental analysis: calcd (%) $C_{17}H_{12}IN_3$ for (385.21): C 53.01, H 3.14; found: C 53.28, H 3.01.

1-Benzyl-4-iodo-5-(4-nitrophenyl)pyrazole 28 : From 1-benzyl-4-iodopyrazole (0.426 g, 1.5 mmol) and 4-bromonitrobenzene (0.202 g, 1 mmol), **28** was obtained in 73% (0.296 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.31 (d, J = 8.6 Hz, 2H), 7.72 (s, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.31-7.26 (m, 3H), 7.01-6.98 (m, 2H), 5.32 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 148.2, 144.7, 142.6, 136.3, 135.9, 131.2, 128.9, 128.1, 126.9, 123.9, 123.8, 54.9.

Elemental analysis: calcd (%)$C_{16}H_{12}IN_3O_2$ for (405.20): C 47.43, H 2.99; found: C 47.65, H 3.28.

4-(1-benzyl-4-iodopyrazol-5-yl)benzaldehyde 29 : From 1-benzyl-4-iodopyrazole (0.426 g, 1.5 mmol) and 4-bromobenzaldehyde (0.185 g, 1 mmol), **29** was obtained in 67% (0.260 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 10.09 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.70 (s, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.28-7.25 (m 3H), 7.02-6.98 (m, 2H), 5.31 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 191.3, 144.5, 143.5, 136.6, 136.4, 135.3, 130.8, 130.3, 129.7, 128.7, 127.9, 126.9, 54.7.

Elemental analysis: calcd (%) $C_{17}H_{13}IN_2O$ for (388.21): C 52.60, H 3.38; found: C 52.95, H 3.61.

3-(1-Benzyl-4-iodopyrazol-5-yl)quinoline 30 : From 1-benzyl-4-iodopyrazole (0.426 g, 1.5 mmol) and 3-bromoquinoline (0.208 g, 1 mmol), **30** was obtained in 47% (0.193 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.82 (s, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.05 (s, 1H), 7.89-7.80 (m, 2H), 7.76 (m, 1H), 7.66 (dd, J = 7.2 and 8.3 Hz, 1H), 7.30-7.28 (m, 3H), 7.05-7.00 (m, 2H), 5.36 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 150.6, 148.0, 144.5, 143.2, 141.8, 137.7, 136.5, 130.7, 129.5, 128.8, 128.1, 127.5, 127.1, 127.0, 126.6, 122.8, 54.9.

Elemental analysis: calcd (%) $C_{19}H_{14}IN_3$ for (411.25): C 55.49, H 3.43; found: C 55.78, H 3.11.

2-(1-Benzyl-4-iodopyrazol-5-yl)benzonitrile 31 : From 1-benzyl-4-iodopyrazole (0.426 g, 1.5 mmol) and 2-bromobenzonitrile (0.182 g, 1 mmol), **31** was obtained in 63% (0.243 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 7.79 (d, J = 7.7 Hz, 1H), 7.72 (s, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.29-7.22 (m, 4H), 6.95-6.90 (m, 2H), 5.37 (d, J = 15.5 Hz, 1H), 5.22 (d, J = 15.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 144.3, 141.3, 135.9, 133.4, 133.3, 132.8, 131.8, 130.0, 128.7, 128.0, 127.2, 116.7, 114.4, 55.2.

Elemental analysis: calcd (%) $C_{17}H_{12}IN_3$ for (385.21): C 53.01, H 3.14; found: C 53.32, H 2.86.

1-(4-(1-Methylpyrazol-5-yl)phenyl)propan-1-one 32 : Autoclave was charged with 1-(4-(4-bromo-1-methylpyrazol-5-yl)phenyl)propan-1-one (**4**) (0.293 g, 1 mmol), Et_3N (270 µL; 2 mmol), Pd/C (29 mg, 10% of the weight of the pyrazole derivative) and EtOH (5 mL) and pressurized with hydrogen (3-5 bar). The crude mixture was heated at 70 ℃ during 5 h, and then the reaction was cooled down and filtered in the pad of Celite. After evaporation of the solvent and purification on silica gel **32** was isolated in 94% (0.201 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 8.06 (d, J = 8.2 Hz, 2H), 7,56-7.52 (m, 3H), 6.39 (d, J = 1.9 Hz, 1H), 3.94 (s, 2H), 3.05 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 200.1, 142.6, 138.6, 136.6, 134.9, 128.8, 128.4, 106.7, 37.8, 31.9, 8.2.

This is a known compound and the spectral data are identical to those reported in literature.[5]

4-(1-Benzyl-4-phenylpyrazol-5-yl)benzonitrile 33: A Schlenk tube was charged with 4-(1-benzyl-4-iodopyrazol-5-yl)benzonitrile (**27**) (0.385 g, 1 mmol, 1 equiv.), phenylboronic acid (122 mg, 0.19 mmol, 1 equiv.), K_2CO_3 (0.415 g, 3 mmol, 3 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.002 mmol, 2 mol%) and 2-3 mL of DMA. The resulting solution was stirred under argon atmosphere at 110 ℃ during 15 h. Then, the solution was poured in water/Et_2O (1:1) solution. The organic phase was washed 2 times with water, dried over $MgSO_4$ and concentrated. Then, the residue was purified using flash chromatography to afford **33** in 74% (0.248 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 7.84 (s, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.30-7.27 (m, 3H), 7.26-7.19 (m, 3H), 7.15-7.10 (m, 2H), 7.04-7.00 (m, 2H), 5.27 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ (ppm) = 138.5, 138.1, 136.9, 135.3, 132.5, 132.2, 131.1, 128.8, 128.6, 127.9, 127.6, 126.9, 126.7, 122.5, 118.2, 112.8, 53.8.

Elemental analysis: calcd (%) $C_{23}H_{17}N_3$ for (335.41): C 82.36, H 5.11; found: C 82.71, H 5.32.

4-(1-Benzylpyrazol-5-yl)benzonitrile 34: In a flask equipped with a condenser, compound (**27**) (0.385 g, 1 mmol, 1 equiv.) was boiled in 2 N hydrochloric acid (5 mL) for 15 h. The resulting mixture was cooled, then the solution was poured in saturated solution of K_2CO_3 and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to dryness to yield an oil. Then, the residue was purified using flash chromatography to afford **34** in 86% (0.223 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm) = 7.69 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.35-7.28 (m, 3H), 7.05-7.03 (m, 2H), 6.45 (d, J = 2.0 Hz, 1H), 5.39 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) =142.1, 139.6, 137.0, 135.2, 132.4, 129.4, 128.8, 127.8, 126.6, 118.3, 112.4, 107.5, 53.6.

Elemental analysis: calcd (%) $C_{17}H_{13}N_3$ for (259.31): C 78.74, H 5.05; found: C 78.87, H 4.86.

4-(1-Benzyl-4-(2-ethyl-4-methylthiazol-5-yl)pyrazol-5-yl)benzonitrile 35: A Schlenk tube was charged with 4-(1-benzyl-4-iodopyrazol-5-yl)benzonitrile (**27**) (0.385 g, 1 mmol, 1 equiv.), 2-ethyl-4-methylthiazole (196 µL, 1.5 mmol, 1.5 equiv.), KOAc (0.196 g, 2 mmol, 2 equiv.), $PdCl(C_3H_5)$(dppb) (5 mg, 0.01 mmol, 1 mol%) and 2-3 mL of DMA. The resulting solution was stirred under argon atmosphere at 110 °C during 15 h. Then, the solution was poured in water/Et_2O (1:1) solution. The organic phase was washed 2 times with water, dried over $MgSO_4$ and concentrated. Then, the residue was purified using flash chromatography to afford **35** in 54% (0.208 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm) = 7.72 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.33-7.27 (m, 5H), 7.06-7.02 (m, 2H), 5.29 (s, 2H), 2.91 (q, J = 7.0 Hz, 2H), 2.17 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ (ppm) = 170.9, 148.7, 139.8, 139.2, 136.5, 134.2, 132.5, 130.7, 128.9, 128.7, 128.0, 127.0, 126.9, 120.3, 108.7, 54.1, 29.7, 26.8, 14.1.

Elemental analysis: calcd (%) $C_{23}H_{20}N_4S$ for (384.50): C 71.85, H 5.24; found: C 72.03, H 5.32.

Acknowledgements

We thank the Centre National de la Recherche Scientifique, "Rennes Metropole", "UTIQUE" and Scientific Ministry of Higher Education Research of Tunisia for providing financial support.

Notes and references

[a] Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1 " Organométalliques, Matériaux et Catalyse",Campus de Beaulieu, 35042 Rennes, France. henri.doucet@univ-rennes1.fr

[b] Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, (UR 11ES56Université de Monastir Faculté des Sciences de Monastir, avenue de l'environnement, Monastir 5000, Tunisie.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1. (a) M. J. Fray, P. Allen, P. R. Bradley, C. E. Challenger, M. Closier, T. J. Evans, M. L. Lewis, J. P. Mathias, C. L. Nichols, Y. M. Po-Ba, H. Snow, M. H. Stefaniak and H. V. Vuong, *Heterocycles*, 2006, **67**, 489-494; (b) F. Beaulieu, C. Ouellet, E. H. Ruediger, M. Belema, Y. Qiu, X. Yang, J. Banville, J. R. Burke, K. R. Gregor, J. F. MacMaster, A. Martel, K. W. McIntyre, M. A. Pattoli, F. C. Zusi and D. Vyas, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1233-1237; (c) G. A. Whitlock, K. Conlon, G. McMurray, L. R. Roberts, A. Stobie and R. J. Thurlow, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2930-2934; (d) C. I. Stathakis, S. Bernhardt, V. Quint and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 9428-9432.
2. (a) X. j. Wang, J. Tan and K. Grozinger, *Tetrahedron Lett.*, 2000, **41**, 4713-4716; (b) A. S. Paulson, J. Eskildsen, P. Vedso and M. Begtrup, *J. Org. Chem.*, 2002, **67**, 3904-3907; (c) S. Beltran-Rodil, M. G. Edwards, D. S. Pugh, M. Reid and R. J. K. Taylor, *Synlett*, 2010, 602-606; (d) R. A. Khera, A. Ali, M. Hussain, J. Tatar, A. Villinger and P. Langer, *Synlett*, 2010, 1923-1926; (e) R. A. Khera, A. Ali, H. Rafique, M. Hussain, J. Tatar, A. Saeed, A. Villinger and P. Langer, *Tetrahedron*, 2011, **67**, 5244-5253; (f) Y. L. Janin, *Chem. Rev.*, 2012, **112**, 3924-3958; (g) L. Zhang, A. Villalobos, E. M. Beck, T. Bocan, T. A. Chappie, L. Chen, S. Grimwood, S. D. Heck, C. J. Helal, X. Hou, J. M. Humphrey, J. Lu, M. B. Skaddan, T. J. McCarthy, P. R. Verhoest, T. T. Wager and K. Zasadny, *J. Med. Chem.*, 2013, **56**, 4568-4579; (h) M. P. Winters, N. Subasinghe, M. Wall, E. Beck, M. R. Brandt, M. F. A. Finley, Y. Liu, M. L. Lubin, M. P. Neeper, N. Qin, C. M. Flores and Z. Sui, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2053-2056.
3. For reviews on C–H bond fonctionalizations see: (a) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318-5365; (b) S. Pascual, P. de Mendoza and A. M. Echavarren, *Org. Biomol. Chem.*, 2007, **5**, 2727-2734; (c) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173-1193; (d) F. Bellina, S. Cauteruccio and R. Rossi, *Curr. Org. Chem.*, 2008, **12**, 774-790; (e) F. Kakiuchi and T. Kochi, *Synthesis*, 2008, 3013-3039; (f) B.-J. Li, S.-D. Yang and Z.-J. Shi, *Synlett*, 2008, 949-957; (g) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792-9826; (h) F. Bellina and R. Rossi, *Chem. Rev.*, 2009, **110**, 1082-1146; (i) F. Bellina and R. Rossi, *Tetrahedron*, 2009, **65**, 10269-10310; (j) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094-5115; (k) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147-1169; (l) E. M. Beck and M. J. Gaunt, *Top. Curr. Chem.*, 2010, **292**, 85-121; (m) J. Roger, A. L. Gottumukkala and H. Doucet, *ChemCatChem*, 2010, **2**, 20-40; (n) T. Satoh and M. Miura, *Synthesis*, 2010, 3395-3409; (o) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.*, 2010, **46**, 677-685; (p) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068-5083; (q) D. Zhao, J. You and C. Hu, *Chem. Eur. J.*, 2011, **17**, 5466-5492; (r) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem. Int. Ed.*, 2012, **51**, 10236-10254; (s) B.-J. Li and Z.-J. Shi, *Chem. Soc. Rev.*, 2012, **41**, 5588-5598; (t) M. C. White, *Synlett*, 2012, **23**, 2746-2748; (u) D.-G. Yu, B.-J. Li and Z.-J. Shi, *Tetrahedron*, 2012, **68**, 5130-5136; (v) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886-896; (w) M. He, J.-F. Soulé and H. Doucet, *ChemCatChem*, 2014, **6**, 1824-1859; (x) R. Rossi, F. Bellina, M. Lessi and C. Manzini, *Adv. Synth. Catal.*, 2014, **356**, 17-117; (y) K. Yuan, J.-F. Soulé and H. Doucet, *ACS Catal.*, 2015, **5**, 978-991; (z) P. Christopher, H. Xin and S. Linic, *Nat Chem*, 2011, **3**, 467-472.
4. R. Goikhman, T. L. Jacques and D. Sames, *J. Am. Chem. Soc.*, 2009, **131**, 3042-3048.
5. A. Beladhria, K. Beydoun, H. Ben Ammar, R. Ben Salem and H. Doucet, *Synthesis*, 2011, 2553-2560.
6. F. Bellina, M. Lessi and C. Manzini, *Eur. J. Org. Chem.*, 2013, 5621-5630.
7. S. I. Gorelsky, *Coord. Chem. Rev.*, 2013, **257**, 153-164.
8. E. T. T. Kumpulainen and A. Pohjakallio, *Adv. Synth. Catal.*, 2014, **356**, 1555-1561.
9. C. Mateos, J. Mendiola, M. Carpintero and J. M. Mínguez, *Org. Lett.*, 2010, **12**, 4924-4927.
10. T. Yan, L. Chen, C. Bruneau, P. H. Dixneuf and H. Doucet, *J. Org. Chem.*, 2012, **77**, 7659-7664.
11. I. Smari, C. Youssef, K. Yuan, A. Beladhria, H. Ben Ammar, B. Ben Hassine and H. Doucet, *Eur. J. Org. Chem.*, 2014, 1778-1786.
12. (a) H. Jung, S. Bae, H.-L. Jang and J. M. Joo, *Bull. Korean Chem. Soc.*, 2014, **35**, 3009-3014; (b) V. O. Iaroshenko, A. Gevorgyan, O. Davydova, A. Villinger and P. Langer, *J. Org. Chem.*, 2014, **79**, 2906-2915.
13. S. A. Ohnmacht, A. J. Culshaw and M. F. Greaney, *Org. Lett.*, 2010, **12**, 224-226.
14. A. Takfaoui, L. Zhao, R. Touzani, P. H. Dixneuf and H. Doucet, *Tetrahedron Lett.*, 2014, **55**, 1697-1701.
15. (a) B. Liegault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047-1060; (b) F. Shibahara, E. Yamaguchi and T. Murai, *J. Org. Chem.*, 2011, **76**, 2680-2693; (c) T. Yamauchi, F. Shibahara and T. Murai, *J. Org. Chem.*, 2014, **79**, 7185-7192.
16. (a) D. Roy, S. Mom, S. Royer, D. Lucas, J.-C. Hierso and H. Doucet, *ACS Catal.*, 2012, **2**, 1033-1041; (b) N. Laidaoui, J. Roger, A. Miloudi, D. El Abed and H. Doucet, *Eur. J. Org. Chem.*, 2011, **2011**, 4373-4385; (c) A. Takfaoui, L. Zhao, R. Touzani, P. H. Dixneuf and H. Doucet, *Tetrahedron Lett.*, 2014, **55**, 1697-1701.
17. M. I. Rodriguez-Franco, I. Dorronsoro, A. I. Hernandez-Higueras and G. Antequera, *Tetrahedron Lett.*, 2001, **42**, 863-865.
18. For other examples of pyrazoles debromination see : (a) J. F. Hansen, Y. I. Kim, L. J. Griswold, G. W. Hoelle, D. L. Taylor and D. E. Vietti, *J. Org. Chem.*, 1980, **45**, 76-80; (b) D. R. Sliskovic, B. D. Roth, M. W. Wilson, M. L. Hoefle and R. S. Newton, *J. Med. Chem.*, 1990, **33**, 31-38; (c) X. Zhang, C. Hou, H. Hufnagel, M. Singer, E. Opas, S. McKenney, D. Johnson and Z. Sui, *ACS Med. Chem. Lett.*, 2012, **3**, 1039-1044; (d) T. W. Johnson, P. F. Richardson, S. Bailey, A. Brooun, B. J. Burke, M. R. Collins, J. J. Cui, J. G. Deal, Y.-L. Deng, D. Dinh, L. D. Engstrom, M. He, J. Hoffman, R. L. Hoffman, Q. Huang, R. S. Kania, J. C. Kath, H. Lam, J. L. Lam, P. T. Le, L. Lingardo, W. Liu, M. McTigue, C. L. Palmer, N. W. Sach, T. Smeal, G. L. Smith, A. E. Stewart, S. Timofeevski, H. Zhu, J. Zhu, H. Y. Zou and M. P. Edwards, *J. Med. Chem.*, 2014, **57**, 4720-4744.
19. For other examples of Suzuki Miyaura couplings of halopyrazoles see : (a) S. D. Walker, T. E. Barder, J. R. Martinelli and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2004, **43**, 1871-1876; (b) T. M. Razler, Y. Hsiao, F. Qian, R. Fu, R. K. Khan and W. Doubleday, *J. Org. Chem.*, 2009, **74**, 1381-1384; (c) A. Chartoire, M. Lesieur, L. Falivene, A. M. Z. Slawin, L. Cavallo, C. S. J. Cazin and S. P. Nolan, *Chem. - Eur. J.*, 2012, **18**, 4517-4521, S4517/4511-S4517/4525; (d) E. Salanouve, P. Retailleau and Y. L. Janin, *Tetrahedron*, 2012, **68**, 2135-2140; (e) J. Galeta, L. Tenora, S. Man and M. Potacek, *Tetrahedron*, 2013, **69**, 7139-7146; (f) N. M. Padial, E. Quartapelle Procopio, C. Montoro, E. Lopez, J. E. Oltra, V. Colombo, A. Maspero, N. Masciocchi, S. Galli, I. Senkovska, S. Kaskel, E. Barea and J. A. R. Navarro, *Angew. Chem., Int. Ed.*, 2013, **52**, 8290-8294; (g) V. Pandarus, D. Desplantier-Giscard, G. Gingras, R. Ciriminna, P. Demma Cara, F. Beland and M. Pagliaro, *Tetrahedron Lett.*, 2013, **54**, 4712-4716; (h) S. D. Ramgren, L. Hie, Y. Ye and N. K. Garg, *Org. Lett.*, 2013, **15**, 3950-3953; (i) E. Bratt, O. Verho, M. J. Johansson and J.-E. Baeckvall, *J. Org. Chem.*, 2014, **79**,

3946-3954; (j) J. Tan, Y. Chen, H. Li and N. Yasuda, *J. Org. Chem.*, 2014, **79**, 8871-8876.
20. S. Guillou, F. J. Bonhomme, M. S. Ermolenko and Y. L. Janin, *Tetrahedron*, 2011, **67**, 8451-8457.

Regioselective and Chemoselective Arylations
Simple Catalytic System, Phosphine-free Conditions