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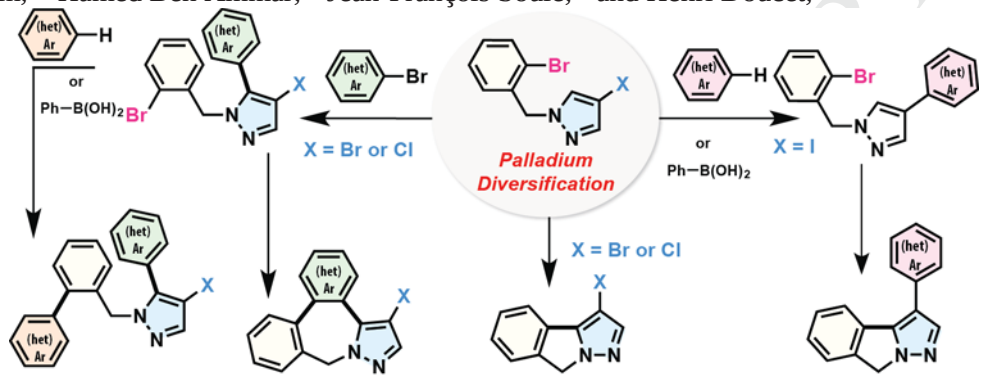

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Reactivity of 1-(2-bromobenzyl)-4-halopyrazoles in intermolecular and intramolecular Pd-Catalysed direct arylations

Mariem Brahim,[a,b] Hamed Ben Ammar,[b*] Jean-François Soulé,[a*] and Henri Doucet,[a*]

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Abstract— The reactivity of 1-(2-bromobenzyl)-4-halopyrazoles in inter- and intra-molecular Pd-catalysed direct arylation was investigated. Conditions allowing the intermolecular C5-arylations of both 1-(2-bromobenzyl)-4-chloropyrazoles and 1-(2-bromobenzyl)-4-bromopyrazoles, without cleavage of the pyrazolyl and benzyl C-halo bonds, are reported. Using KOAc as the base, DMA as the solvent and 2 mol% of an air stable palladium catalyst, the target C5-arylated pyrazoles were obtained in moderate to good yields with a wide variety of aryl bromides. The synthesis of 3-halopyrazolo[5,1-*a*]isoindoles via intramolecular Pd-catalysed direct arylation, without cleavage of the pyrazolyl C-halo bonds is also described. Moreover, sequential Pd-catalysed C5-arylations followed by intramolecular direct arylation allowed the access to dibenzo[*c*,*e*]pyrazolo[1,5-*a*]azepine derivatives. The reactivity of the 2-bromobenzyl moiety of C5-arylated 1-(2-bromobenzyl)-4-halopyrazoles in intermolecular direct arylation or in Suzuki coupling is also described.

1. Introduction

Pyrazole derivatives including those bearing alkyl-, aryl- or halo-substituents are important structures due to their biological properties (Fig 1). For example, Deracoxib and Mavacoxib are non-steroidal anti-inflammatory drugs used in veterinary medicine to treat osteoarthritis in dogs. Afuresertib shows activity in multiple myeloma. Meclinertant is a drug which acts as a selective, non-peptide antagonist at the neurotensin receptor NTS_1. Nelotanserin exhibits properties in neurological diseases. Due to these multiple uses, the discovery of simpler routes for accesses to a variety of alkyl-, aryl- or halo-substituted pyrazoles remains an important research topic in organic synthesis.

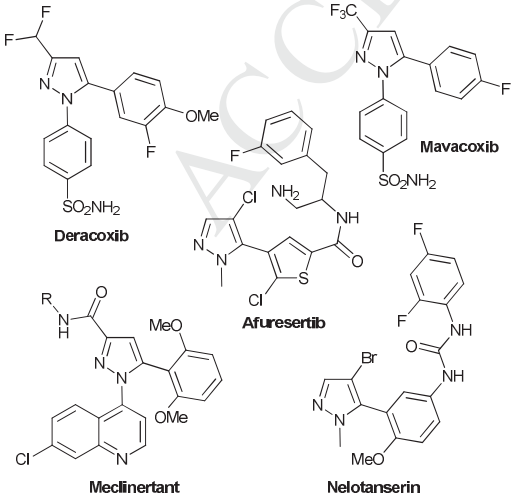
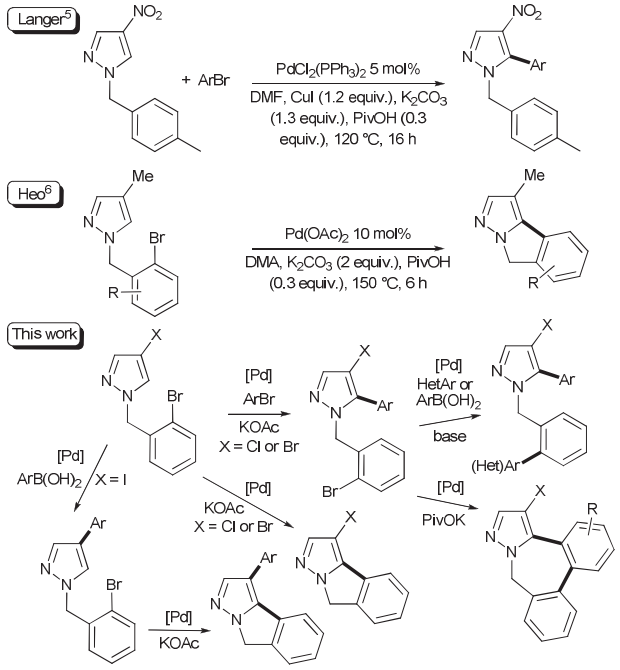


Figure 1. Examples of bioactive 5-(hetero)arylpyrazoles

Stille, Suzuki or Negishi Pd-catalysed coupling reactions represent some of the most efficient methods to prepare (hetero)arylpyrazoles; however, such reactions require the previous preparation of an organometallic derivative.[1] In 1985, Ohta et al. reported the Pd-catalysed direct arylation of heteroaromatics *via* a C–H bond activation using aryl halides as arylating agents.[2] Since these results, this methodology proved to be a very powerful tool for a simpler and greener access to a very wide variety of arylated heterocycles, as it avoids the preparation of an organometallic derivative and as the major by-products of the reaction are a base associated to HX.[3] Several examples of Pd-catalysed direct arylations of pyrazoles using aryl halides as coupling partners have been reported in recent years.[4] However, to our knowledge, only a few examples of such arylations dealing with the reactivity of *N*-benzylpyrazoles have been described.[5,6] In 2014, the C5-arylation of a 4-nitro-*N*-benzylpyrazole has been reported by Langer et al. (Scheme 1, top).[5] The introduction of a nitro-substituent at pyrazolyl C4-position allowed to control the regioselectivity of the reaction. The intramolecular Pd-catalysed direct arylation of 1-(2-bromobenzyl)-pyrazoles for the synthesis of pyrazolo[5,1-a]isoindoles has been reported by Heo et al. (Scheme 1, middle).[6] They observed that the use of 10 mol% of $Pd(OAc)_2$ catalyst promotes this intramolecular reaction. So far, only a few examples of Pd-catalysed direct C5-arylations of 4-halo-substituted pyrazoles have been reported.[7]

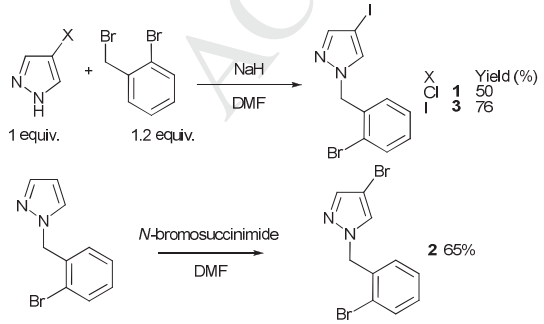


Scheme 1.

To our knowledge, Pd-catalysed direct inter- or intramolecular arylations using 1-(2-bromobenzyl)-4-halopyrazoles have not been described. Therefore, their reactivity needed to be investigated. Here, we wish to report conditions allowing the sequential C5-arylation of such 1-(2-bromobenzyl)-4-halopyrazoles, without cleavage of the pyrazolyl and benzyl C-halo bonds, followed by i) heteroarylation of the benzyl unit via an intermolecular Pd-catalysed reaction, ii) arylation of the benzyl unit via Suzuki coupling, iii) intramolecular Pd-catalysed direct arylation for access to dibenzo[*c*,*e*]pyrazolo[1,5-*a*]azepines. The reactivity of 1-(bromobenzyl)-4-halopyrazoles in intramolecular Pd-catalysed direct arylation is also reported.

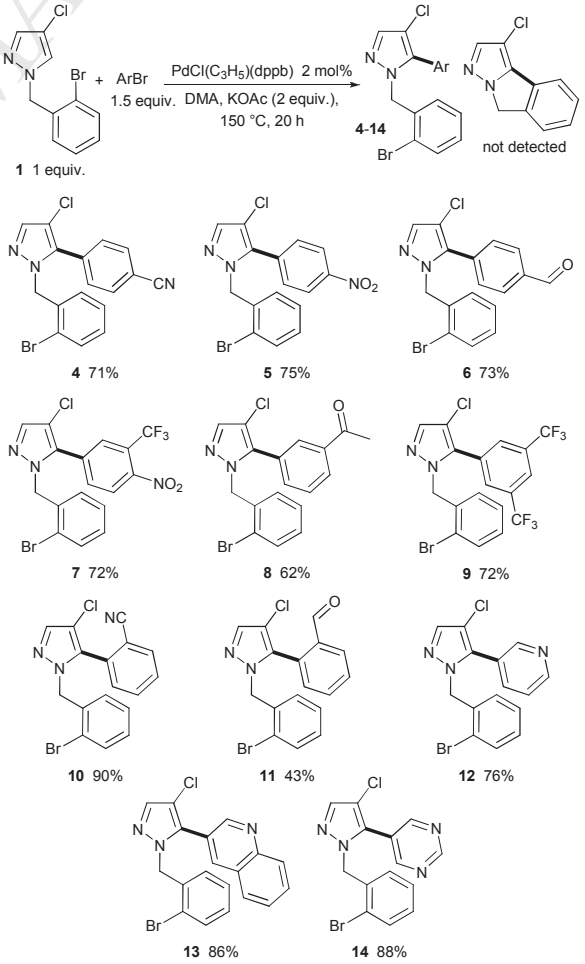
2. Results and discussion

The 1-(2-bromobenzyl)-4-halopyrazoles **1** and **3** were prepared by reaction of 4-chloropyrazole or 4-iodopyrazole with 2-bromobenzyl bromide (Scheme 2, top). Compound **2** was prepared by reaction of 1-(2-bromobenzyl)-pyrazole with *N*-bromosuccinimide (Scheme 2, bottom).



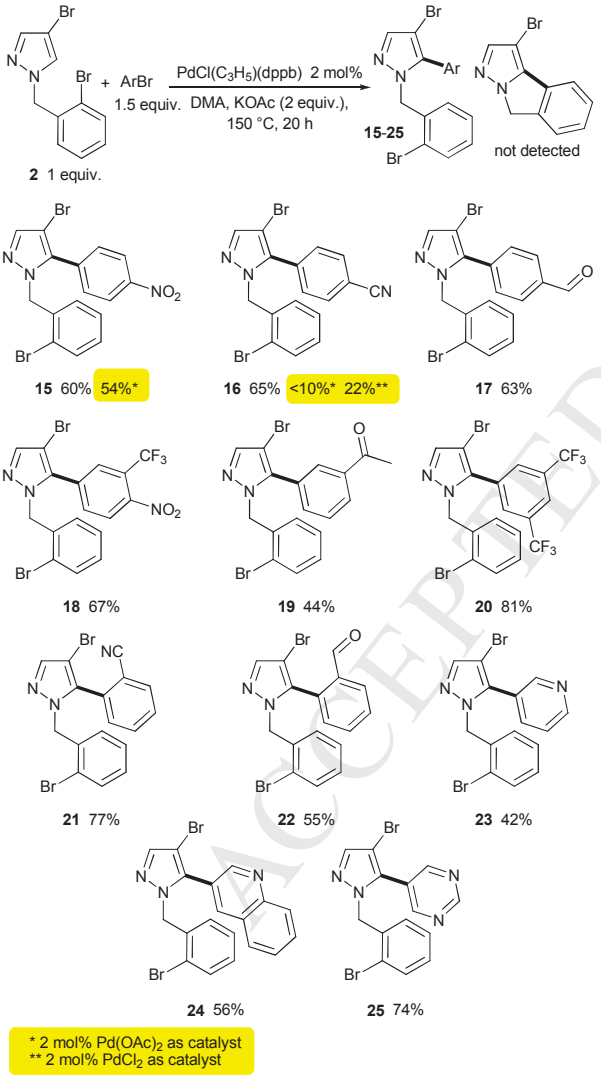
Scheme 2. Synthesis of the 1-(2-bromobenzyl)-4-halopyrazoles **1-3**.

Then, the reactivity of **1-3** in both inter- and intramolecular Pd-catalysed direct arylations was investigated. Firstly, we studied the intermolecular reaction of **1-3** with aryl bromides (Schemes 3-5). Based on our previous results, DMA was chosen as the solvent and KOAc as the base.[8] The reactions were conducted at 150 °C under argon using $PdCl(C_3H_5)$(dppb) catalyst. The reaction of 1 equiv. of 1-(2-bromobenzyl)-4-chloropyrazole **1** with 1.5 equiv. of 4-bromobenzonitrile affords the desired C5-arylated pyrazoles **4** in 71% yield (Scheme 3). Both $Pd(OAc)_2$ and $PdCl_2$ catalysts (2 mol%) were found to be completely ineffective for this reaction. It should be mentioned that no intramolecular direct arylation of **1** was observed and that both C-Cl and C-Br bonds of **1** remained untouched. A similar reactivity was observed in the presence of 4-bromonitrobenzene, 4-bromobenzaldehyde, 4-bromo-1-nitro-2-(trifluoromethyl)benzene, 3-bromoacetophenone or 3,5-bis(trifluoromethyl)bromobenzene with the formation of compounds **5-9** in 62-75% yields. A very high yield of 90% in **10** was obtained for the coupling of **1** with 2-bromobenzonitrile; whereas, the use of 2-bromobenzaldehyde gave **11** in only 43%, due to the formation of side products. The reaction proceeds very smoothly with 3-bromopyridine, 3-bromoquinoline and also 5-bromopyrimidine affording the products **12-14** in 76-88% yields.



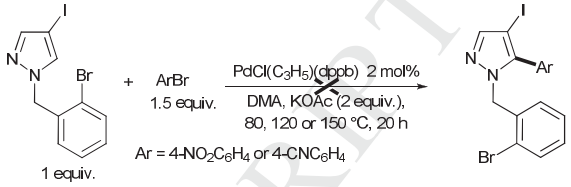
Scheme 3. Reactivity of 1-(2-bromobenzyl)-4-chloropyrazole **1** with (hetero)aryl bromides.

Then, the reactivity of 1-(2-bromobenzyl)-4-bromopyrazole **2** in intermolecular C5-arylation was explored using 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst, KOAc as base in DMA at 150 °C (Scheme 4). From a set of electron-deficient aryl bromides, the C5-arylated pyrazoles **15-25** were obtained in moderate to high yields. The reaction tolerates *para*-, *meta*- and *ortho*-substituted aryl bromides and also heteroaryl bromides. Again, no formation of cyclized product *via* intramolecular Pd-catalysed direct arylation of **2** was observed. Moreover, although a quite elevated temperature was employed for these couplings, no cleavage of the pyrazolyl C-Br bond was detected. The reactivity of **2** with 4-bromonitrobenzene or 4-bromobenzonitrile using 2 mol% $Pd(OAc)_2$ or $PdCl_2$ catalysts was also investigated. However, **15** and **16** were obtained in lower yields than in the presence of $PdCl(C_3H_5)(dppb)$ catalyst.



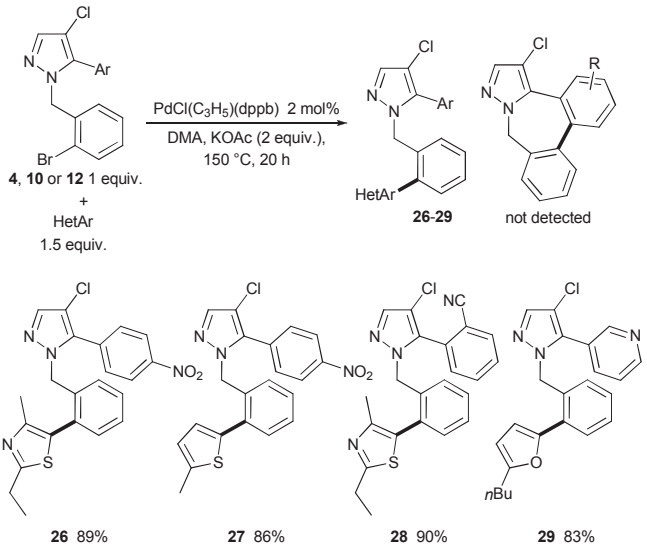
Scheme 4. Reactivity of 1-(2-bromobenzyl)-4-bromopyrazole **2** with (hetero)aryl bromides.

If both 4-chloro- and 4-bromo-subtituents on *N*-(2-bromobenzyl)pyrazoles are tolerated in Pd-catalysed intermolecular direct C5-arylation; on the other hand, a mixture of the 4-iodo-substituted pyrazole **3** and 4-bromobenzonitrile or 4-bromonitrobenzene failed to afford the desired C5-arylated pyrazoles (Scheme 5). At 150°C or 120°C, a large amount of de-iodination side-product was observed via GC/MS analysis; whereas, at 80°C, **3** was recovered.



Scheme 5. Reactivity of 1-(2-bromobenzyl)-4-iodopyrazole **3** with aryl bromides.

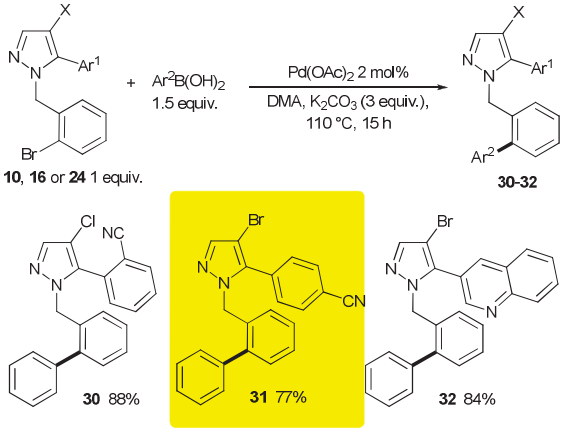
The reactivity of the 2-bromobenzyl moiety in intermolecular Pd-catalysed arylation with an heteroarene was then studied (Scheme 6). The reaction of 1-(2-bromobenzyl)-4-chloro-5-(4-nitrophenyl)-pyrazole **4** and 2-ethyl-4-methylthiazole in the presence of 2 mol% $PdCl(C_3H_5)(dppb)$ gave **26** in 89% yield. A similar result was observed with 2-methylthiophene as reaction partner, and **27** was produced in 86% yield. The 1-(2-bromobenzyl)-pyrazole **10** bearing a benzonitrile at C5-position also reacted nicely with 2-ethyl-4-methylthiazole affording **28** in 90% yield. A slightly lower yield of 83% in **29** was obtained from a pyrazole substituted at C5 by a pyridine and 2-*n*-butylfuran. In all cases, no intramolecular reaction with activation of a C-H bond of the nitrophenyl, benzonitrile or pyridyl moieties was observed, and again the pyrazolyl C-Cl bond remained untouched.



Scheme 6. Reactivity of C5-arylated 1-(2-bromobenzyl)-4-chloropyrazoles **4**, **10** and **12** with heteroarenes.

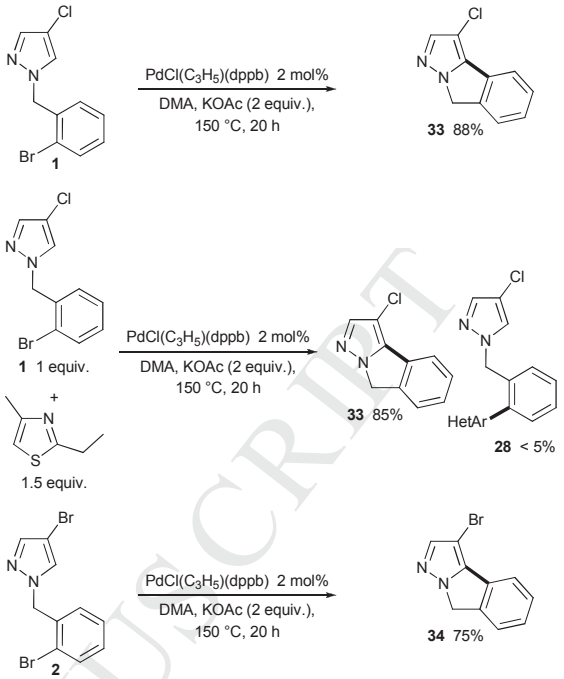
The reactivity of the two C5-arylated 1-(2-bromobenzyl)-4-chloropyrazoles **10** and **24** in Suzuki type coupling was

also evaluated (Scheme 7). From **10** and phenylboronic acid in the presence of 2 mol% $Pd(OAc)_2$, the desired product **30** was obtained in 88% yield. No cleavage of the pyrazolyl C-Cl bonds was observed. Similar results were obtained from **16** and **24**, as the desired compounds **31** and **32** were isolated in 77% and 84% yield, respectively. These results reveal that in **16** and **24**, the benzyl C-Br bond is more reactive than the pyrazolyl C-Br bond.



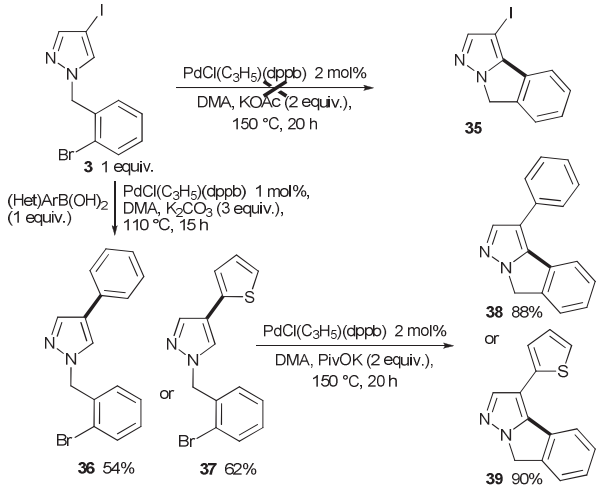
Scheme 7. Reactivity of C5-arylated 1-(2-bromobenzyl)-4-halopyrazoles **10** and **24** with arylboronic acids.

The intramolecular Pd-catalysed direct arylation using **1-3** for the formation of 5-membered rings was also attempted (Scheme 8). 4-Chloro-substituted pyrazole **1** reacts nicely in the presence of 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst affording **32** in 88% yield. In order to determine the reactivity of **1** in intermolecular *vs* intramolecular direct arylation, the reaction outcome of a mixture of **1** and 2-ethyl-4-methylthiazole in the presence of 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst was studied. An almost exclusive formation of the intramolecular reaction product **33** was observed. A good yield in desired cyclised product **34** was obtained from the 4-bromo-substituted pyrazole **2**. Moreover, the pyrazoly C-Br bond remained untouched. Again, the oxidative addition of the benzyl C-Br bond to palladium appears to be faster than the pyrazoly C-Br bond.



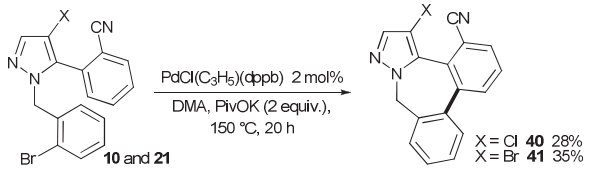
Scheme 8. Reactivity of 1-(2-bromobenzyl)-4-halopyrazoles **1** and **2** in Pd-catalysed intramolecular arylation.

On the other hand, from the 4-iodo-substituted pyrazole **3**, under the same reaction conditions, no formation of the desired cyclised product **35** was observed in GC/MS analysis of the crude mixture (Scheme 9). As in **3**, pyrazolyl C-I bond should exhibit a higher reactivity than the benzyl C-Br bond, it was employed to introduce (hetero)aryls substituents at C4. The reaction of **3** with phenylboronic acid or 2-thienylboronic acid in the presence of 1 mol% $PdCl(C_3H_5)(dppb)$ affords **36** and **37** in 54% and 62% yields, respectively. Then, intramolecular Pd-catalysed arylation of **36** and **37** gave the 3-(hetero)arylpyrazolo[5,1-*a*]isoindoles **38** and **39** in almost quantitative yields. It should be mentioned that no intermolecular Pd-catalysed arylation involving a C-H bond of the thienyl moiety of **36** was observed.



Scheme 9. Reactivity of 1-(2-bromobenzyl)-4-iodopyrazole **3** in Pd-catalysed intramolecular arylation.

Finally, the intramolecular Pd-catalysed direct arylation of the two C5-arylated 1-(2-bromobenzyl)-4-halopyrazoles **10** and **21**, in order to prepare dibenzo[*c*,*e*]pyrazolo[1,5-*a*]azepine derivatives, *via* the formation of a 7-membered ring, was attempted (Scheme 10). It should be mentioned that, to our knowledge, such structures have not yet been described, revealing that their access is quite challenging. The reaction of **10** in the presence of 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst and PivOK as base led to the target product **40** in 28% yield. For this reaction the use of KOAc as base was ineffective. A similar influence of the nature of the base had been previously observed in the Pd-catalysed intramolecular direct arylation of imidazole derivatives.[9] A slightly higher yield of 35% in **41** was obtained from the 4-bromosubstituted pyrazole derivative **21**. Even if the yields of these two reactions are moderate, this is the first method allowing the preparation of this type of dibenzopyrazoloazepine derivatives.



Scheme 10. Reactivity of 1-(2-bromobenzyl)-4-halopyrazoles **10** and **21** in Pd-catalysed intramolecular arylation.

Conclusion

We established that under appropriate reaction conditions, the intermolecular palladium-catalysed C5-arylation of 1-(2-bromobenzyl)-4-chloropyrazole **1** or 1-(2-bromobenzyl)-4-bromopyrazole **2** proceeds nicely, without cleavage of both pyrazolyl and benzyl C-halo bonds. A wide variety of aryl bromides was successfully employed. On the other hand, with 1-(2-bromobenzyl)-4-iodopyrazole **3**, degradation products were formed. The synthesis of 3-halopyrazolo[5,1-*a*]isoindoles (with halo = Br or Cl) via intramolecular Pd-catalysed direct arylation, without cleavage of the pyrazolyl C-halo bonds, was also found to proceed in high yields. The sequential Pd-catalysed C5-arylation followed by intramolecular direct arylation allowed the preparation of dibenzo[*c*,*e*]pyrazolo[1,5-*a*]azepine derivatives. The intermolecular direct arylation or Suzuki coupling of the 2-bromobenzyl moiety of C5-arylated 1-(2-bromobenzyl)-4-halopyrazoles is also reported. These results demonstrate that the use of an appropriate C4-halo substituent associated to a 2-bromobenzyl moiety on pyrazoles allows to prepare a wide variety of pyrazoles derivatives via successive inter- or intra-molecular Pd-catalysed couplings.

Acknowledgments

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.

Experimental section

General Remarks: All catalytic reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA (*N*,*N*-dimethylacetamide) (99%) was purchased from Acros. KOAc (99%) was purchased from Alfa Aesar. These compounds were not purified before use. The 4-halopyrazoles were prepared from NCS, NBS or I_2 and pyrazoles according to reported procedures.[10] ^{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.

1-(2-Bromobenzyl)-4-chloropyrazole (1) 4-Chloropyrazole (1.02 g, 10 mmol), 2-bromobenzylbromide (3.00 g, 12 mmol) and NaH (0.24 g, 10 mmol) in DMF (50 mL) were stirred at 0°C during 14 h. The mixture was poured on ice, extracted with ethyl acetate, dried over $MgSO_4$ and filtered. After concentration in vacuum, the residue was purified by flash-chromatography on silica gel to afford **1** in 50% (1.36 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 1H), 7.47 (s, 1H), 7.42 (s, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 135.3, 133.1, 130.0, 129.9, 128.0, 127.8, 123.2, 110.4, 56.4.

4-Bromo-1-(2-bromobenzyl)-pyrazole (2) 1-(2-bromobenzyl)-pyrazole (2.37 g, 10 mmol) and *N*-bromosuccinimide (2.14, 12 mmol) in MeCN (50 mL) were stirred at 25°C during 3 h. The mixture was poured on ice, extracted with ethyl acetate, dried over $MgSO_4$ and filtered. After concentration in vacuum, the residue was purified by flash-chromatography on silica gel to afford **2** in 65% (2.05 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 1H), 7.51 (s, 1H), 7.47 (s, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 5.39 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 135.5, 133.3, 130.3, 130.2 (x2), 128.3, 123.5, 93.8, 56.6.

1-(2-Bromobenzyl)-4-iodopyrazole (3) 4-Iodopyrazole (1.94 g, 10 mmol), 2-bromobenzylbromide (3.00 g, 12 mmol) and NaH (0.24 g, 10 mmol) in DMF (50 mL) were stirred at 0°C during 14 h. The mixture was poured on ice, extracted with ethyl acetate, dried over $MgSO_4$ and filtered. After concentration in vacuum, the residue was purified by flash-chromatography on silica gel to afford **3** in 76% (2.76 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2

Hz, 1H), 7.57 (s, 1H), 7.50 (s, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.42 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 135.6, 134.5, 133.3, 130.2, 128.2, 123.5, 56.4.

Preparation of the PdCl(C_3H_5)(dppb) catalyst:[11] An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for the preparation of 4-25: The reaction of the 4-halopyrazole derivative (1 mmol), aryl bromide (1.5 mmol), and KOAc (0.196 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of PdCl(C_3H_5)(dppb) (12.2 mg, 0.02 mmol) under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

4-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)benzonitrile (4) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 4-bromobenzonitrile (0.273 g, 1.5 mmol) product **4** was obtained in 71% (0.264 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.5, 135.8, 133.0, 132.7, 132.2, 130.3, 129.7, 128.4, 128.1, 122.0, 118.3, 113.3, 110.3, 54.6. $C_{17}H_{11}BrClN_3$ (372.65): Calcd C 54.79, H 2.98; Found C 54.70, H 3.10.

1-(2-Bromobenzyl)-4-chloro-5-(4-nitrophenyl)-pyrazole (5) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 4-bromonitrobenzene (0.303 g, 1.5 mmol) product **5** was obtained in 75% (0.294 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 139.0, 138.6, 136.1, 134.4, 133.4, 130.9, 130.1, 128.7, 128.4, 124.5, 122.3, 110.9, 55.0. $C_{16}H_{11}BrClN_3O_2$ (392.63): Calcd C 48.94, H 2.82; Found C 48.78, H 2.74.

4-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)benzaldehyde (6) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 4-bromobenzaldehyde (0.278 g, 1.5 mmol) product **6** was obtained in 73% (0.273 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.67 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 139.2, 138.6, 136.7, 136.0, 133.5, 133.0, 130.3, 130.1, 129.6, 128.4, 128.0, 122.0, 110.2, 54.6. $C_{17}H_{12}BrClN_2O$ (375.65): Calcd C 54.35, H 3.22; Found C 54.40, H 3.04.

1-(2-Bromobenzyl)-4-chloro-5-(4-nitro-3-(trifluoromethyl)phenyl)-pyrazole (7) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 4-bromo-1-nitro-2-(trifluoromethyl)benzene (0.405 g, 1.5 mmol) product **7** was obtained in 72% (0.331 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.69 (s, 2H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 138.6, 136.7, 135.4, 134.0, 133.2, 132.7, 130.0, 129.1 (q, *J* = 5.4 Hz), 128.5, 128.2, 125.8, 124.5 (q, *J* = 34.5 Hz), 122.0, 121.5 (q, *J* = 273.0 Hz), 111.1, 54.9. $C_{17}H_{10}BrClF_3N_3O_2$ (460.63): Calcd C 44.33, H 2.19; Found C 44.14, H 2.12.

1-(3-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)phenyl)ethanone (8) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 3-bromoacetophenone (0.299 g, 1.5 mmol) product **8** was obtained in 62% (0.241 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dm, *J* = 3.8 Hz, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 7.59-7.48 (m, 3H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.34 (s, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 139.5, 138.4, 137.7, 136.3, 134.0, 132.9, 129.6, 129.5, 129.4, 129.1, 128.4, 128.2, 128.1, 121.9, 109.9, 54.5, 26.6. $C_{18}H_{14}BrClN_2O$ (389.67): Calcd C 55.48, H 3.62; Found C 55.36, H 3.47.

5-(3,5-Bis(trifluoromethyl)phenyl)-1-(2-bromobenzyl)-4-chloropyrazole (9) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 3,5-bis(trifluoromethyl)bromobenzene (0.440 g, 1.5 mmol) product **9** was obtained in 72% (0.347 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.69 (s, 1H), 7.68 (s, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.1, 135.4, 133.0, 132.3 (q, *J* = 33.9 Hz), 129.8, 129.7, 129.6 (m), 128.5, 128.0, 122.6 (q, *J* = 273.0 Hz), 123.1 (m), 121.9, 110.7, 54.7. $C_{18}H_{10}BrClF_6N_2$ (483.63): Calcd C 44.70, H 2.08; Found C 44.89, H 2.32.

2-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)benzonitrile (10) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 2-bromobenzonitrile (0.273 g, 1.5 mmol) product **10** was obtained in 90% (0.335 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.69 (s, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.40 (d, *J* = 16.1 Hz, 1H), 5.31 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 138.4, 137.0, 135.6, 133.8, 133.3, 132.9, 131.7, 131.5, 130.4, 129.8, 129.3, 128.3, 122.4, 117.1, 114.4, 112.0, 54.9. $C_{17}H_{11}BrClN_3$ (372.65): Calcd C 54.79, H 2.98; Found C 54.99, H 3.14.

2-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)benzaldehyde (11) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 2-bromobenzaldehyde (0.278 g, 1.5 mmol) product **11** was obtained in 43% (0.161 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.70-7.58 (m, 3H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.30-7.27 (m, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.36 (d, *J* = 15.9 Hz, 1H), 5.23 (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 137.6, 136.4, 135.2, 134.5, 134.0, 132.6, 131.1, 130.3, 129.9, 129.4, 128.9, 128.6, 127.6, 122.2, 111.7, 54.3. $C_{17}H_{12}BrClN_2O$ (375.65): Calcd C 54.35, H 3.22; Found C 54.24, H 3.00.

3-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)pyridine (12) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 3-bromopyridine (0.237 g, 1.5 mmol) product **12** was obtained in 76% (0.264 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (bs, 1H), 8.57 (s, 1H), 7.68 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.37 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 150.4, 138.8, 137.6, 137.3, 136.2, 133.3, 129.9, 128.7, 128.4, 124.4, 124.0, 122.3, 110.8, 54.9. $C_{15}H_{11}BrClN_3$ (348.62): Calcd C 51.68, H 3.18; Found C 51.42, H 3.30.

3-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)quinoline (13) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 3-bromoquinoline (0.312 g, 1.5 mmol) product **13** was obtained in 86% (0.342 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.07 (s, 1H), 7.82-7.77 (m, 2H), 7.71 (s, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 148.0, 138.5, 137.4, 137.1, 136.0, 132.9, 130.9, 129.6, 126.5, 128.5, 128.3, 128.0, 127.6, 127.3, 122.0, 121.0, 110.7, 54.6. $C_{19}H_{13}BrClN_3$ (398.68): Calcd C 57.24, H 3.29; Found C 57.04, H 3.07.

5-(1-(2-Bromobenzyl)-4-chloropyrazol-5-yl)pyrimidine (14) From 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and 5-bromopyrimidine (0.239 g, 1.5 mmol) product **14** was obtained in 88% (0.307 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.67 (s, 2H), 7.70 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 156.7, 138.4, 135.1, 133.7, 132.9, 129.6, 128.2, 127.9, 122.6, 121.8, 111.1, 54.5. $C_{14}H_{10}BrClN_4$ (349.61): Calcd C 48.10, H 2.88; Found C 48.32, H 2.71.

4-Bromo-1-(2-bromobenzyl)-5-(4-nitrophenyl)-pyrazole (15) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 4-bromonitrobenzene (0.303 g, 1.5 mmol) product **15** was obtained in 60% (0.262 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 140.5, 139.6, 135.5, 134.3, 132.7, 130.5, 129.4, 128.1, 127.8, 123.8, 121.7, 94.9, 54.4. $C_{16}H_{11}Br_2N_3O_2$ (437.08): Calcd C 43.97, H 2.54; Found C 43.80, H 2.41.

4-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)benzonitrile (16) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 4-bromobenzonitrile (0.273 g, 1.5 mmol) product **16** was obtained in 65% (0.271 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 139.9, 135.5, 132.7, 132.4, 132.3, 130.1, 129.3, 128.1, 127.7, 121.7, 117.9, 113.1, 94.7, 54.3. $C_{17}H_{11}Br_2N_3$ (417.10): Calcd C 48.95, H 2.66; Found C 48.99, H 2.48.

4-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)benzaldehyde (17) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 4-bromobenzaldehyde (0.278 g, 1.5 mmol) product **17** was obtained in 63% (0.265 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.70 (s, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 141.0, 140.9, 136.8, 136.2, 134.2, 133.1, 130.6, 130.2, 129.7, 128.6, 128.2, 122.1, 95.0, 54.8. $C_{17}H_{12}Br_2N_2O$ (420.10): Calcd C 48.60, H 2.88; Found C 48.41, H 2.64.

4-Bromo-1-(2-bromobenzyl)-5-(4-nitro-3-(trifluoromethyl)phenyl)-pyrazole (18) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 4-bromo-1-nitro-2-(trifluoromethyl)benzene (0.405 g, 1.5 mmol) product **18** was obtained in 67% (0.338 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.72 (s, 1H), 7.67 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.38 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 141.1, 138.7, 135.7, 134.6, 133.5, 133.4, 130.3, 129.7 (q, *J* = 5.3 Hz), 128.9, 128.5, 126.1, 124.8 (q, *J* = 34.6 Hz), 122.4, 121.9 (q, *J* = 274.0 Hz), 96.1, 55.3. $C_{17}H_{10}Br_2F_3N_3O_2$ (505.08): Calcd C 40.43, H 2.00; Found C 40.54, H 1.88.

1-(3-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)phenyl)ethanone (19) From 1-(2-bromobenzyl)-4-

bromopyrazole **2** (0.315 g, 1 mmol) and 3-bromoacetophenone (0.299 g, 1.5 mmol) product **19** was obtained in 44% (0.191 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.57-7.47 (m, 3H), 7.26 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 5.35 (s, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 141.4, 140.8, 137.9, 136.6, 134.5, 133.2, 130.1, 129.8, 129.7, 129.5, 129.0, 128.8, 128.4, 122.2, 94.9, 54.9, 26.9. $C_{18}H_{14}Br_2N_2O$ (434.12): Calcd C 49.80, H 3.25; Found C 49.99, H 3.35.

5-(3,5-Bis(trifluoromethyl)phenyl)-4-bromo-1-(2-bromobenzyl)-pyrazole (20) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 3,5-bis(trifluoromethyl)bromobenzene (0.440 g, 1.5 mmol) product **20** was obtained in 81% (0.427 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.70 (s, 1H), 7.66 (s, 2H), 7.49 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 138.9, 135.5, 133.1, 132.5 (q, J = 33.9 Hz), 130.4, 130.0 (m), 129.9, 128.7, 128.1, 123.3 (m), 123.0 (q, J = 273.0 Hz), 122.1, 95.5, 54.9. $C_{18}H_{10}Br_2F_6N_2$ (528.08): Calcd C 40.94, H 1.91; Found C 41.10, H 2.04.

2-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)benzonitrile (21) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 2-bromobenzonitrile (0.273 g, 1.5 mmol) product **21** was obtained in 77% (0.321 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 1H), 7.69 (s, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.42 (d, J = 16.1 Hz, 1H), 5.33 (d, J = 16.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.4, 133.6, 133.1, 132.8, 131.9, 131.6, 130.3, 129.7, 129.2, 128.1, 122.3, 116.9, 114.4, 96.6, 54.8. $C_{17}H_{11}Br_2N_3$ (417.10): Calcd C 48.95, H 2.66; Found C 48.87, H 2.70.

2-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)benzaldehyde (22) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 2-bromobenzaldehyde (0.278 g, 1.5 mmol) product **22** was obtained in 55% (0.231 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.70 (s, 1H), 7.69-7.58 (m, 2H), 7.42 (d, J = 8.2 Hz, 1H), 7.30-7.27 (m, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 5.37 (d, J = 15.9 Hz, 1H), 5.24 (d, J = 15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 139.8, 138.3, 135.3, 134.6, 134.1, 132.8, 131.3, 130.7, 130.4, 129.6, 129.1, 128.7, 127.8, 122.3, 96.9, 54.5. $C_{17}H_{12}Br_2N_2O$ (420.10): Calcd C 48.60, H 2.88; Found C 48.78, H 2.98.

3-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)pyridine (23) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 3-bromopyridine (0.237 g, 1.5 mmol) product **23** was obtained in 42% (0.165 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (bs, 1H), 8.56 (bs, 1H), 7.70 (s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.37 (dd, J = 7.7, 4.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 150.5, 141.0, 139.3, 137.6, 136.3, 133.3, 129.9, 128.8, 128.4, 125.0, 124.0, 122.4, 95.6, 54.9. $C_{15}H_{11}Br_2N_3$ (393.07): Calcd C 45.83, H 2.82; Found C 45.71, H 2.59.

3-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)quinoline (24) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 3-bromoquinoline (0.312 g, 1.5 mmol) product **24** was obtained in 56% (0.248 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.07 (s, 1H), 7.82-7.77 (m, 2H), 7.71 (s, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 5.41 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 148.3, 140.9, 139.4, 137.6, 136.3, 133.2, 131.2, 129.9, 129.8, 128.8, 128.6, 128.4, 127.9, 127.6, 122.4, 121.9, 95.8, 55.0. $C_{19}H_{13}Br_2N_3$ (443.13): Calcd C 51.50, H 2.96; Found C 51.31, H 2.74.

5-(4-Bromo-1-(2-bromobenzyl)-pyrazol-5-yl)pyrimidine (25) From 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and 5-bromopyrimidine (0.239 g, 1.5 mmol) product **25** was obtained in 74% (0.291 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.66 (s, 2H), 7.72 (s, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 156.9, 140.5, 135.4, 135.1, 132.8, 129.6, 128.3, 127.9, 123.1, 121.8, 95.8, 54.5. $C_{14}H_{10}Br_2N_4$ (394.06): Calcd C 42.67, H 2.56; Found C 42.78, H 2.40.

General procedure for the preparation of 26-29: The reaction of the 1-(2-bromobenzyl)-4-chloro-5-arylpyrazole derivative (1 mmol), heteroarene (1.5 mmol), and KOAc (0.196 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

5-(2-((4-Chloro-5-(4-nitrophenyl)-pyrazol-1-yl)methyl)phenyl)-2-ethyl-4-methylthiazole (26) From 1-(2-bromobenzyl)-4-chloro-5-(4-nitrophenyl)-pyrazole **4** (0.392 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.191 g, 1.5 mmol) product **26** was obtained in 89% (0.390 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.2 Hz, 2H), 7.62 (s, 1H), 7.40-7.20 (m, 5H), 6.97 (d, J = 8.2 Hz, 1H), 5.17 (s, 2H), 2.94 (q, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.35 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 149.2, 148.2, 138.5, 138.0, 136.2, 134.1, 132.1, 130.6,

130.2, 129.5, 128.3, 127.7, 127.1, 124.1, 110.6, 52.9, 27.1, 15.6, 14.3. $C_{22}H_{19}ClN_4O_2S$ (438.93): Calcd C 60.20, H 4.36; Found C 60.34, H 4.18.

4-Chloro-1-(2-(5-methylthiophen-2-yl)benzyl)-5-(4-nitrophenyl)-pyrazole (27) From 1-(2-bromobenzyl)-4-chloro-5-(4-nitrophenyl)-pyrazole **4** (0.392 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) product **27** was obtained in 86% (0.352 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.2 Hz, 2H), 7.64 (s, 1H), 7.34-7.24 (m, 5H), 7.00 (t, J = 7.8 Hz, 1H), 6.66-6.62 (m, 1H), 6.56 (d, J = 3.3 Hz, 1H), 5.42 (s, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 140.7, 138.0, 137.9, 137.5, 134.2, 133.8, 133.1, 130.8, 130.1, 128.1, 127.8, 127.3, 126.8, 125.3, 123.6, 110.1, 52.3, 15.1. $C_{21}H_{16}ClN_3O_2S$ (409.89): Calcd C 61.53, H 3.93; Found C 61.64, H 3.75.

2-(4-Chloro-1-(2-(2-ethyl-4-methylthiazol-5-yl)benzyl)-pyrazol-5-yl)benzonitrile (28) From 2-(1-(2-bromobenzyl)-4-chloropyrazol-5-yl)benzonitrile **10** (0.373 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.191 g, 1.5 mmol) product **28** was obtained in 90% (0.376 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.19 (d, J = 15.9 Hz, 1H), 5.06 (d, J = 15.9 Hz, 1H), 2.96 (q, J = 7.6 Hz, 2H), 1.95 (s, 3H), 1.37 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 148.6, 137.7, 136.2, 135.6, 133.2, 132.6, 131.4, 131.1, 130.9, 129.7, 129.6, 129.1, 127.7, 127.5, 126.8, 116.5, 113.8, 111.4, 52.4, 26.7, 15.0, 13.9. $C_{23}H_{19}ClN_4S$ (418.94): Calcd C 65.94, H 4.57; Found C 65.87, H 4.41.

3-(1-(2-(5-Butylfuran-2-yl)benzyl)-4-chloropyrazol-5-yl)pyridine (29) From 3-(1-(2-bromobenzyl)-4-chloropyrazol-5-yl)pyridine **12** (0.348 g, 1 mmol) and 2-butylfuran (0.186 g, 1.5 mmol) product **29** was obtained in 83% (0.324 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (bs, 1H), 8.56 (bs, 1H), 7.67 (s, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.35-7.24 (m, 2H), 7.20 (t, J = 7.8 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 6.02 (d, J = 3.2 Hz, 1H), 5.52 (s, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.60 (quint., J = 7.6 Hz, 2H), 1.34 (sext., J = 7.6 Hz, 2H), 0.91 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 150.4, 149.9, 149.7, 138.1, 137.9, 136.8, 136.5, 132.9, 128.8, 127.7, 127.6, 127.4, 126.5, 110.0, 109.4, 106.5, 52.7, 29.9, 27.6, 22.0, 13.6. $C_{23}H_{22}ClN_3O$ (391.89): Calcd C 70.49, H 5.66; Found C 70.71, H 5.47.

2-(1-(Biphenyl-2-ylmethyl)-4-chloropyrazol-5-yl)benzonitrile (30) The reaction of 2-(1-(2-bromobenzyl)-4-chloropyrazol-5-yl)benzonitrile **10** (0.372 g, 1 mmol), phenylboronic acid (0.183 g, 1.5 mmol) and K_2CO_3 (0.414 g, 3 mmol) at 110°C during 15 h in DMA (4 mL) in the presence of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **30** in 88% (0.325 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.63 (m, 1H), 7.60 (s, 1H), 7.53-7.47 (m, 2H), 7.35-7.22 (m, 5H), 7.13-7.09 (m, 1H), 7.04-6.90 (m, 4H), 5.25 (d, J = 16.1 Hz, 1H), 5.16 (d, J = 16.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 139.9, 137.7, 136.3, 133.5, 132.8, 131.4, 131.3, 130.0, 129.8, 129.0, 128.4, 128.2, 127.9, 127.8, 127.5, 116.8, 114.1, 111.6, 52.7. $C_{23}H_{16}ClN_3$ (369.84): Calcd C 74.69, H 4.36; Found C 74.80, H 4.30.

4-(1-(Biphenyl-2-ylmethyl)-4-bromopyrazol-5-yl)benzonitrile (31) The reaction of 4-(4-bromo-1-(2-bromobenzyl)-pyrazol-5-yl)benzonitrile **16** (0.417 g, 1 mmol), phenylboronic acid (0.183 g, 1.5 mmol) and K_2CO_3 (0.414 g, 3 mmol) at 110°C during 15 h in DMA (4 mL) in the presence of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **31** in 77% (0.319 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.38-7.27 (m, 5H), 7.20-7.13 (m, 3H), 7.06-6.96 (m, 3H), 5.23 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.2, 139.9, 139.7, 133.7, 132.9, 132.4, 130.4, 130.2, 129.0, 128.5, 128.1, 128.0, 127.6, 127.5, 118.3, 113.0, 94.8, 52.7. $C_{23}H_{16}BrN_3$ (414.30): Calcd C 66.68, H 3.89; Found C 66.49, H 4.04.

3-(1-(Biphenyl-2-ylmethyl)-4-bromopyrazol-5-yl)quinoline (32) The reaction of 3-(4-bromo-1-(2-bromobenzyl)-pyrazol-5-yl)quinoline **24** (0.443 g, 1 mmol), phenylboronic acid (0.183 g, 1.5 mmol) and K_2CO_3 (0.414 g, 3 mmol) at 110°C during 15 h in DMA (4 mL) in the presence of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **32** in 84% (0.370 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.76 (s, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.35-7.27 (m, 2H), 7.20-7.05 (m, 5H), 6.84 (d, J = 8.2 Hz, 2H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 148.0, 141.1, 140.2, 139.9, 138.8, 137.3, 134.1, 130.9, 130.3, 129.7, 128.9, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 121.9, 95.6, 52.9. $C_{25}H_{18}BrN_3$ (440.33): Calcd C 68.19, H 4.12; Found C 68.00, H 4.05.

3-Chloropyrazolo[5,1-*a*]isoindole (33) The reaction of 1-(2-bromobenzyl)-4-chloropyrazole **1** (0.271 g, 1 mmol) and KOAc (0.196 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **33** in 88% (0.167 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 7.48-7.40 (m, 2H), 7.36 (t, J = 7.8 Hz, 1H), 5.09 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 142.1, 140.1, 130.0, 128.7, 128.0, 123.7, 120.9, 102.1, 53.2. $C_{10}H_7ClN_2$ (190.63): Calcd C 63.01, H 3.70; Found C 62.89, H 3.71.

3-Bromopyrazolo[5,1-*a*]isoindole (34) The reaction of 1-(2-bromobenzyl)-4-bromopyrazole **2** (0.315 g, 1 mmol) and KOAc (0.196 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **34** in 75% (0.176 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 1H), 7.56 (s, 1H), 7.48-7.40 (m, 2H), 7.37 (t, J = 7.8 Hz, 1H), 5.10 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 144.1, 140.3, 130.2, 128.7, 128.1, 123.7, 120.7, 84.9, 53.1. $C_{10}H_7BrN_2$ (235.08): Calcd C 51.09, H 3.00; Found C 51.24, H 3.17.

1-(2-Bromobenzyl)-4-phenylpyrazole (36)[6] The reaction of 1-(2-bromobenzyl)-4-iodopyrazole **3** (0.726 g, 2 mmol), phenylboronic acid (0.244 g, 2 mmol) and K_2CO_3 (0.828 g, 6 mmol) at 110°C during 15 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.04 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **36** in 54% (0.338 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.71 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.31-7.15 (m, 3H), 7.03 (d, J = 8.3 Hz, 1H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 135.8, 132.7, 132.2, 129.5, 129.4, 128.7, 127.8, 126.6, 126.3, 125.4, 123.4, 122.8, 55.8.

1-(2-Bromobenzyl)-4-(thiophen-2-yl)-pyrazole (37) The reaction of 1-(2-bromobenzyl)-4-iodopyrazole **3** (0.726 g, 2 mmol), 2-thienylboronic acid (0.256 g, 2 mmol) and K_2CO_3 (0.828 g, 6 mmol) at 110°C during 15 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.04 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **37** in 62% (0.395 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.64 (s, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.33 (dd, J = 5.0, 3.0 Hz, 1H), 7.30-7.15 (m, 4H), 7.01 (d, J = 8.3 Hz, 1H), 5.44 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.5, 133.7, 133.5, 130.2, 130.1, 128.5, 127.3, 126.7, 126.6, 123.5, 119.5, 118.9, 56.5.

3-Phenylpyrazolo[5,1-*a*]isoindole (38)[6] The reaction of 1-(2-bromobenzyl)-4-phenylpyrazole **36** (0.313 g, 1 mmol) and PivOK (0.280 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **38** in 88% (0.204 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 1H), 7.77 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.51-7.43 (m, 3H), 7.42-7.30 (m, 3H), 5.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 142.1, 140.4, 133.0, 130.9, 128.7, 128.0, 127.3, 127.2, 126.4, 123.4, 120.2, 115.8, 52.0.

3-(Thiophen-2-yl)-pyrazolo[5,1-*a*]isoindole (39) The reaction of 1-(2-bromobenzyl)-4-(thiophen-2-yl)-pyrazole **37** (0.319 g, 1 mmol) and PivOK (0.280 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **39** in 90% (0.214 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 1H), 7.74 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.46-7.31 (m, 5H), 5.15 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 142.5, 140.6, 133.6, 131.2, 128.4, 127.6, 127.5, 126.2, 123.7, 120.5, 120.3, 110.8, 52.3. $C_{14}H_{10}N_2S$ (238.31): Calcd C 70.56, H 4.23; Found C 70.54, H 4.50.

5-Chlorodibenzo[*c*,*e*]pyrazolo[1,5-*a*]azepine-4-carbonitrile (40) The reaction of 2-(1-(2-bromobenzyl)-4-chloropyrazol-5-yl)benzonitrile **10** (0.372 g, 1 mmol) and PivOK (0.280 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **40** in 28% (0.081 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.48-7.40 (m, 4H), 5.30 (d, J = 14.3 Hz, 1H), 4.99 (d, J = 14.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 138.3, 137.5, 137.1, 134.9, 133.6, 133.1, 130.3, 130.0, 129.7, 129.5, 129.0, 128.4, 118.0, 113.8, 112.6, 55.0. $C_{17}H_{10}ClN_3$ (291.73): Calcd C 69.99, H 3.45; Found C 70.17, H 3.57.

5-Bromodibenzo[*c*,*e*]pyrazolo[1,5-*a*]azepine-4-carbonitrile (41) The reaction of 2-(4-bromo-1-(2-bromobenzyl)-pyrazol-5-yl)benzonitrile **21** (0.417 g, 1 mmol) and PivOK (0.280 g, 2 mmol) at 150°C during 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **41** in 35% (0.117 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.47-7.40 (m, 3H), 5.32 (d, J = 14.3 Hz, 1H), 5.01 (d, J = 14.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 140.4, 137.4, 136.9, 134.7, 133.5, 130.1, 129.8, 129.6, 129.4, 129.2, 128.3, 118.0, 113.8, 112.6, 97,2, 54.8. $C_{17}H_{10}BrN_3$ (336.19): Calcd C 60.73, H 3.00; Found C 60.54, H 2.88.

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