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Graphical Abstract

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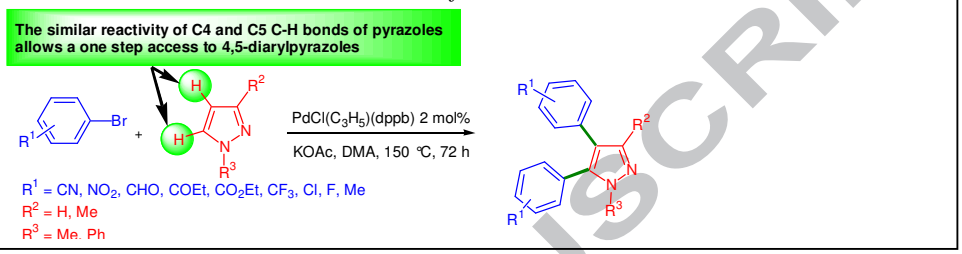

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Palladium-Catalysed Direct Diarylations of Pyrazoles with Aryl Bromides: A One Step Access to 4,5-Diarylpyrazoles

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ABSTRACT

The palladium-catalysed direct arylation of pyrazoles with aryl halides, using $PdCl(C_3H_5)(dppb)$/KOAc catalyst, reveals the similar reactivity of C4 and C5 C-H bonds of pyrazoles, whereas C3 C-H bond is almost unreactive, and gives access in one step to a variety of 4,5-diarylpyrazoles. This C–H bond functionalisation reaction tolerates a variety of substituents on the aryl bromide such as nitro, cyano, formyl, propionyl, ester, chloro, fluoro or trifluoromethyl groups.

Among heterocycles, several (di)arylpyrazoles display important biological properties. For example, Celecoxib is an antiinflammatory drug, Ruxolitinib is employed for the treatment of myelofibrosis, Ipazilide has antiarrhythmic properties and Fezolamine is an antidepressant agent (Fig. 1).

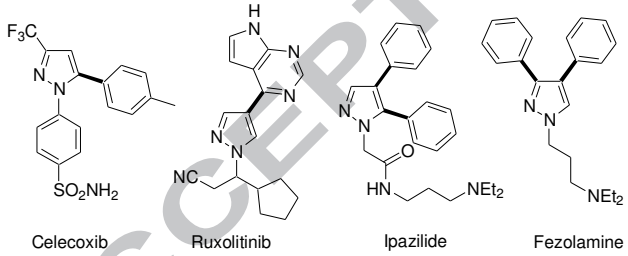

Fig. 1 Examples of bioactive pyrazoles

The synthesis of such arylpyrazoles can be performed using classical palladium-catalysed cross-coupling reactions such as Suzuki, Negishi or Stille couplings.[1-5] However, these methods are not very convenient as usually stoichiometric amounts of two organometallic derivatives have to be prepared for the cross-coupling reactions. Moreover, they are not environmentally attractive as they provide an organometallic or a salt (MX) as by-product. Therefore, to overcome these limitations, the discovery of more straightforward methods for the functionalisation of pyrazoles is highly desirable.

The palladium-catalysed direct arylation of several (hetero)aromatics *via* a C–H bond activation using aryl halides has led to successes in recent years.[6-8] Such couplings are very attractive compared to classical palladium-catalysed couplings such as Stille, Suzuki or Negishi reactions as they avoid the preliminary synthesis of organometallic derivatives. The direct catalytic arylations of sp^2C-H bonds provide only HX associated to a base as by-product and therefore are offer advantages both in terms of atom-economy and inert wastes. However, there are still limitations for these reactions to reach large substrate scope. Only a few examples of palladium-catalysed direct arylations of pyrazoles have been reported to date.[9-12] This is due to the lack of regioselectivity observed in the course of these couplings.[9] Sames and co-workers have established the regioselectivity of the catalytic C–H arylation of pyrazoles (Fig. 2).[9a] SEM-pyrazole (SEM = 2-(trimethylsilyl)ethoxymethyl), reacted with bromobenzene using 5 mol% of $Pd(OAc)_2$ associated to 7.5 mol% of $P(nBu)(Ad)_2$ as the catalyst, gave a mixture of products, which indicated the higher reactivity of the 5-position relative to the 4-position, and very low reactivity of the 3-position (Fig 2).

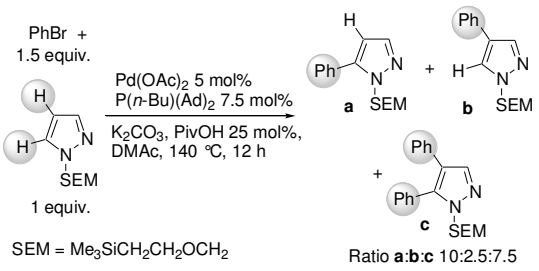

Fig. 2 Regioselectivity of palladium-catalysed direct arylation of pyrazoles

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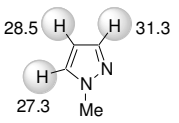
In the course of this reaction, the 5-phenylpyrazole **a** was obtained in 40% yield, and the 4-phenylpyrazole **b** in only 10% yield. Moreover, the formation of an important amount of 4,5-diarylated pyrazole **c** (30%) was also observed.

According to Gorelsky calculations, in the concerted metallation deprotonation (CMD) process, the carbon 5 of 1-methylpyrazole should be slightly more reactive than carbon 4 (energies of activation: 27.3 vs 28.5); whereas carbon 3 has an higher energy of activation of 31.3 (Fig. 3).[13] This minor difference of energy of activation between positions 4 and 5 explains the poor regioselectivity observed for Pd-catalysed arylations of pyrazoles which proceed via a CMD process.

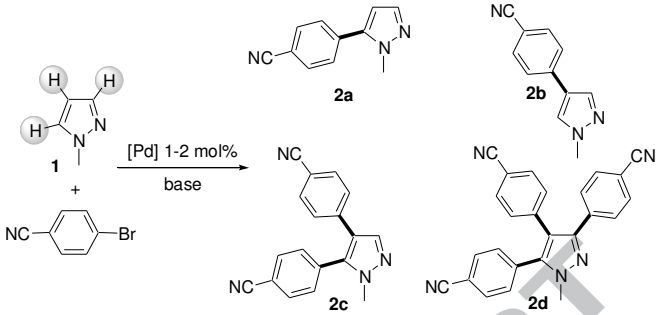


Gibbs free energies of activation (ΔG_{298K}) of the cleavage of C-H bonds for 1-methylpyrazole in the CMD process using the [Pd(C_6H_5)(PMe_3)(OAc)] catalyst.

Fig. 3 1-Methylpyrazole Gibbs free energies of activation for CMD process[13]

To our knowledge, the palladium-catalysed direct diarylation of pyrazoles to produce 4,5-diarylpyrazoles has not been investigated, although it would allow a one step access to useful compounds. Here, taking advantage of relatively similar reactivities of C4-H and C5-H bonds *vs* C3 position, we report on effective conditions for the direct 4,5-diarylations of pyrazoles using a variety of aryl bromides.

We had previously observed that the use of PdCl(C_3H_5)(dppb) as catalyst, KOAc as the base and DMA as solvent are effective conditions for the direct arylation of aryl bromides with several heteroaromatics.[8b] For this study, we initially employed 1 mol% of PdCl(C_3H_5)(dppb) as the catalyst, 4 equiv. of KOAc and DMA at 150 °C during 20 h for the coupling of 1-methylpyrazole **1** with 3 equiv. of 4-bromobenzonitrile (Scheme 1, table 1). However, these conditions resulted in the formation of a mixture of the two mono-arylated pyrazoles **2a** and **2b**, whereas the desired diarylated product **2c** was only obtained in 42% selectivity and the triarylated product **2d** was not detected (Table 1, entry 1). Lower selectivities in **2c** were observed in the presence of K_2CO_3 or NaOAc as bases (Table 1, entries 2 and 3). CsOAc base allowed to increase the selectivity in **2c** to 52%; however, the formation of several unidentified side-products was also observed (Table 1, entry 4). This might be due to the partial degradation of the nitrile function with this stronger and more soluble base. The use of 2 mol% PdCl(C_3H_5)(dppb) and 6 equiv. of KOAc as base also allowed to increase the selectivity in **2c** to 47% (Table 1, entry 5). Then we employed longer reaction times, and we observed that after 48 h, **2c** was formed in 58% selectivity (Table 1, entry 6). The best selectivity was obtained using a reaction time of 72h, with an isolated yield of **2c** of 60% (Table 1, entry 7). The use of $Pd(OAc)_2$ catalyst without ligand was also very effective for this coupling, as the desired product **2c** was produced in 73% selectivity and in 59% isolated yield after only 20h (Table 1, entry 8). It should be noted that, in all cases, no significant amount of triarylation product **2d** was detected by GC/MS analysis of the crude mixtures.



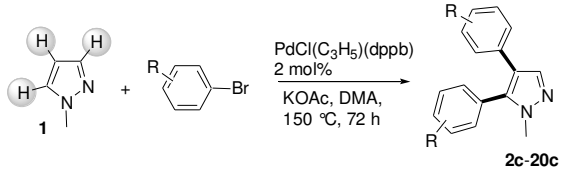
Scheme 1 Arylation of 1-methylpyrazole **1** with 4-bromobenzonitrile

Table 1. Influence of the reaction conditions for palladium-catalysed direct arylation of 4-bromobenzonitrile with 1-methylpyrazole **1** (Scheme 1).[14,15]

Entry	Catalyst (mol%)	Base (eq.)	Time (h)	Ratio **2a+2b**:**2c**	Yield in **2c** (%)
1	PdCl(C_3H_5)(dppb) (1)	KOAc (4)	20	58:42	
2	PdCl(C_3H_5)(dppb) (2)	K_2CO_3 (4)	20	75:25	
3	PdCl(C_3H_5)(dppb) (1)	NaOAc (4)	20	70:30	
4	PdCl(C_3H_5)(dppb) (1)	CsOAc (4)	20	48:52	30
5	PdCl(C_3H_5)(dppb) (2)	KOAc (6)	20	53:47	35
6	PdCl(C_3H_5)(dppb) (2)	KOAc (6)	48	42:58	
7	PdCl(C_3H_5)(dppb) (2)	KOAc (6)	72	33:67	60
8	$Pd(OAc)_2$ (2)	KOAc (6)	20	27:73	59

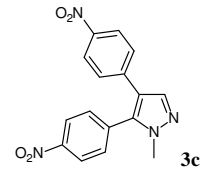
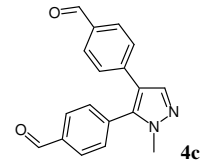
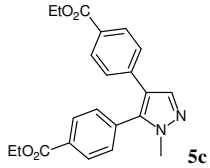
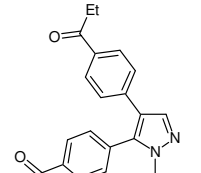
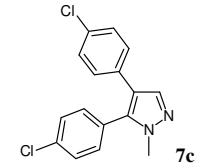
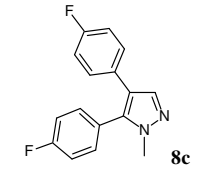
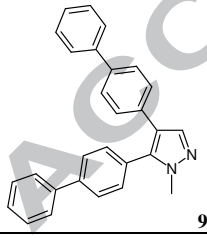
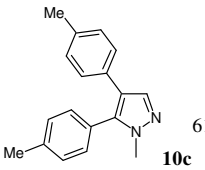
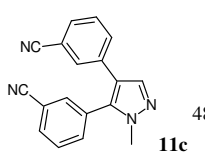
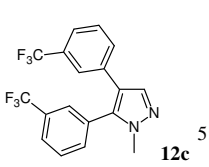
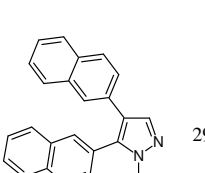
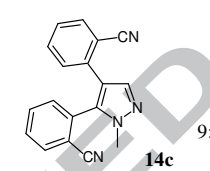
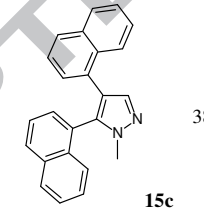
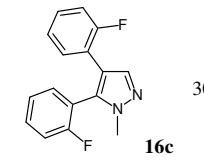
Conditions: 4-bromobenzonitrile (3 equiv.), 1-methylpyrazole **1** (1 equiv.), DMA, under argon, 150 °C.

Then, we examined the scope of the coupling of 1-methylpyrazole **1** with a variety of aryl bromides using 2 mol% PdCl(C_3H_5)(dppb) catalyst, 6 equiv. of KOAc as base in DMA during 72 h (Scheme 2, Tables 2 and 3). From 4-bromonitrobenzene, 4-bromobenzaldehyde and ethyl 4-bromobenzoate, the diarylation products **3c-5c** were selectively produced in 38-41% yields (Table 2, entries 1, 4 and 7). Better results were obtained in the presence of 4-bromopropiophenone, 4-bromochlorobenzene and 4-bromofluorobenzene as the desired products **6c-8c** were isolated in 54-64% yields (Table 2, entries 9, 11 and 12). In the presence of the electron-rich 4-bromotoluene, the desired coupling product **10c** was only obtained in 34% yield due to the formation of an important amount of mono-arylation products (Table 2, entry 14). A few reactions were also performed using 2 mol% $Pd(OAc)_2$ catalyst; however, similar or lower yields than in the presence of PdCl(C_3H_5)(dppb) catalyst were obtained (Table 2, entries 2, 5, 8, 10). Next, we studied the reactivity of *meta*- and *ortho*-substituted aryl bromides in the presence of 1-methylpyrazole **1**. Quite similar results than with *para*-substituted aryl bromides were obtained. Again, regioselective diarylations at C4 and C5 positions were observed in most cases. In the presence of 3-bromobenzonitrile, 3-(trifluoromethyl)bromobenzene or 2-bromonaphthalene, **11c-13c** were isolated in 44%, 65% and 61% yields, respectively (Table 2, entries 15-17). Even the more congested aryl bromides, 2-bromobenzonitrile and 1-bromonaphthalene led to the desired coupling products **14c** and **15c** in 81% and 51% yields, respectively (Table 2, entries 18 and 19). From 2-fluorobromobenzene and **1** as the coupling partner, **16c** was also isolated in 60% (Table 2, entry 20). For all these reactions, no trace of unreacted **1** was detected by GC analysis of the crude mixtures.



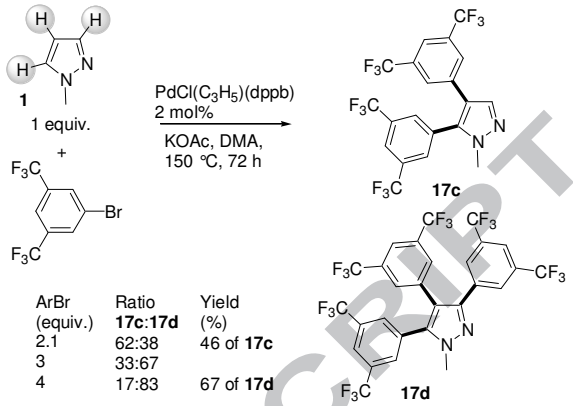
Scheme 2 Palladium-catalysed diarylation of 1-methylpyrazole **1** with aryl bromides.

Table 2. Palladium-catalysed diarylation of 1-methylpyrazole **1** with substituted aryl bromides (Scheme 2).[14,15]

Entry	Product	Ratio **a+b**:**c**	Yield (%)
1	 **3c**	33:67	41
2		33:67	42[a]
3		38:62	30[b]
4	 **4c**	39:61	38
5		40:60	37[a]
6		38:62	28[b]
7	 **5c**	38:62	40
8		59:41	34[a]
9	 **6c**	29:71	64
10		51:49	32[a]
11	 **7c**	30:70	60
12	 **8c**	40:60	54
13	 **9c**	39:61	52
14	 **10c**	61:39	34
15	 **11c**	48:52	44
16	 **12c**	5:95	65[c]
17	 **13c**	29:71	61
18	 **14c**	9:91	81
19	 **15c**	38:62	51
20	 **16c**	30:70	60

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), aryl bromide (3 mmol.), 1-methylpyrazole **1** (1 mmol.), KOAc (6 mmol.), DMA (6 mL), 72 h, 150 °C, isolated yields. [a] $Pd(OAc)_2$ (0.02 mmol), 20 h. [b] CsOAc (6 mmol.). [c] Formation of triarylated pyrazole was also observed by GC/MS analysis in < 10% yield.

The reactivity of 3,5-bis(trifluoromethyl)bromobenzene was found to be very different to other aryl bromides, as in the presence of 3 equiv. of this reactant the formation of a large amount of 3,4,5-triarylated pyrazole **17d** was observed with a ratio **17c**:**17d** of 33:67 (Scheme 3). In order to obtain higher selectivities, we performed two other coupling reactions using 2.1 and 4 equiv. of this aryl bromide. In the presence of only 2.1 of the aryl bromide, the 4,5-diarylated pyrazole **17c** was obtained in 46% yield, whereas with 4 equiv. of aryl bromide, **17d** was isolated in 67% yield.

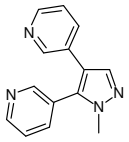
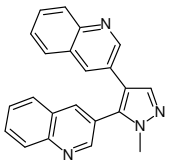
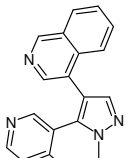


ArBr (equiv.)	Ratio **17c**:**17d**	Yield (%)
2.1	62:38	46 of **17c**
3	33:67	
4	17:83	67 of **17d**

Scheme 3 Palladium-catalysed di- and tri-arylation of 1-methylpyrazole **1** with 3,5-bis(trifluoromethyl)bromobenzene.

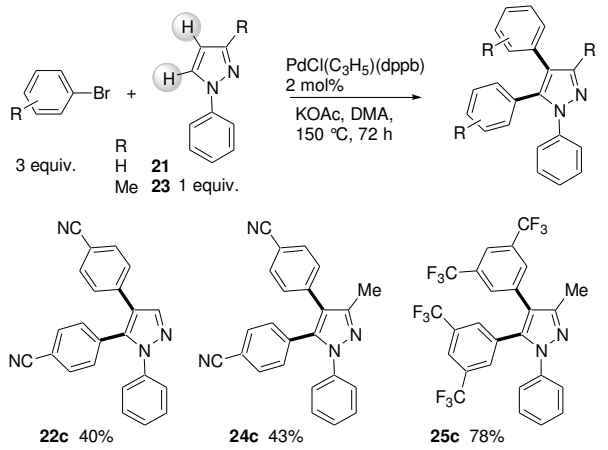
We also studied the reactivity of three heteroaryl bromides containing coordinating atoms (Table 3). From 3-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline the desired diarylation products **18c-20c** were obtained in moderate yields.

Table 3. Palladium-catalysed diarylation of 1-methylpyrazole **1** with heteroaryl bromides (Scheme 2).[14,15]

Entry	Product	Ratio **a+b**:	Entry	Product	Ratio **a+b**
1	 **18c** 48%	37:63	3	 **20c** 53%	34:66
2	 **19c** 42%	40:60			

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), aryl bromide (3 mmol.), 1-methylpyrazole **1** (1 mmol.), KOAc (6 mmol.), DMA (6 mL), 72 h, 150 °C, isolated yields.

Finally, the reactivity of two 1-phenylpyrazoles was evaluated (Scheme 4). The presence of phenyl substituent on nitrogen atom or of a methyl substituent at C3 does not significantly modify the reactivity of pyrazoles. From 1 equiv. of 1-phenylpyrazole **21** or 1-phenyl-3-methylpyrazole **23**, and 3 equiv. of 4-bromobenzonitrile, the target products **22c** and **24c** were obtained in similar yields of 40% and 43%, respectively. A high yield of 78% in **25c** was obtained in the presence of 3,5-bis(trifluoromethyl)bromobenzene and **23** as the coupling partners.



Scheme 4 Palladium-catalysed diarylation of 1-phenylpyrazoles **21** and **23** with aryl bromides.

In summary, taking advantage of the relatively similar energies of activation of positions C4 and C5 of pyrazoles *vs* C3 for palladium-catalysed couplings *via* C-H bonds activation/functionalisation reactions, we have shown here that a range of (hetero)aryl bromides react similarly at both C4 and C5 positions of pyrazoles, but without arylation at C3, except by using 3,5-bis(trifluoromethyl)bromobenzene, to give in only one step 4,5-diarylpyrazoles. It should be noted that this protocol, which employs a moderate loading of an air stable catalyst and an inexpensive base, is compatible with a range of functions, including electron-withdrawing reactive ones, such as chloro, formyl, propionyl, ester, nitrile or nitro on the aryl bromide allowing further transformations. The major by-products of these couplings are KBr/AcOH instead of metallic salts with more classical coupling procedures. For these reasons, this process gives a simpler and greener access to these diarylpyrazoles.

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References and notes

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14. General procedure for the direct diarylation of 1-methylpyrazole **1**, 1-phenylpyrazole **21** and 3-methyl-1-phenylpyrazole **23**: In a typical experiment, the aryl bromide (3 mmol), heteroaromatic **1**, **21** or **23** (1 mmol), KOAc (0.588 g, 6 mmol) and $PdCl(C_3H_5)(dppb)$[16] (0.012 g, 0.02 mmol) were dissolved in DMA (4 mL) under an argon atmosphere. The reaction mixture was stirred at 150 °C for 72 h. Then, the solvent was evaporated and the product was purified by silica gel column chromatography.
15. All new compounds gave satisfactory ^1H, ^{13}C and elementary analysis. **4-(2-Methylpyrazol-3-yl)-benzonitrile (2a):**[9b] ^1H (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 1.8 Hz, 1H), 6.39 (d, *J* = 1.8 Hz, 1H), 3.92 (s, 3H). **4-(1-Methylpyrazol-4-yl)-benzonitrile (2b):**[9b] ^1H (400 MHz, $CDCl_3$) δ = 7.82 (s, 1H), 7.71 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 3.99 (s, 3H). **1-Methyl-4,5-bis[(4-cyanophenyl)]-pyrazole (2c):**[9b] ^1H (400 MHz, $CDCl_3$) δ= 7.81 (d, *J* = 8.5 Hz, 2H), 7.79 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 3H).
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