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Palladium-Catalyzed Direct Arylation of 5-Chloropyrazoles: A Selective Access to 4-Aryl Pyrazoles

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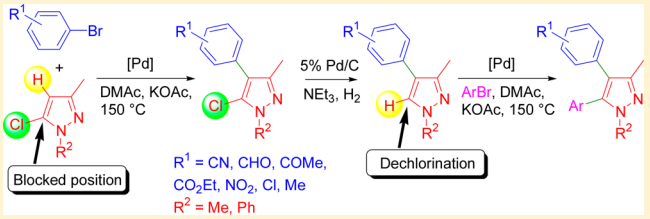
Supporting Information

ABSTRACT: The use of a temporary protection by a chloro group at C5 of pyrazoles allows the synthesis of the 4-arylated pyrazoles, which were previously inaccessible by palladium-catalyzed direct arylation, with complete regioselectivity and in high yields using in most cases as little as 0.5−0.1 mol % $Pd(OAc)_2$ as the catalyst with electron-deficient aryl bromides. Moreover, from 5-chloro-1,3-dimethylpyrazole, sequential catalytic C4 arylation, dechlorination, catalytic C5 arylation reactions allowed the synthesis of a 4,5-diarylated pyrazole derivative.



The palladium-catalyzed direct arylation of several heteroaromatics via a C−H bond activation using aryl halides has led to successes in recent years. Very exciting results have been reported by several groups using thiophenes, furans, pyrroles, thiazoles, oxazoles, imidazoles or triazoles.[1−3] Such couplings are very attractive compared to classical palladium-catalyzed reactions such as Stille, Suzuki or Negishi couplings, as they do not require the preliminary synthesis of organometallic derivatives.[4] Among heterocycles, pyrazoles display important biological properties. For example, among the 4-arylated pyrazoles, Fezolamine is an antidepressant agent, Pirazolac an antirheumatic and antiinflammatory agent, Ipazilide a antiarrhythmic agent and Crizotinib an antineoplastic agent (Figure 1).

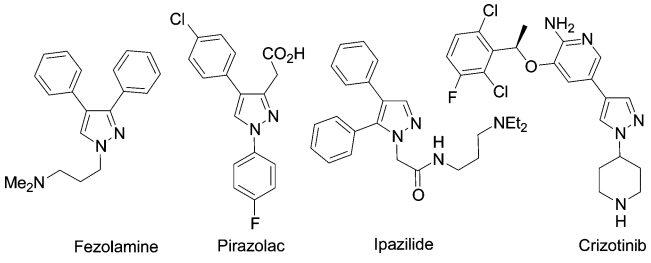


Figure 1. Examples of bioactive 4-arylpyrazole derivatives.

However, only a few examples of palladium-catalyzed direct arylations of pyrazoles have been reported to date.[5−9] This is due to the formation of several regioisomers and lack of regioselectivity. Recently, Sames and co-workers have established the regioselectivity of the catalytic C−H arylation of pyrazoles (Figure 2).[5] SEM-pyrazole (SEM = 2-(trimethylsilyl)-ethoxymethyl), reacted with bromobenzene using 5 mol % $Pd(OAc)_2$ and 7.5 mol % of electron-rich and congested phosphine $Pd(n\text{Bu})(Ad)_2$ as the catalyst, gave a mixture of

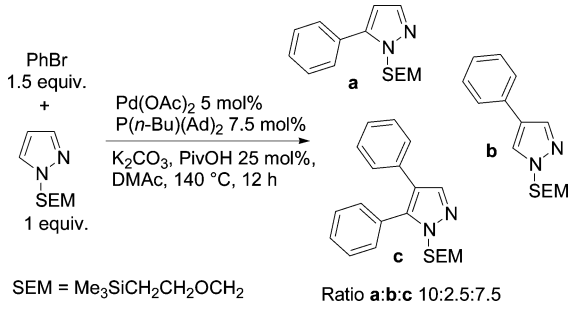


Figure 2. Regioselectivity for the direct arylation of a pyrazole with bromobenzene.[5]

products, which indicated the higher reactivity of the 5-position relative to the 4-position and very low reactivity of the 3-position. 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.

So far, either 5-arylations of pyrazoles[6,7] or 4-arylation of 3,5-disustituted pyrazoles have been described.[8] Intramolecular arylations with the activation of the C−H bond in positions 3 or 4 of pyrazoles have also been reported.[9] By contrast, the regioselective direct arylation at C4−H bond of unsubstituted pyrazoles has not been described. Therefore, the discovery of an effective method, for the direct coupling of pyrazole derivatives with aryl halides at C4 carbon, especially under low catalyst loading conditions would be a considerable advantage for industrial applications.

Recently, Fagnou and co-workers have reported the use of chloro substituents as blocking groups to produce alternative

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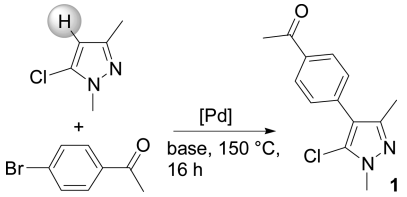
regioisomers for the palladium-catalyzed direct arylation of thiazoles, thiophenes or indoles.[10] Here, we wish to report the efficient palladium-catalyzed 4-arylation of 5-chloropyrazoles with a wide variety of electronically and sterically diverse (hetero)aryl bromides using moderate to low loadings of a phosphine-free palladium catalyst. The catalytic dechlorination of some coupling products has been performed, allowing the production of a 4,5-biarylpyrazole via a second direct arylation.

The commercially available 5-chloro-1,3-dimethylpyrazole and 4-bromoacetophenone were employed as model substrates for our study (Table 1). We initially examined the influence of

Table 1. Influence of Conditions on the 4-Arylation of 5-Chloro-1,3-dimethylpyrazole with 4-Bromoacetophenone[a]



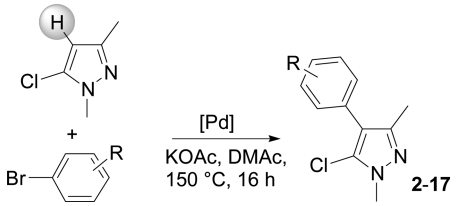
entry	solvent	base	$Pd(OAc)_2$ (mol %)	convn. (%)
1	DMAc	K_2CO_3	0.1	19
2	DMAc	Cs_2CO_3	0.1	4
3	DMAc	KOAc	0.1	100 (92)
4	DMAc	CsOAc	0.1	76
5	DMAc	NaOAc	0.1	31
6	DMF	KOAc	0.1	41
7	NMP	KOAc	0.1	15
8	xylene	KOAc	0.1	18
9	pentan-1-ol	KOAc	0.5	95 (62)
10	diethyl carbonate	KOAc	0.5	40[b]
11	cyclopentyl methyl ether	KOAc	0.5	13[b]

[a]Conditions: $Pd(OAc)_2$ (0.01 or 0.05 equiv), 4-bromoacetophenone (1 equiv), 5-chloro-1,3-dimethylpyrazole (1.5 equiv), KOAc (2 equiv), 16 h, 150 °C; conversion of 4-bromoacetophenone; isolated yields of **1** are given in parentheses. [b]125 °C.

the nature of the base on the conversion for this reaction using DMAc as the solvent and 0.1 mol % $Pd(OAc)_2$ as the catalyst. We had previously observed that these conditions allowed the coupling of several heteroaromatics such as thiazoles, furans, pyrroles or imidazoles derivatives with aryl bromides.[11] K_2CO_3 or Cs_2CO_3 gave low conversions of 4-bromoacetophenone (Table 1, entries 1 and 2). On the other hand, in the presence of KOAc as the base and ligand, a complete conversion of 4-bromoacetophenone was observed, and 4-arylpyrazole derivative **1** was obtained in 92% yield indicating that no significant cleavage of the C−Cl bond took place under these reaction conditions (Table 1, entry 3). A good conversion was also obtained in the presence of CsOAc as the base, whereas NaOAc led only to a conversion of 31% of 4-bromoacetophenone (Table 1, entries 4 and 5). The good performance of acetate as the base/ligand is consistent with a concerted metalation deprotonation (CMD) pathway.[12] The nature of the solvent often modifies the catalyst activity in cross-coupling reactions, thus we observed that NMP, DMF or xylene in the presence of 0.1 mol % $Pd(OAc)_2$ with KOAc as the catalyst gave **1** in low to moderate yields (Table 1, entries 6−8). Some solvents that can be considered as "greener" than DMAc have also been employed. Pentan-1-ol[13a] in the presence of 0.5 mol % $Pd(OAc)_2$/KOAc led to a high conversion of 4-bromoacetophenone and to a good yield in **1** (Table 1, entry 9). On the other hand, cyclopentyl methyl ether[13b] and diethyl carbonate[1g] gave poor yields of coupling product (Table 1, entries 10 and 11).

Then, 5-chloro-1,3-dimethylpyrazole was coupled with several aryl bromides in the presence of 0.5−0.1 mol % $Pd(OAc)_2$, KOAc as the base in DMAc or pentan-1-ol (Table 2). Selective 4-arylations were observed using the *para*-

Table 2. Scope of the Direct Arylation of 5-Chloro-1,3-dimethylpyrazole with (Hetero)aryl Bromides[a]



entry	R or aryl bromide	catalyst (mol %)	prod.	yield (%)
1	4-CN	$Pd(OAc)_2$ (0.1)	**2**	81
2	4-CHO	$Pd(OAc)_2$ (0.1)	**3**	47
3	4-CHO	$Pd(OAc)_2$ (0.5)	**3**	83
4	4-CO_2Et	$Pd(OAc)_2$ (0.5)	**4**	55
5	4-NO_2	$Pd(OAc)_2$ (0.1)	**5**	90
6	4-NO_2	$Pd(OAc)_2$ (0.5)	**5**	65[b]
7	4-Cl	$Pd(OAc)_2$ (0.5)	**6**	41
8	4-Cl	$PdCl(C_3H_5)$(dppb) (1)	**6**	62
9	4-Me	$Pd(OAc)_2$ (0.5)	**7**	3
10	4-Me	$PdCl(C_3H_5)$(dppb) (1)	**7**	42
11	4-NMe_2	$PdCl(C_3H_5)$(dppb) (1)	**8**	0
12	3-CN	$Pd(OAc)_2$ (0.1)	**9**	72
13	3-CHO	$Pd(OAc)_2$ (0.1)	**10**	58
14	3-CHO	$Pd(OAc)_2$ (0.5)	**10**	91
15	3-COMe	$Pd(OAc)_2$ (0.1)	**11**	72
16	3-NO_2	$Pd(OAc)_2$ (0.5)	**12**	64
17	3-NO_2	$Pd(OAc)_2$ (2)	**12**	88
18	2-CN	$Pd(OAc)_2$ (0.1)	**13**	89
19	1-bromonaphthalene	$Pd(OAc)_2$ (0.5)	**14**	27
20	1-bromonaphthalene	$PdCl(C_3H_5)$(dppb) (1)	**14**	68
21	3-bromopyridine	$Pd(OAc)_2$ (0.5)	**15**	71
22	3-bromopyridine	$Pd(OAc)_2$ (1)	**15**	90
23	3-bromoquinoline	$Pd(OAc)_2$ (0.2)	**16**	88
24	3-bromoquinoline	$Pd(OAc)_2$ (0.5)	**16**	80[b]
25	4-bromoisoquinoline	$Pd(OAc)_2$ (0.5)	**17**	50
26	4-bromoisoquinoline	$Pd(OAc)_2$ (2)	**17**	93

[a]Conditions: [Pd], aryl bromide (1 equiv), 5-chloro-1,3-dimethylpyrazole (1.5 equiv), KOAc (2 equiv), 16 h, 150 °C. [b]Pentan-1-ol instead of DMAc.

substituted electron-deficient aryl bromides: 4-bromobenzonitrile, 4-bromobenzaldehyde or 4-bromonitrobenzene producing 81−90% yields of the products **2**, **3** and **5** (Table 2, entries 1−3 and 5). In all cases, the expected 4-arylated 5-chloropyrazoles were selectively obtained. It should be noted that 4-chlorobromobenzene could also be employed to give **6** in 62% yield. However, 1 mol % of the more stable catalyst $PdCl(C_3H_5)(dppb)$[3b] had to be employed to obtain a high conversion of this aryl bromide (Table 2, entry 8). In the course of this reaction, no aryl-C−Cl bond cleavage was observed, allowing further transformations. The use of electron-rich aryl bromides was then explored. 4-Bromotoluene led to **7**

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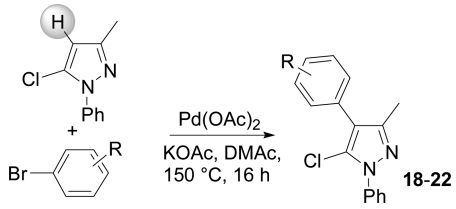
in a moderate yield of 42%, whereas 4-bromo-*N*,*N*-dimethylaniline was recovered unreacted (Table 2, entries 10 and 11). Thus, electron-withdrawing substituents are preferably used. The *meta*-substituted aryl bromides, 3-bromobenzonitrile, 3-bromobenzaldehyde or 3-bromoacetophenone gave **9**–**11** in 72–91% yields using 0.5–0.1 mol % $Pd(OAc)_2$ (Table 2, entries 12–15). 3-Bromonitrobenzene was less reactive, and 2 mol % $Pd(OAc)_2$ had to be employed to produce **12** in high yield (Table 2, entries 16 and 17). Then, we employed the *ortho*-substituted 2-bromobenzonitrile with again only 0.1 mol % $Pd(OAc)_2$ as the catalyst. Product **13** was obtained in a high yield of 89% (Table 2, entry 18). On the other hand, a low yield in **14** was obtained from 1-bromonaphthalene with 0.5 mol % $Pd(OAc)_2$ as the catalyst. With this congested substrate, a better yield was obtained with 1 mol % of $PdCl(C_3H_5)(dppb)$ catalyst (Table 2, entries 19 and 20). Some pyrazoles substituted at C4 by pyridines such as Crizotinib have been found to be efficient as an antineoplastic agent (Figure 1). Therefore, the introduction of pyridine, quinoline or pyrimidine motifs on pyrazoles would be also be very useful. We observed that the coupling of 3-bromopyridine, 3-bromoquinoline, 4-bromoisoquinoline with 5-chloro-1,3-dimethylpyrazole also proceeds nicely to give **15**–**17** in 88–93% yields (Table 2, entries 21–23, 25 and 26). It should be noted that 4-bromonitrobenzene and 3-bromoquinoline reacted with 5-chloro-1,3-dimethylpyrazole in pentan-1-ol to give the desired products **5** and **16** in moderate to high yields (Table 2, entries 6 and 24).

5-Chloro-3-methyl-1-phenylpyrazole was then evaluated for C4 arylation. It was successfully coupled with 2-, 3- or 4-bromobenzonitriles, 4-bromobenzaldehyde or 4-bromoacetophenone to give **18**–**22** in 84–92% yields (Table 3). However, with this pyrazole derivative, slower reactions were observed, and 1 mol % of $Pd(OAc)_2$ had to be employed in order to obtain complete conversion of the aryl bromides.

Table 3. Scope of the Direct Arylation of 5-Chloro-3-methyl-1-phenylpyrazole with Aryl Bromides[a]

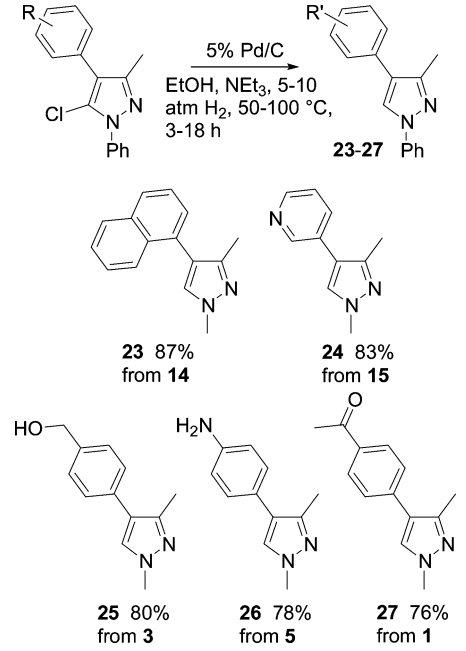


entry	R	catalyst mol %	prod.	yield (%)
1	4-CN	0.1	**18**	25
2	4-CN	1	**18**	88
3	4-CHO	1	**19**	90
4	4-COMe	1	**20**	84
5	3-CN	1	**21**	87
6	2-CN	1	**22**	92

[a]Conditions: $Pd(OAc)_2$, aryl bromide (1 equiv), 5-chloro-3-methyl-1-phenylpyrazole (1.5 equiv), KOAc (2 equiv), 16 h, 150 °C.

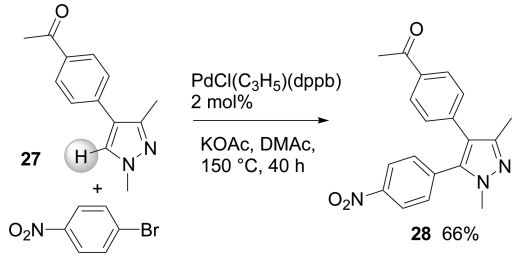
The dechlorination of some of these 4-arylated pyrazoles was then studied (Scheme 1). In the presence of 5% Pd/C (6 mass % of the pyrazole derivative) in ethanol and triethylamine under 5–10 bar of hydrogen at 95–100 °C for 4 or 18 h, **14** and **15** gave the dechlorinated products **23** and **24** in 87 and 83% yields, respectively. On the other hand, from 5-chloro-1,3-dimethyl-4-(4-formylphenyl)-pyrazole **3** and 5-chloro-1,3-dimethyl-4-(4-nitrophenyl)-pyrazole **5**, as expected the chlorine atom was removed, but the formyl or nitro functions were also reduced to give the corresponding aniline and benzyl alcohol derivatives **25** and **26** in 80 and 78% yields, respectively. When appropriate reaction conditions were employed (100 °C, 3 h), the treatment of **1** with catalytic amount of 5% Pd/C under 5 bar of hydrogen gave the dechlorinated product **27** in 76% yield, without reduction of the acetyl group.

Scheme 1. Palladium-Catalyzed Dechlorination of 5-Chloro-4-arylpyrazoles



The arylation at C5 of dechlorinated compound **27** using 4-bromonitrobenzene as the coupling partner proceed nicely to give **28** in 66% yield (Scheme 2).

Scheme 2. C5 Arylation of 27



Finally, we show a sequential transformation allowing the C4 catalytic arylation of 5-chloro-1,3-dimethylpyrazole, dechlorination and C5 catalytic arylation leading to a 4-aryl[1]-5-aryl[2]pyrazole (Scheme 3). From 2-bromonaphthalene and 4-bromobenzonitrile as successive reactants, the target compound **31** was obtained in a 64% overall yield.

In summary, we have demonstrated that the presence of a chloro substituent, as a labile protecting group at the C5 position of pyrazoles, allows the regioselective access to 4-arylated pyrazoles, which were previously inaccessible by palladium-catalyzed direct arylation. The chloro substituent prevents both the favored arylation at C5 of the pyrazole and also diarylation products at C4 and C5. The reaction proceeds

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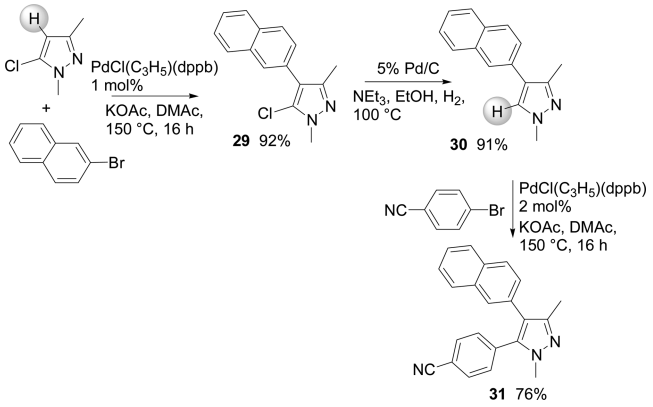
Scheme 3. Sequential C4 Arylation, Dechlorination, C5 Arylation of 5-Chloro-1,3-dimethylpyrazole



in moderate to very high yields in the presence of electron-deficient aryl bromides or heteroaryl bromides using as little as 1−0.1 mol % of $Pd(OAc)_2$ as the catalyst precursor. We also observed that pentan-1-ol, which is considered as a "greener" solvent than DMAc, can be employed. Sequential catalytic C4 arylation, dechlorination, catalytic C5 arylation provides the controlled double arylation of pyrazole at C4 and C5 in good yield.

EXPERIMENTAL SECTION

General Procedure for Palladium-Catalyzed Direct Arylations. The reaction of the aryl bromide (1 mmol), 5-chloro-1,3-dimethylpyrazole (0.196 g, 1.5 mmol) or 5-chloro-3-methyl-1-phenylpyrazole (0.289 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 16 h in DMAc (4 mL) in the presence of $Pd(OAc)_2$ (0.224 mg, 0.001 mmol or 1.12 mg, 0.005 mmol) or $PdCl(C_3H_5)$-(dppb) (6.1 mg, 0.01 mmol) (see Tables or Schemes), under argon affords the coupling products **1**−**22** and **29** after evaporation of the solvent and purification on silica gel. Eluent: pentane/diethylether 3:2 for compounds **1**−**14**, **18**−**22**, **29**; diethylether for compounds **15**−**17**, **23**, **25**, **27**, **28**, **30**, **31**; ethanol/diethylether 1:9 for compounds **24**, **26**.

1-[4-(5-Chloro-1,3-dimethylpyrazol-4-yl)-phenyl]-ethanone (1). 4-Bromoacetophenone (0.199 g, 1 mmol) affords **1** in 92% (0.228 g) yield; amorphous yellow solid: mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 2.51 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 146.2, 136.7, 135.4, 128.8, 128.5, 125.5, 116.4, 36.2, 26.6, 13.4. Elemental analysis calcd (%) for $C_{13}H_{13}ClN_2O$ (248.71): C 62.78, H 5.27. Found: C 62.71, H 5.33.

4-(5-Chloro-1,3-dimethylpyrazol-4-yl)-benzonitrile (2). 4-Bromobenzonitrile (0.182 g, 1 mmol) affords **2** in 81% (0.187 g) yield; light amorphous yellow solid: mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 136.7, 132.3, 129.3, 125.7, 118.9, 115.8, 110.4, 36.3, 13.4. Elemental analysis calcd (%) for $C_{12}H_{10}ClN_3$ (231.68): C 62.21, H 4.35. Found: C 62.30, H 4.47.

4-(5-Chloro-1,3-dimethylpyrazol-4-yl)-benzaldehyde (3). 4-Bromobenzaldehyde (0.185 g, 1 mmol) affords **3** in 83% (0.194 g) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 3.86 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 146.3, 138.2, 134.7, 129.9, 129.3, 125.7, 116.4, 36.3, 13.4. Elemental analysis calcd (%) for $C_{12}H_{11}ClN_2O$ (234.68): C 61.41, H 4.72. Found: C 61.18, H 4.60.

Ethyl 4-(5-chloro-1,3-dimethylpyrazol-4-yl)-benzoate (4). Ethyl 4-bromobenzoate (0.229 g, 1 mmol) affords **4** in 55% (0.153 g) yield; amorphous yellow solid: mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.7 Hz, 2H), 7.37 (d, J = 7.7 Hz, 2H), 4.31 (q, J = 7.7 Hz, 2H), 3.77 (s, 3H), 2.22 (s, 3H), 1.32 (t, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 146.2, 136.4, 129.7, 128.8, 128.7, 125.5, 116.6, 60.9, 36.3, 14.4, 13.4. Elemental analysis calcd (%) for $C_{14}H_{15}ClN_2O_2$ (278.73): C 60.33, H 5.42. Found: C 60.21, H 5.57.

5-Chloro-1,3-dimethyl-4-(4-nitrophenyl)-pyrazole (5). 4-Bromonitrobenzene (0.202 g, 1 mmol) affords **5** in 90% (0.226 g) yield; light amorphous yellow solid: mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 3.79 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 146.3, 138.7, 129.3, 125.9, 123.8, 115.6, 36.3, 13.4. Elemental analysis calcd (%) for $C_{11}H_{10}ClN_3O_2$ (251.67): C 52.50, H 4.01. Found: C 52.50, H 4.15.

5-Chloro-4-(4-chlorophenyl)-1,3-dimethylpyrazole (6). 4-Bromochlorobenzene (0.191 g, 1 mmol) affords **6** in 62% (0.149 g) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 3.76 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 132.8, 130.3, 130.2, 128.7, 125.2, 116.4, 36.2, 13.2. Elemental analysis calcd (%) for $C_{11}H_{10}Cl_2N_2$ (241.12): C 54.79, H 4.18. Found: C 54.90, H 4.11.

5-Chloro-1,3-dimethyl-4-*p*-tolylpyrazole (7). 4-Bromotoluene (0.171 g, 1 mmol) affords **7** in 42% (0.093 g) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 7.5 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 3.76 (s, 3H), 2.31 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 136.7, 129.2, 128.8, 128.7, 125.1, 117.4, 36.1, 21.2, 13.2. Elemental analysis calcd (%) for $C_{12}H_{13}ClN_2$ (220.70): C 65.31, H 5.94. Found: C 65.34, H 6.08.

3-(5-Chloro-1,3-dimethylpyrazol-4-yl)-benzonitrile (9). 3-Bromobenzonitrile (0.182 g, 1 mmol) affords **9** in 72% (0.166 g) yield; light amorphous yellow solid: mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.15 (m, 4H), 3.77 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 133.3, 133.2, 132.3, 130.4, 129.4, 125.5, 118.7, 115.4, 112.8, 36.3, 13.2. Elemental analysis calcd (%) for $C_{12}H_{10}ClN_3$ (231.68): C 62.21, H 4.35. Found: C 62.14, H 4.30.

3-(5-Chloro-1,3-dimethylpyrazol-4-yl)-benzaldehyde (10). 3-Bromobenzaldehyde (0.185 g, 1 mmol) affords **10** in 91% (0.213 g) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.82 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.60−7.50 (m, 2H), 3.79 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 146.2, 136.7, 134.9, 132.9, 130.1, 129.2, 128.2, 125.5, 116.2, 36.2, 13.2. Elemental analysis calcd (%) for $C_{12}H_{11}ClN_2O$ (234.68): C 61.41, H 4.72. Found: C 61.19, H 4.81.

1-[3-(5-Chloro-1,3-dimethylpyrazol-4-yl)-phenyl]-ethanone (11). 3-Bromoacetophenone (0.199 g, 1 mmol) affords **11** in 72% (0.178 g) yield; amorphous yellow solid: mp 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.55−7.40 (m, 2H), 3.78 (s, 3H), 2.55 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 146.1, 137.4, 133.5, 132.3, 128.9, 128.8, 126.8, 125.4, 116.6, 36.2, 26.7, 13.2. Elemental analysis calcd (%) for $C_{13}H_{13}ClN_2O$ (248.71): C 62.78, H 5.27. Found: C 62.89, H 5.40.

5-Chloro-1,3-dimethyl-4-(3-nitrophenyl)-pyrazole (12). 3-Bromonitrobenzene (0.202 g, 1 mmol) affords **12** in 88% (0.221 g) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 3.77 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 146.1, 134.8, 133.5, 129.4, 125.6, 123.6, 121.7, 115.3, 36.3, 13.2. Elemental analysis calcd (%) for $C_{11}H_{10}ClN_3O_2$ (251.67): C 52.50, H 4.01. Found: C 52.34, H 4.08.

2-(5-Chloro-1,3-dimethylpyrazol-4-yl)-benzonitrile (13). 2-Bromobenzonitrile (0.182 g, 1 mmol) affords **13** in 89% (0.205 g) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 3.77 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 135.5, 133.3, 132.7, 131.5, 128.0, 126.5, 118.1, 114.8, 113.6, 36.3, 12.9. Elemental analysis calcd (%) for $C_{12}H_{10}ClN_3$ (231.68): C 62.21, H 4.35. Found: C 62.14, H 4.20.

5-Chloro-1,3-dimethyl-4-naphthalen-1-ylpyrazole (14). 1-Bromonaphthalene (0.207 g, 1 mmol) affords **14** in 68% (0.174 g) yield; orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.75 (m, 2H), 7.54 (d, J = 7.5 Hz, 1H), 7.45−7.35 (m, 3H), 7.32 (d, J = 7.5 Hz, 1H), 3.80 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 133.8, 132.2, 129.1, 128.6, 128.4, 128.3, 126.6, 126.1, 125.9, 125.8,

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125.4, 116.2, 36.2, 13.0. Elemental analysis calcd (%) for $C_{15}H_{13}ClN_2$ (256.73): C 70.18, H 5.10. Found: C 70.02, H 5.25.

3-(5-Chloro-1,3-dimethylpyrazol-4-yl)-pyridine (15). 3-Bromopyridine (0.158 g, 1 mmol) affords **15** in 90% (0.186 g) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (bs, 1H), 8.49 (bs, 1H), 7.62 (d, J = 6.2 Hz, 1H), 7.28 (t, J = 6.2 Hz, 1H), 3.78 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 148.0, 146.3, 136.1, 127.9, 125.7, 123.4, 114.1, 36.2, 13.2. Elemental analysis calcd (%) for $C_{10}H_{10}ClN_3$ (207.66): C 57.84, H 4.85. Found: C 57.79, H 5.08.

3-(5-Chloro-1,3-dimethylpyrazol-4-yl)-quinoline (16). 3-Bromoquinoline (0.208 g, 1 mmol) affords **16** in 88% (0.226 g) yield; light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.07−8.03 (m, 2H), 7.78 (d, J = 7.2 Hz, 1H), 7.68−7.60 (m, 2H), 3.82 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 146.9, 146.6, 135.2, 129.5, 129.3, 127.9, 127.8, 127.0, 126.0, 125.1, 114.3, 36.3, 13.3. Elemental analysis calcd (%) for $C_{14}H_{12}ClN_3$ (257.72): C 65.25, H 4.69. Found: C 65.12, H 4.48.

4-(5-Chloro-1,3-dimethylpyrazol-4-yl)-isoquinoline (17). 4-Bromoisoquinoline (0.208 g, 1 mmol) affords **17** in 93% (0.239 g) yield; light amorphous yellow solid: mp 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (bs, 1H), 8.36 (s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.65−7.55 (m, 3H), 3.84 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 147.8, 144.5, 134.8, 130.6, 128.0, 127.3, 127.1, 124.7, 112.7, 36.3, 13.0. Elemental analysis calcd (%) for $C_{14}H_{12}ClN_3$ (257.72): C 65.25, H 4.69. Found: C 65.41, H 4.68.

4-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-benzonitrile (18). 4-Bromobenzonitrile (0.182 g, 1 mmol) affords **18** in 88% (0.258 g) yield; colorless crystals: mp 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.52−7.30 (m, 4H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 138.0, 136.3, 132.4, 129.7, 129.1, 128.5, 125.3, 125.1, 118.8, 117.7, 110.8, 13.5. Elemental analysis calcd (%) for $C_{17}H_{12}ClN_3$ (293.75): C 69.51, H 4.12. Found: C 69.34, H 4.35.

4-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-benzaldehyde (19). 4-Bromobenzaldehyde (0.185 g, 1 mmol) affords **19** in 90% (0.266 g) yield; light amorphous yellow solid: mp 99−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 148.0, 138.1, 137.8, 135.0, 129.9, 129.6, 129.0, 128.4, 125.3, 125.2, 118.3, 13.5. Elemental analysis calcd (%) for $C_{17}H_{13}ClN_2O$ (296.75): C 68.81, H 4.42. Found: C 68.70, H 4.32.

4-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-acetophenone (20). 4-Bromoacetophenone (0.199 g, 1 mmol) affords **20** in 84% (0.260 g) yield; yellow crystals: mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 2.56 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 148.0, 138.2, 136.4, 135.7, 129.2, 129.1, 128.6, 128.3, 125.2, 125.1, 118.4, 26.6, 13.5. Elemental analysis calcd (%) for $C_{18}H_{15}ClN_2O$ (310.78): C 69.57, H 4.86. Found: C 69.50, H 4.99.

3-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-benzonitrile (21). 3-Bromobenzonitrile (0.182 g, 1 mmol) affords **21** in 87% (0.256 g) yield; light amorphous yellow solid: mp 106−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.62−7.45 (m, 5H), 7.41 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 138.1, 133.6, 132.8, 132.6, 130.7, 129.5, 129.1, 128.5, 125.2, 125.1, 118.7, 117.3, 112.9, 13.3. Elemental analysis calcd (%) for $C_{17}H_{12}ClN_3$ (293.75): C 69.51, H 4.12. Found: C 69.60, H 4.04.

2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-benzonitrile (22). 2-Bromobenzonitrile (0.182 g, 1 mmol) affords **22** in 92% (0.270 g) yield; light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.5 Hz, 2H), 7.52−7.45 (m, 4H), 7.34 (t, J = 7.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 138.1, 135.2, 133.4, 132.8, 131.7, 129.1, 128.4, 128.3, 126.2, 125.1, 118.1, 116.8, 113.7, 13.1. Elemental analysis calcd (%) for $C_{17}H_{12}ClN_3$ (293.75): C 69.51, H 4.12. Found: C 69.59, H 4.09.

General Procedure for Dechlorination Reaction. The reaction of the chloropyrazole (1 mmol), NEt_3 (0.202 g, 2 mmol), at 95−100 °C during 3−18 h in the presence of 5% Pd/C (6% of the weight of the pyrazole derivative), under hydrogen pressure (5 or 10 bar), in ethanol (5 mL)), under argon affords the dechlorinated product **23**−**27** and **29** after evaporation of the solvent and purification on silica gel.

1,3-Dimethyl-4-naphthalen-1-ylpyrazole (23). 5-Chloro-1,3-dimethyl-4-naphthalen-1-ylpyrazole **14** (0.257 g, 1 mmol) at 95 °C during 18 h under 10 bar of hydrogen affords **23** in 87% (0.193) yield; colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.68 (m, 3H), 7.40−7.30 (m, 3H), 7.26−7.20 (m, 2H), 3.81 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 133.8, 132.5, 131.2, 130.5, 128.3, 127.8, 127.5, 126.0, 125.9, 125.8, 125.4, 119.2, 38.7, 12.4. Elemental analysis calcd (%) for $C_{15}H_{14}N_2$ (222.29): C 81.05, H 6.35. Found: C 81.14, H 6.21.

3-(1,3-Dimethylpyrazol-4-yl)-pyridine (24). 3-(5-Chloro-1,3-dimethylpyrazol-4-yl)-pyridine **15** (0.208 g, 1 mmol) at 100 °C during 4 h under 5 bar of hydrogen affords **24** in 83% (0.143) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (bs, 1H), 8.43 (bs, 1H), 7.61 (d, J = 6.2 Hz, 1H), 7.42 (s, 1H), 7.23 (bs, 1H), 3.82 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.2, 145.8, 134.3, 129.5, 129.0, 123.4, 117.5, 38.7, 13.0. Elemental analysis calcd (%) for $C_{10}H_{11}N_3$ (173.21): C 69.34, H 6.40. Found: C 69.27, H 6.32.

[4-(1,3-Dimethylpyrazol-4-yl)-phenyl]-methanol (25). 4-(5-Chloro-1,3-dimethylpyrazol-4-yl)-benzaldehyde **3** (0.235 g, 1 mmol) at 100 °C during 14 h under 5 bar of hydrogen affords **25** in 80% (0.162) yield; light amorphous yellow solid: mp 170−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.30 (s, 4H), 4.63 (d, J = 5.2 Hz, 2H), 3.79 (s, 3H), 1.96 (bs, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 138.7, 133.0, 128.9, 127.6, 127.4, 120.8, 65.1, 38.6, 13.1. Elemental analysis calcd (%) for $C_{12}H_{14}N_2O$ (202.25): C 71.26, H 6.98. Found: C 71.41, H 6.84.

4-(1,3-Dimethylpyrazol-4-yl)-phenylamine (26). 5-Chloro-1,3-dimethyl-4-(4-nitrophenyl)-pyrazole **5** (0.251 g, 1 mmol) at 100 °C during 15 h under 5 bar of hydrogen affords **26** in 78% (0.146) yield; orange crystals: mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 3.60 (bs, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 144.8, 128.5, 128.3, 123.9, 121.2, 115.3, 38.6, 13.1. Elemental analysis calcd (%) for $C_{11}H_{13}N_3$ (187.24): C 70.56, H 7.00. Found: C 70.64, H 6.87.

1-[4-(1,3-Dimethylpyrazol-4-yl)-phenyl]-ethanone (27). 1-[4-(5-Chloro-1,3-dimethylpyrazol-4-yl)-phenyl]-ethanone **1** (0.249 g, 1 mmol) at 100 °C during 3 h under 5 bar of hydrogen affords **27** in 76% (0.163) yield; yellow crystals: mp 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 2H), 7.50 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 3.86 (s, 3H), 2.58 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 145.9, 138.7, 134.6, 139.4, 128.8, 126.9, 120.0, 38.7, 26.5, 13.5. Elemental analysis calcd (%) for $C_{13}H_{14}N_2O$ (214.26): C 72.87, H 6.59. Found: C 72.68, H 6.41.

1-{4-[1,3-Dimethyl-5-(4-nitrophenyl)-pyrazol-4-yl]-phenyl}-ethanone (28). The reaction of 4-bromonitrobenzene (0.303 g, 1.5 mmol) 1-[4-(1,3-dimethylpyrazol-4-yl)-phenyl]-ethanone **27** (0.214 g, 1 mmol), KOAc (0.196 g, 2 mmol) and $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol), at 150 °C during 40 h in DMAc (4 mL) under argon affords the coupling product **28** after evaporation of the solvent and purification on silica gel in 66% (0.221) yield; yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 3.75 (s, 3H), 2.50 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 147.7, 146.2, 139.2, 137.9, 136.5, 135.2, 130.8, 129.5, 128.6, 124.0, 119.8, 37.2, 26.5, 12.5. Elemental analysis calcd (%) for $C_{19}H_{17}N_3O_3$ (335.36): C 68.05, H 5.11. Found: C 68.6814 H 5.20.

5-Chloro-1,3-dimethyl-4-naphthalen-2-ylpyrazole (29). 2-Bromonaphthalene (0.207 g, 1 mmol) affords **29** in 92% (0.235 g) yield; amorphous yellow solid: mp 61−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.70 (m, 4H), 7.45−7.38 (m, 3H), 3.78 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 133.4, 132.3, 129.2,

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128.0, 127.9, 127.8, 127.7, 127.2, 126.2, 126.0, 125.5, 117.4, 36.2, 13.4. Elemental analysis calcd (%) for $C_{15}H_{13}ClN_2$ (256.73): C 70.18, H 5.10. Found: C 70.30, H 5.02.

1,3-Dimethyl-4-naphthalen-2-ylpyrazole (30). 5-Chloro-1,3-dimethyl-4-naphthalen-2-ylpyrazole **29** (0.257 g, 1 mmol) at 100 °C during 16 h under 10 bar of hydrogen affords **30** in 91% (0.202) yield; light amorphous yellow solid: mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.40−7.30 (m, 4H), 3.71 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 133.7, 131.9, 131.1, 129.2, 128.2, 127.8, 127.7, 126.4, 126.3, 125.5, 125.4, 121.1, 38.7, 13.4. Elemental analysis calcd (%) for $C_{15}H_{14}N_2$ (222.29): C 81.05, H 6.35. Found: C 81.14, H 6.21.

4-(2,5-Dimethyl-4-naphthalen-2-ylpyrazol-3-yl)-benzonitrile (31). The reaction of 4-bromobenzonitrile (0.273 g, 1.5 mmol), 1,3-dimethyl-4-naphthalen-2-ylpyrazole **30** (0.222 g, 1 mmol), KOAc (0.196 g, 2 mmol) and $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol), at 150 °C during 16 h in DMAc (4 mL) under argon affords the coupling product **31** after evaporation of the solvent and purification on silica gel in 76% (0.246) yield; orange solid: mp 184−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.60 (m, 3H), 7.50 (d, J = 8.0 Hz, 2H), 7.47 (s, 1H), 7.40−7.30 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 139.4, 135.0, 133.4, 132.4, 132.0, 130.7, 130.3, 128.3, 128.0, 127.9, 127.8, 127.7, 126.2, 125.9, 120.6, 118.4, 112.2, 37.3, 12.6. Elemental analysis calcd (%) for $C_{22}H_{17}N_3$ (323.39): C 81.71, H 5.30. Found: C 81.87, H 5.17.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **1**−**7** and **9**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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