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Article

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L-(-)-Quebrachitol as a Ligand for Selective Copper (0)-Catalyzed *N*-Arylation of Nitrogen-Containing Heterocycles

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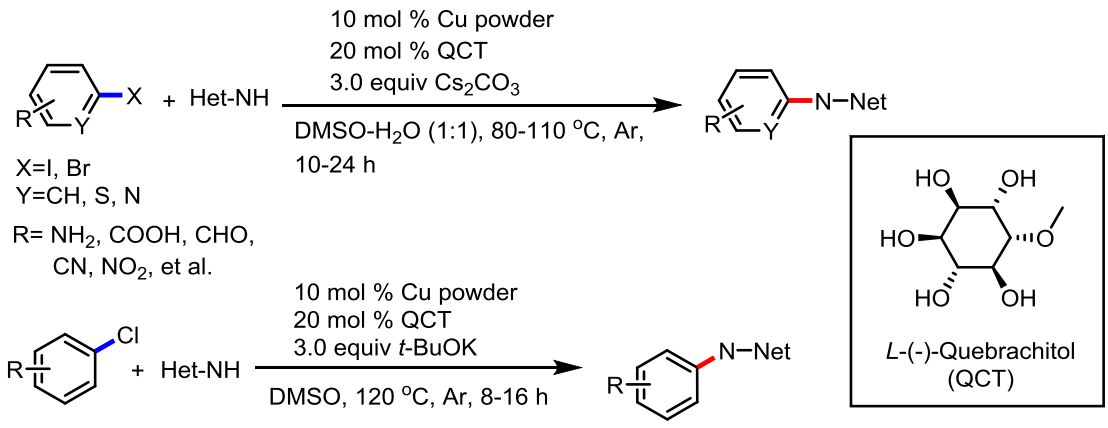
Abstract



L-(-)-quebrachitol has been found as a ligand of copper powder for selective *N*-arylation of nitrogen-containing heterocycles with aryl halides. Furthermore, another potential catalytic system (copper powder/QCT/*t*-BuOK) was successfully adapted to unactivated aryl chlorides.

Introduction

N-arylazoles are ubiquitous structural motifs in numerous biologically active compounds, natural products and pharmaceuticals and also as precursors of versatile *N*-heterocyclic carbines and auxiliary ligands for transition-metal catalysis. [1] Traditional synthetic approaches of *N*-arylazoles often depend on using highly activated aryl

halides (S_NAr reaction), [2] the classical Ullmann-type coupling reactions,[3]or the Buchwald-Hartwig reactions. [4] The classical Ullmann reactions normally requires harsh reaction conditions (high temperature, long reaction time, the narrow substrate and erratic yields). [5] However, due to the low cost and toxicity of the copper catalyst, Cu-catalyzed *N*-arylation is still attractive in synthetic applications.

To overcome the drawbacks in classical Ullmann reactions, various modified Ullmann catalytic systems have been reported continuously over the past decades, for example, the use of bidentate ligands, which allowed the coupling reaction to be conducted smoothly under the mild conditions [6] (Figure 1). However, because many ligands are not commercially available in industrial-scale, it seriously hampers their synthetic application. [6c] Notably, the toxicity and sustainability of these ligands must been taken in consideration for meeting the requirements of green chemistry.

On the other hand, quebrachitol (1-*L*-(-)-2-*O*-methyl-chiro-inositol, QCT, Figure 1) is an optically active inositol with superior water solubility, existing in a variety of plants, could be used as a chiral source in organic synthesis. [7] QCT is mainly extracted from waste water of natural rubber industry by using the matured extraction technology. [8] Arguably, developing the use of QCT could also contribute to facilitate problem solving like waste water of natural rubber industry.

Herein, we discovered that Cu (0)-catalyzed *N*-arylation could be smoothly carried out under the mild condition with the assistance of QCT. Due to its stable physicochemical properties and good water solubility, QCT could be employed as a green auxiliary ligand in Ullmann-type reaction, which simultaneously extends the industrial application of natural rubber.

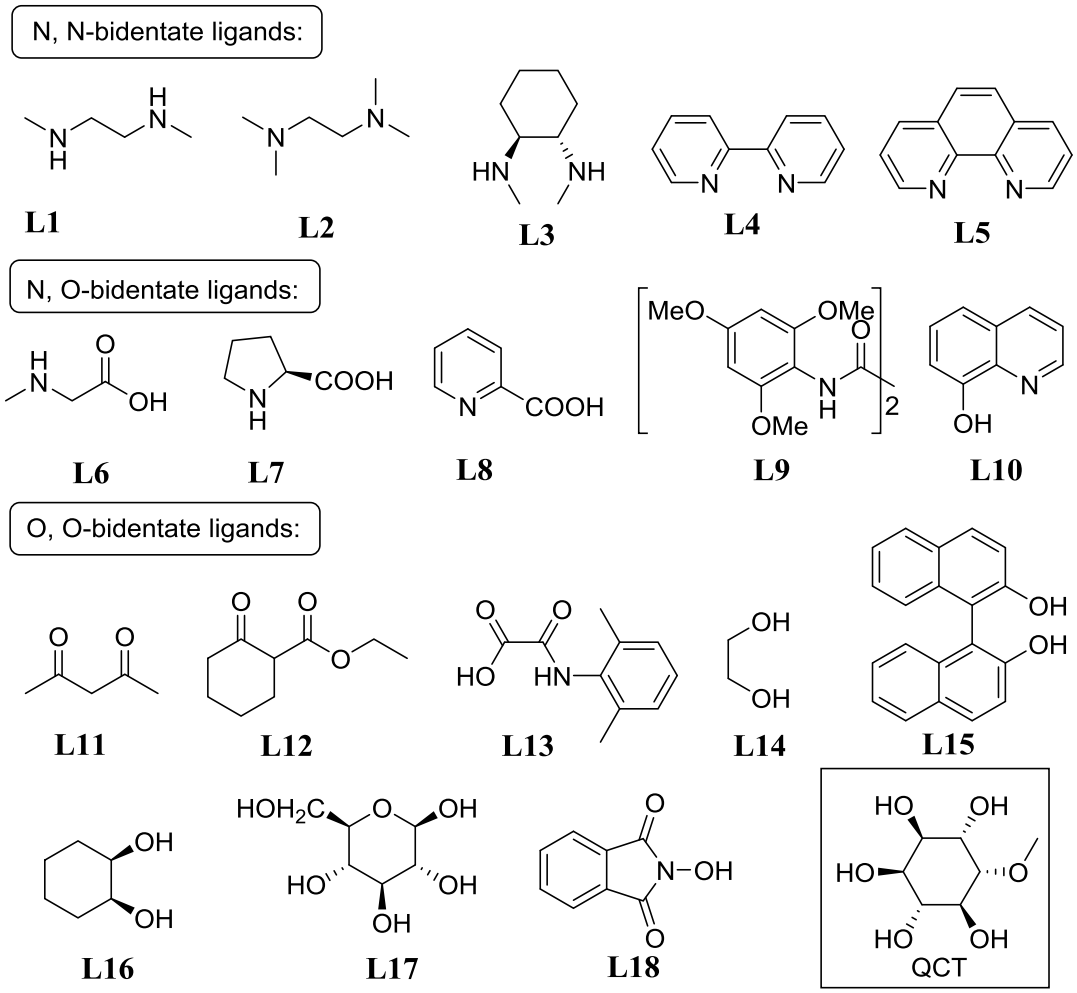


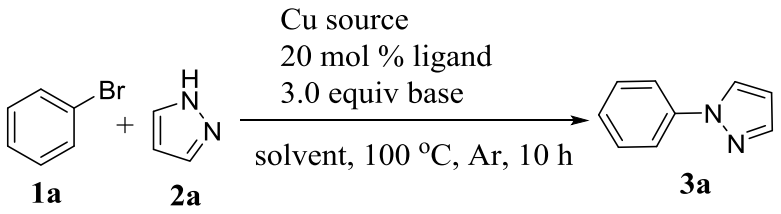
Figure 1. Chemical structures of general bidentate ligands and QCT.

Results and Discussion

As described in Table 1, we chose Cu-catalyzed coupling of bromobenzene and pyrazole as model substrates to explore optimal conditions. Initially, under basic conditions in the presence of CuI, CuBr, CuCl or Cu_2O, only a small quantity target product **3a** was observed, along with unreacted starting material (Table 1, entries 1-4). With the use of Cu_2SO_4, no desired product was seen (entry 5). Surprisingly, the C-N coupling product was obtained in 90% yield when the Cu powder was used as catalyst, and the loading of catalyst could be reduced to 10 mol % (entries 6, 7). Further studies revealed a significant effect of bases, with Cs_2CO_3 or K_2CO_3 being proved to be optimal in terms of yield (entries 7-12). Subsequent evidence showed that Cs_2CO_3 was more potential in the coupling reaction of 1-bromo-4-methoxybenzene and pyrazole (data not

shown). Polar solvents (DMSO, DMF and ethylene glycol) favored this reaction, with DMSO-H_2O being the most effective (entries 13-18). We postulated that the addition of water promoted oxidization of copper powder into Cu (I) specie. In order to investigate its effectiveness, the coupling reaction was conducted on a 10 gram scale, and 8.50 g of **3a** was obtained in 92% yield (entry 19).

Table 1. Identification of Reaction Conditions [a]



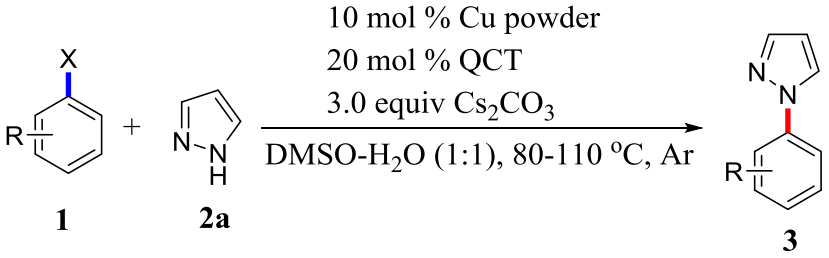
entry	Cu (mol %)	base	solvent	yield (%) [b]
1	CuI (20)	K_2CO_3	DMSO	56
2	CuBr (20)	K_2CO_3	DMSO	55
3	CuCl (20)	K_2CO_3	DMSO	21
4	Cu_2O (20)	K_2CO_3	DMSO	trace
5	$CuSO_4$ (20)	K_2CO_3	DMSO	0
6	Cu (20)	K_2CO_3	DMSO	90
7	Cu (10)	K_2CO_3	DMSO	90
8	Cu (10)	$K_3PO_4 \cdot 3H_2O$	DMSO	75
9	Cu (10)	Et_3N	DMSO	0
10	Cu (10)	Cs_2CO_3	DMSO	93
11	Cu (10)	$NaHCO_3$	DMSO	0
12	Cu (10)	*t*-BuOK	DMSO	86
13	Cu (10)	Cs_2CO_3	DMSO-H_2O (1:1)	94
14	Cu (10)	Cs_2CO_3	DMF	88
15	Cu (10)	Cs_2CO_3	dioxane	0
16	Cu (10)	Cs_2CO_3	dichloroethane	0
17	Cu (10)	Cs_2CO_3	toluene	0
18	Cu (10)	Cs_2CO_3	ethylene glycol	86

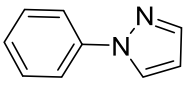
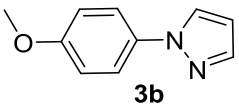
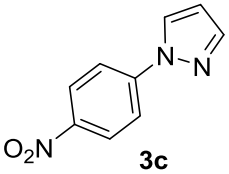
19 [c]	Cu (10)	Cs_2CO_3	DMSO-H_2O (1:1)	92

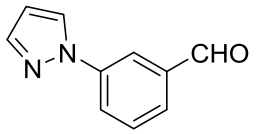
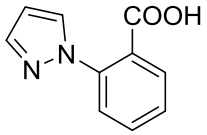
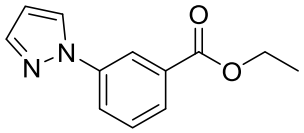
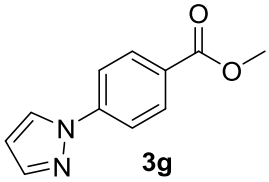
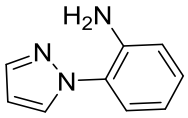
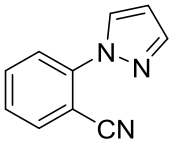
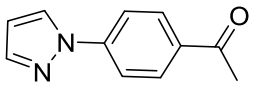
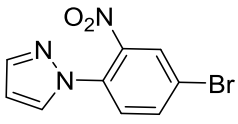
[a] Standard condition: **1a** (0.8 mmol), **2a** (1.0 mmol), 20 mol % QCT, solvent (2.0 mL), 100 °C, 10 h, Ar. [b] Isolated yield. [c] The loading of **1a** was 10 gram.

With optimized conditions in hand, we explored the scope of the coupling reactions of aryl halides with pyrazole in the presence of Cu powder (10 mol %), QCT (20 mol %) and Cs_2CO_3 (3.0 equiv), and the results were summarized in Table 2. Notably, the catalytic system could facilitate the coupling reactions of aryl iodides and pyrazole in excellent yields at 80 °C, while the aryl bromides also proceeded well at higher temperature (100 °C) to afford products in 68-99% yields. Furthermore, electron-rich substitutions on aryl bromides were not conducive and led to lower yields (**3a** *vs*. **3b**). A range of reactive functional groups (*e.g.* NH_2, CHO, COOH, CN.) was proved to be compatible, and the coupling products (*e.g.* **3d**, **3e**, **3h**, **3i**) were obtained in excellent yields from corresponding aryl halides and pyrazole. Consequently, this protocol has offered an alternative scheme for the synthesis of highly functional azoles.

Table 2. Scope with Respect to Aryl Halides [a]



entry	X	temp (°C)/time (h)	product	yield (%) [b]
1	Br	100/10	 **3a**	94
2	Br	110/20	 **3b**	68
3	I	80/10		93
4	Br	80/10	 **3c**	99

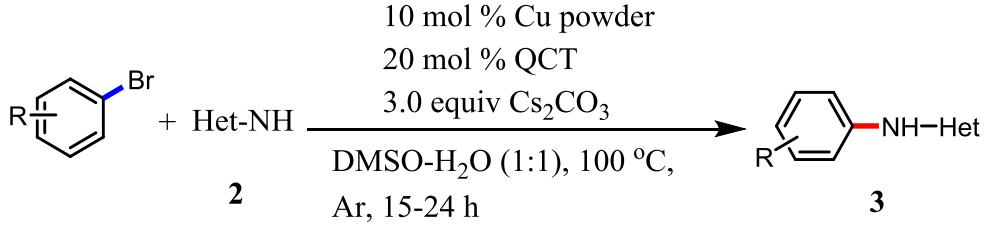
5	Br	80/16	 **3d**	93
6	I	80/10	 **3e**	98
7	I	80/10	 **3f**	95 [c]
8	I	80/10	 **3g**	96 [c]
9	Br	110/24	 **3h**	82
10	Br	110/24	 **3i**	89
11	Br	110/16	 **3j**	90
12	I	80/10	 **3k**	91

[a] Reaction conditions: **1** (0.8 mmol), **2a** (1.0 mmol), 10 mol % Cu powder, 20 mol % QCT, Cs_2CO_3 (2.4 mmol), DMSO-H_2O (1 mL: 1 mL). [b] Isolated yield. [c] DMSO (2 mL) as solvent to avoid hydrolysis of esters.

The reaction also enjoys wide substrate scope with respect to *N*-heterocycles (Table 3). The coupling reactions also could go smoothly by changing pyrazole with pyrroles, imidazoles, indoles, benzimidazoles. Not surprisingly, the electron-rich aryls were

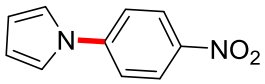
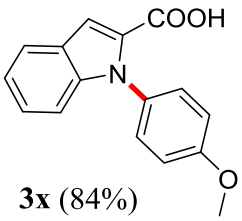
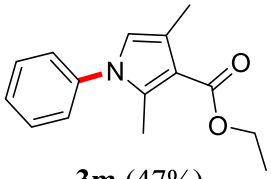
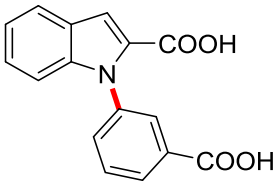
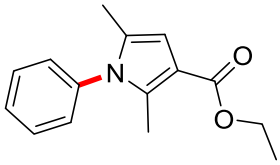
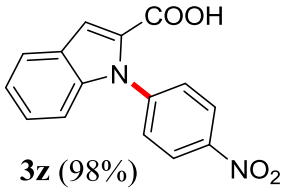
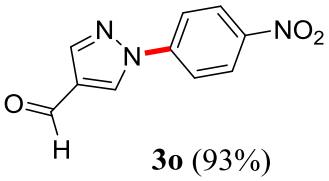
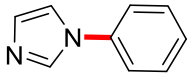
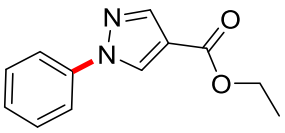
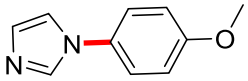
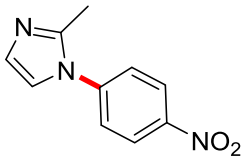
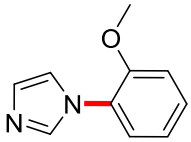
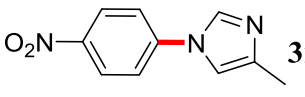
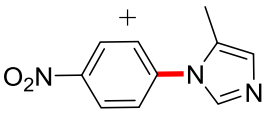
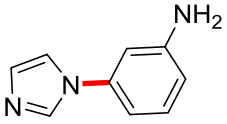
superior to electron-deficient aryls, for example, **3t** and **3u** with the yield of 65% and 95%, respectively. Pyrrole gave the desired compound in moderate yield (54%), which might result from the acidity of pyrrole. Sufficient evidence showed that the reaction with unsymmetrical heterocycles proceeded with regioselectivity. [6b-6c] Accordingly, using asymmetric imidazole afforded two imidazole tautomers **3r** and **3s** with a ratio of 12:1 in 89% yield. As evidenced by the example presented in Table 3, the catalytic system displayed more regioselectivity than using CuI system. [6c] Not suppursingly, the C-N coupling reactions were hindered in steric pyrroles, it explained the fact that affording **3m** only in 47% and **3n** was not observed. In our cases, bi-functional compound 2-mercaptobenzimidazole was selectively *S*-arylated (**3v**) without *N*-arylation (entry 10). The 5-hydroxyindole was selectively *N*-arylated by providing **3w** in excellent yield without *O*-arylation (entry 11). However, utilizing CuI/*L*-Proline [6b] gave **3w** and **3ah** in 65% and 20% yield, respectively (Scheme 1A). For 2-indolecarboxylic acid substrates, *N*-arylation reactions were readily conducted in excellent yields, from 84% to 98%. According to the reports that pyrrole-2-carboxylic acid and 2-picolinic acid could be generally applied as chelating ligands of transition metal, [9] we postulated that 2-indolecarboxylic acid also acted as an efficient auxiliary ligand of copper, and it accounted for the excellent yields. The imidazole could also participate in C-N coupling reaction, especially the unactivated aryl bromines, for example, 4-bromoanisole, 2-bromoanisole and 3-bromoaniline yielded corresponding desire compounds in moderate yield (**3ab**, **3ac**, and **3ad**). Moreover, the sterically hindered 2-methyl-1*H*-benzo[*d*]imidazole afforded the product (**3ag**) only in 54% yield.

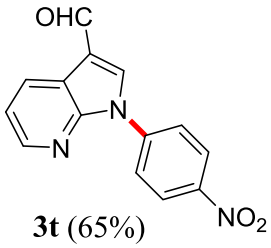
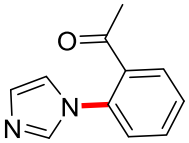
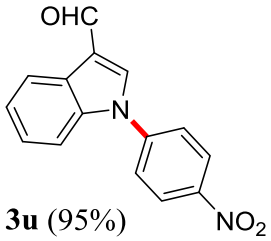
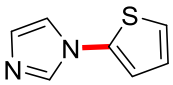
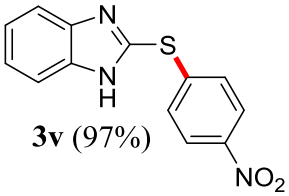
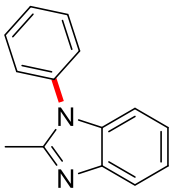
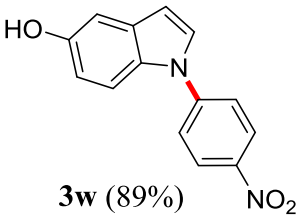
Table 3. Scope with Respect to *N*-Containing Heterocyclic [a]



2 **3**

entry	product (yield) [b]	entry	product (yield) [b]

1	 **3l** (54%)	12	 **3x** (84%)
2[c]	 **3m** (47%)	13	 **3y** (98%)
3[c]	 **3n** (0%)	14	 **3z** (98%)
4	 **3o** (93%)	15	 **3aa** (88%)
5[c]	 **3p** (91%)	16	 **3ab** (69%)
6	 **3q** (88%)	17	 **3ac** (63%)
7	 **3r** (12) +  **3s** (1) 89%	18	 **3ad** (72%)

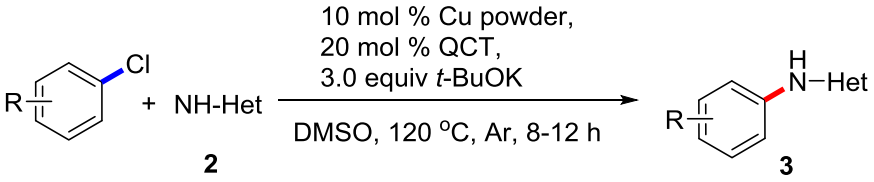
8	 **3t** (65%)	19	 **3ae** (85%)
9	 **3u** (95%)	20	 **3af** (81%)
10	 **3v** (97%)	21	 **3ag** (54%)
11	 **3w** (89%)		

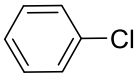
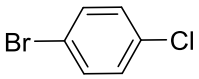
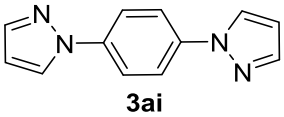
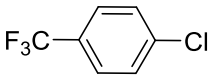
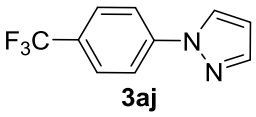
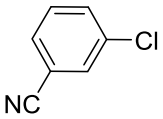
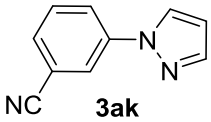
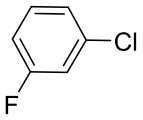
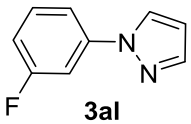
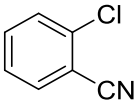
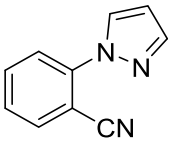
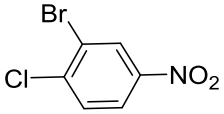
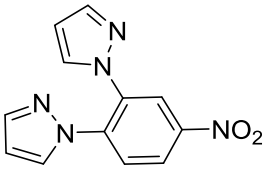
[a] Reaction conditions: Aryl bromides (0.8 mmol), **2** (1.0 mmol), 10 mol % Cu powder, 20 mol % QCT, Cs_2CO_3 (2.4 mmol), DMSO-H_2O (1 mL: 1 mL), 100 °C, unless otherwise noted. [b] Isolated yield. [c] DMSO (2 mL) as solvent.

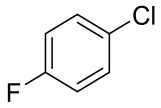
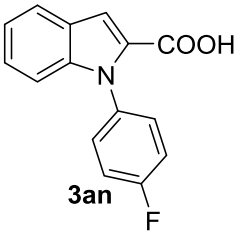
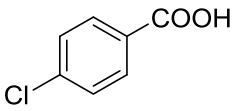
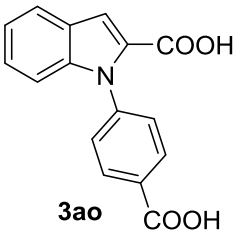
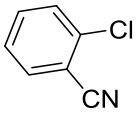
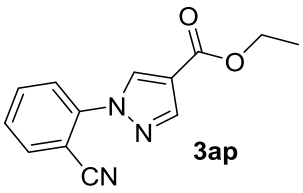
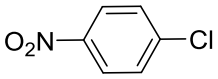
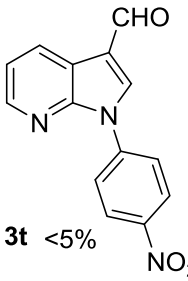
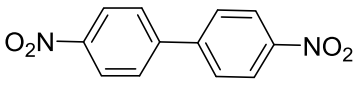
Inspired by the excellent performance of Cu/QCT catalytic system, the inert aryl chlorides were also examined for the coupling reactions (Table 4). Regrettably, only a trace of **3a** was observed using chlorobenzene and pyrazole as starting materials. After subsequent optimization, the coupling reaction could proceed at 120 °C with Cu/QCT catalytic system by replacing Cs_2CO_3 with *t*-BuOK. The scope of Cu-catalyzed reaction has been further tested using a wide range of aryl chlorides. The corresponding *N*-arylazoles were formed in 70-92% yields in relatively short time (8-16 h). Apparently, aryl chlorides and aryl bromides could undergo the *N*-arylation reaction with quantitative conversion except for the aryl fluorides (entries 2, 5, 7). Notably, only a trace (<5%) of **3t** was detected when *p*-nitrochlorobenzene was reacted with the unactivated 7-azaindole-3-carbaldehyde. The major product was Ullmann biaryl

homocoupling compound **3aq** (30% yield).

Table 4. Cu/QCT-catalyzed Coupling of Aryl Chloride with Pyrazol in the Presence of *t*-BuOK [a]



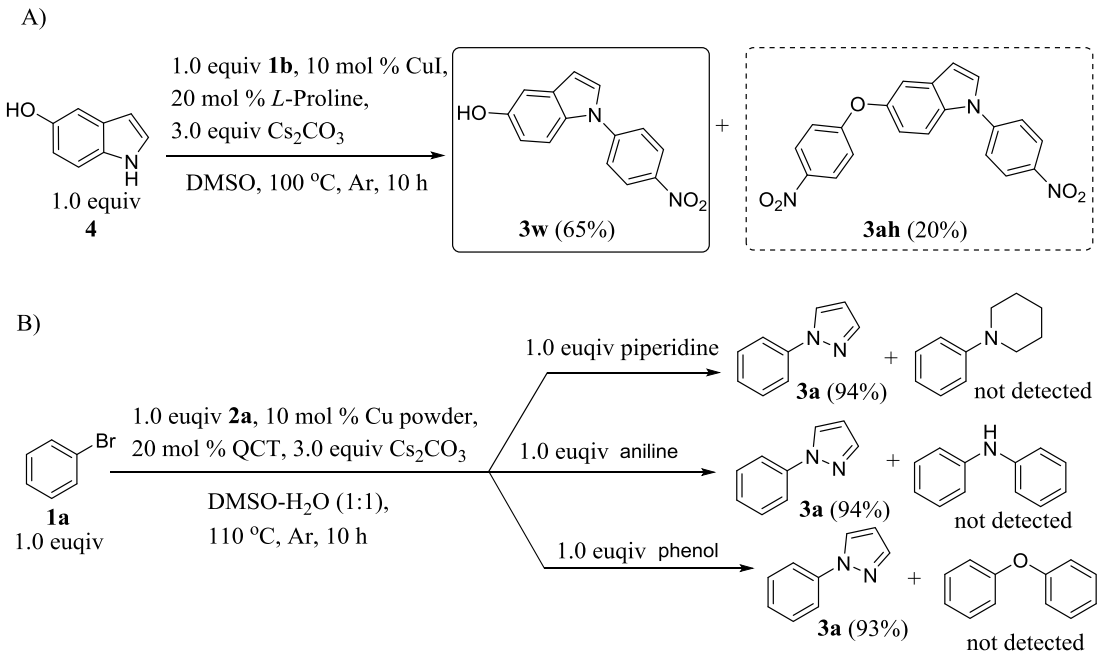
entry	substrate	product	time (h)	yield (%) [b]
1		 **3a**	8	70
2[c]		 **3ai**	12	75
3		 **3aj**	8	72
4		 **3ak**	8	85
5		 **3al**	10	70
6		 **3i**	10	87/54[d]
7[c]		 **3am**	16	81

8		 **3an**	12	79
9		 **3ao**	12	85
10		 **3ap**	8	90
11		 **3t** <5%  **3aq** 30%	12	--

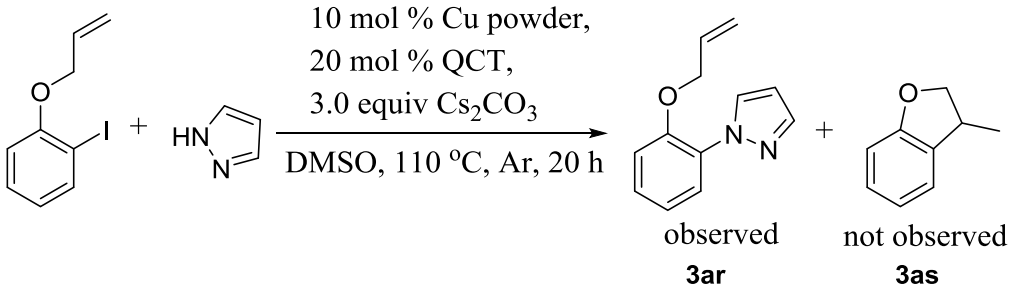
[a] Reaction conditions: Aryl chlorides (0.8 mmol), **2** (1.0 mmol), 10 mol % Cu powder, 20 mol % QCT, *t*-BuOK (2.4 mmol), DMSO (2 mL). [b] Isolated yield. [c] The loading of pyrazole was 2.0 mmol. [d] Control experiment conditions: 2-chlorobenzonitrile (0.8 mmol), pyrazole (1.0 mmol), 20 mol % QCT, *t*-BuOK (2.4 mmol), DMSO (2 mL).

To further explore the selectivity, competition reactions among different nucleophiles using bromobenzene in Cu/QCT catalytic system were next investigated in Scheme 1B. When the competitive reaction was conducted between pyrazole and piperidine, it was encouraging to observe the sole formation of **3a** in good yield at 110 °C. Consistent results were also obtained for pyazole competing with aniline and phenol.

Scheme 1. Competition Reactions



Scheme 2. Reaction between 2-(Allyloxy)iodobenzene and Pyrazole



Finally, to gain insight into the mechanism of cross coupling reaction, we used the radical clock 1-allyloxy-2-iodobenzene as substrate to determine if the aryl halide activation step proceeds *via* radical intermediate.[10] Results showed that no conversation of ring closure product **3as** was observed, only affording the C-N coupling compound **3ar** (Scheme 2). Thus, this catalytic reaction might run *via* a prototypical Cu (I)/Cu (III) catalytic cycle instead of a radical pathway. [11]

Conclusion

In summary, we have developed an efficient and environmentally friendly catalytic system for assemble of *N*-arylazoles with aryl halides and related *N*-heterocycles, where the inexpensive copper powder and a green ligand QCT were employed. Herein, the direct usage of readily available QCT in ligand-promoted Ullmann-type is

unprecedented. This catalytic system has displayed highly selectivity towards the formation of *N*-arylazoles against other competitive nucleophiles, and enjoyed a large scope with respect to *N*-containing heterocyclics and aryl halides. Applications of QCT to other coupling reactions, along with detailed mechanistic studies, are under progress.

Experimental Section

General information

All of the starting materials, reagents, and solvents are commercially available and used without further purification. Melting points were determined with a X-4 apparatus and were uncorrected. The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Electrospray ionization mass spectrometry (ESI-MS) analyses were recorded in an Agilent 1100 Series MSD Trap SL (Santa Clara, CA, USA). The reactions were monitored by thin-layer chromatography (TLC: HG/T2354-92, GF254), and compounds were visualized on TLC with UV light.

General Procedure for Catalytic Experiments.

To a 10 mL vial was charged with Cu powder (5 mg, 0.08 mmol), QCT (30 mg, 0.16 mmol), Cs_2CO_3 (78 mg, 2.4 mmol) or *t*-BuOK (0.27 g, 2.4 mmol), nitrogen-containing heterocycle (1.0 mmol), aryl halide (0.8 mmol), and DMSO-H_2O (1:1, 2 mL) or DMSO (2 mL). The flask was evacuated and backfilled with argon three times, and the resulting suspension was heated in appropriate temperature oil bath with rapid stirring for the indicated time. After the complete consumption of aryl halide monitored by TLC, the reactor was cooled to rt, the flask was opened to air and the reaction mixture was the mixture (If the product was acidic, the mixture was acidified.) diluted with ethyl acetate (5 mL), filtered *via* a celite pad, and washed with ethyl acetate (10-20 mL). The combined organic phase was concentrated, and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

Larg scale synthesis of 1-phenyl-1*H*-pyrazole (3a)

To a solution of Cu powder (0.41 g, 6.40 mmol), QCT (2.49 g, 12.8 mmol), Cs_2CO_3 (62.7 g, 0.19 mol), pyrazole (5.06 g, 80.1 mmol), DMSO (25 mL) and H_2O (25 mL) were added bromobenzene (10 g, 64.1 mmol). The flask was evacuated and backfilled with argon three times, and the resulting suspension was heated in a 100 °C oil bath with rapid stirring for 10 h. The reactor was cooled to room temperature, the flask was opened to air and the reaction mixture was diluted with ethyl acetate (50 mL), filtered *via* a celite pad, washed with ethyl acetate (50 mL). The combined organic phase was concentrated, and the resulting residue was purified by column chromatography on silica gel to provide the **3a** as colorless liquid (8.50 g, 92%).

Compound characterization data

1-Phenyl-1H-pyrazole (3a). [13] According to the general procedure, the **3a** was obtained as colorless liquid (0.11 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93-7.92 (d, *J*=2.4 Hz, 1 H), 7.73-7.68 (m, 3H), 7.47-7.43 (m, 2H), 7.30-7.25 (m, 1H), 6.46 (t, *J*=2.3 Hz, 1H). MS (ESI$^+$): m/z 145.04 $[M+H]^+$.

1-(4-Methoxyphenyl)-1H-pyrazole (3b). [14] According to the general procedure, the **3b** was obtained as white solid (0.13 g, 93%). m.p. 40-42 °C (lit. 42 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (d, *J*=2.4 Hz, 1H), 7.70 (d, *J*=1.4 Hz, 1H), 7.61-7.57 (m, 2H), 6.99-6.95 (m, 2H), 6.44 (t, *J*=1.9 Hz, 1H), 3.84 (s, 3H). MS (ESI$^+$): m/z 175.12 $[M+H]^+$.

1-(4-Nitrophenyl)-1H-pyrazole (3c). [15] According to the general procedure, the **3c** was obtained as yellow solid (0.15 g, 99%). m.p. 167-168 °C (lit. 168.5-169 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.37-8.33 (m, 2H), 8.04 (d, *J*=2.6 Hz, 1H), 7.91-7.87 (m, 2H), 7.81 (d, *J*=1.5 Hz, 1H), 6.57-5.56 (q, *J*=2.4 Hz, 1.9 Hz, 1H). MS (ESI$^+$): m/z 190.08 $[M+H]^+$.

3-(1H-Pyrazol-1-yl)benzaldehyde (3d) [16]**.** According to the general procedure, the **3d** was obtained as off-white solid (0.13 g, 93%). m.p. 28-30 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.08 (s, 1H), 8.19 (t, *J*=1.8 Hz, 1H), 8.05-8.02 (m, 2H), 7.81-7.76 (m,

2H), 7.64 (t, *J*=7.9 Hz, 1H), 6.52 (t, *J*=2.1 Hz, 1H). MS (ESI^+): m/z 173.07 $[M+H]^+$.

2-(1H-Pyrazol-1-yl)benzoic acid (3e) [17]**.** According to the general procedure, the **3e** was obtained as white solid (0.15 g, 98%). m.p. 128-129 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 11.41 (br, 1H), 8.06-8.04 (dd, *J*=7.8 Hz, 1.1 Hz, 1H), 7.77-7.75 (m, 2H), 7.63-7.59 (m, 1H), 7.50-7.46 (t, *J*=7.5 Hz, 1H), 7.43 (d, *J*=7.8 Hz, 1H), 6.49-6.48 (t, *J*=2.1 Hz, 1H). MS (ESI^-): m/z 187.05 $[M-H]^-$.

Ethyl 3-(1H-Pyrazol-1-yl)benzoate (3f) [18]**.** According to the general procedure, the **3f** was obtained as yellow liquid (0.16 g, 95%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32 (t, *J*=1.9 Hz, 1H), 8.00 (d, *J*=2.4 Hz, 1H), 7.98-7.94 (m, 2H), 7.76 (d, *J*=1.6 Hz, 1H), 7.54 (t, *J*=7.9 Hz, 1H), 6.50 (t, *J*=2.0 Hz, 1H), 4.45-4.39 (q, *J*=14.3 Hz, 7.1 Hz, 2H), 1.42 (t, *J*=7.2 Hz, 3H). MS (ESI^+): m/z 217.10 $[M+H]^+$.

Methyl 4-(1H-pyrazol-1-yl)benzoate (3g) [19]**.** According to the general procedure, the **3g** was obtained as white solid (0.16 g, 96%). m.p. 103-105 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15-8.12 (m, 2H), 8.01 (d, *J*=2.4 Hz, 1H), 7.81-7.78 (m, 2H), 7.77 (d, *J*=1.4 Hz, 1H), 6.51 (t, *J*=2.1 Hz, 1H), 3.94 (s, 3H). MS (ESI^+): m/z 203.11 $[M+H]^+$.

2-(1H-Pyrazol-1-yl)aniline (3h). [20] According to the general procedure, the **3h** was obtained as brown oil (0.10 g, 82%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75-7.72 (dd, *J*=8.6 Hz, 1.2 Hz, 2H), 7.20-7.13 (m, 2H), 6.86-6.84 (dd, *J*=8.0 Hz, 0.9 Hz, 1H), 6.81-6.77 (dt, *J*=7.7 Hz, 1.1 Hz, 1H), 6.45 (t, *J*=2.0 Hz, 1H), 4.63 (br, 2H). MS (ESI^+): m/z 160.09 $[M+H]^+$.

2-(1H-Pyrazol-1-yl)benzonitrile (3i) [21]**.** According to the general procedure, the **3i** was obtained as yellow oil (0.12 g, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15 (d, *J*=2.5 Hz, 1H), 7.81-7.70 (m, 3H), 7.73-7.69 (dt, *J*=7.6 Hz, 1.5 Hz, 1H), 7.45-7.41 (dt, *J*=7.6 Hz, 1.0 Hz, 1H), 6.55 (t, *J*=2.1 Hz, 1H). MS (ESI^+): m/z 170.10 $[M+H]^+$.

1-(4-(1H-Pyrazol-1-yl)phenyl)ethan-1-one (3j).[22] According to the general procedure, the **3j** was obtained as white solid (0.13 g, 90%). m.p. 93-94 °C (lit. 106-108 °C). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.08-8.05 (m, 2H), 8.02 (d, *J*=2.5 Hz, 1H), 7.83-7.81 (m, 2H), 7.78 (d, *J*=1.5 Hz, 1H), 6.52 (t, *J*=2.0 Hz, 1H), 2.63 (s, 3H). MS (ESI^+): m/z 187.13 $[M+H]^+$.

1-(4-Bromo-2-nitrophenyl)-1H-pyrazole (3k)[23]**.** According to the general procedure,

the **3k** was obtained as yellow solid (0.19 g, 91%). m.p. 74-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.00 (d, *J*=2.1 Hz, 1H), 7.81-7.78 (dd, *J*=8.5 Hz, 2.2 Hz, 1H), 7.75 (d, *J*=1.6 Hz, 1H), 7.69 (d, *J*=2.5 Hz, 1H), 7.49 (d, *J*=8.5 Hz, 1H), 6.51 (t, *J*=2.1 Hz, 1H). MS (ESI^+): m/z 267.98 $[M+H]^+$, 269.97 $[M+H]^+$.

1-(4-Nitrophenyl)-1H-pyrrole (3l). [24] According to the general procedure, the **3l** was obtained as yellow solid (51 mg, 54%). m.p. 180-182 °C (lit. 179-180 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.33-8.30 (m, 2H), 7.54-7.50 (m, 2H), 7.18 (t, *J*=2.2 Hz, 2H), 6.43 (t, *J*=2.2 Hz, 2H). MS (ESI^+): m/z 189.13 $[M+H]^+$.

Ethyl 2,4-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate (3m) [25]**.** According to the general procedure, the **3m** was obtained as yellow solid (91 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47-7.36 (m, 3H), 7.26-7.23 (m, 2H), 6.48 (s, 1H), 4.33-4.28 (q, *J*=14.2 Hz, 7.1 Hz, 2H), 2.41 (s, 3H), 2.28 (s, 3H), 1.37 (t, *J*=7.1 Hz, 3H). MS (ESI^+): m/z 244.18 $[M+H]^+$.

1-(4-Nitrophenyl)-1H-pyrazole-4-carbaldehyde (3o).[26] According to the general procedure, the **3o** was obtained as yellow solid (0.16 g, 93%). m.p. 158-160 °C (lit. 84 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.02 (s, 1H), 8.55 (s, 1H), 8.41-8.38 (m,2 H), 8.23 (s, 1H), 7.97-7.94 (m, 2H). MS (ESI^+): m/z 218.34 $[M+H]^+$.

Ethyl 1-phenyl-1H-pyrazole-4-carboxylate (3p). [27] According to the general procedure, the **3p** was obtained as brown solid (0.16 g, 91%). m.p. 90-91 °C (lit. 96-99 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.41 (s, 1H), 8.10 (s, 1H), 7.72-7.70 (m, 2H), 7.49 (t, *J*=7.6 Hz, 2H), 7.36 (t, *J*=7.2 Hz, 1H), 4.37-4.32 (q, *J*=14.3 Hz, 7.1 Hz, 2H), 1.38 (t, *J*=7.1 Hz, 3H). MS (ESI^+): m/z 217.09 $[M+H]^+$.

2-Methyl-1-(4-nitrophenyl)-1H-imidazole (3q). [28] According to the general procedure, the **3q** was obtained as light yellow solid (0.14 g, 88%). m.p. 128-130 °C (lit. 140-142 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.38 (d, *J*=9.0 Hz, 2H), 7.78 (d, *J*=9.0 Hz, 2H), 7.45 (d, *J*=1.3 Hz, 2H), 7.0 (d, *J*=1.2 Hz, 1H), 2.38 (s, 3H). MS (ESI^+): m/z 204.11 $[M+H]^+$.

4-Methyl-1-(4-nitrophenyl)-1H-imidazole (3r) **and** ***5-Methyl-1-(4-nitrophenyl)-1H-imidazole (3s)*** [29]**.** According to the general procedure, the **3r** and **3s** was obtained as light yellow solid (0.14 g, 89%). m.p. 125-133 °C (mixture solid). ^{1}H NMR (3r:

3s=12:1, 400 MHz, $CDCl_3$): δ (ppm) 8.42-8.39 (m, 0.18 H), 8.38-8.34 (m, 2H), 7.92 (d, *J*=1.0 Hz, 1H), 7.67 (br, 0.07 H), 7.56-7.52 (m, 2H), 7.52-7.49 (m, 0.17H), 7.10 (s, 1H), 6.99 (br, 0.07 H), 2.32 (d, *J*=0.6 Hz, 3H), 2.26 (s, 0.26 H). MS (ESI^+): m/z 204.09 $[M+H]^+$.

1-(4-Nitrophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (3t). According to the general procedure, the **3t** was obtained as yellow solid (0.14 g, 65%). m.p. 150-152 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.09 (s, 1H), 9.12 (s, 1H), 8.59-8.56 (dd, *J*=7.8 Hz, 1.6 Hz, 1H), 8.53-8.52 (dd, *J*=7.8 Hz, 1.6 Hz, 1H), 8.51-8.47 (m, 2H), 8.38-8.34 (m, 2H), 7.51-7.48 (q, *J*=7.8 Hz, 4.8 Hz, 1H). ^{13}C {1H} NMR (400 MHz, $CDCl_3$): δ (ppm) 184.8, 150.7, 146.1, 142.3, 135.9, 131.7, 126.0, 125.2, 124.0, 123.8, 119.0, 118.7. MS (ESI^+): m/z 268.07 $[M+H]^+$.

1-(4-Nitrophenyl)-1H-indole-3-carbaldehyde (3u). [22] According to the general procedure, the **3u** was obtained as yellow solid (0.20 g, 95%). m.p. 251-252 °C (lit. 251-252 °C). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.09 (s, 1H), 8.77 (s, 1H), 8.50 (d, *J*=9.0 Hz, 2H), 8.26-8.24 (m, 1H), 8.04 (d, *J*=9.0 Hz, 2H), 7.73-7.71 (m, 1H), 7.45-7.38 (m, 2H). MS (ESI^+): m/z 267.06 $[M+H]^+$.

2-((4-nitrophenyl)thio)-1H-benzo[d]imidazole(3v). [30] According to the general procedure, the **3v** was obtained as yellow solid (0.21 g, 97%). m.p. 166-169 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.22 (br, 1H), 8.22 (d, *J*=7.6 Hz, 2H), 7.70-7.51 (m, 4H), 7.30-7.24 (m, 2H). ESI-MS: m/z 272.04 $[M+H]^+$.

1-(4-Nitrophenyl)-1H-indol-5-ol (3w). According to the general procedure, the **3w** was obtained as yellow solid (0.18 g, 89%). m.p. 188-191 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.40 (d, *J*=9.0 Hz, 2H), 7.67 (d, *J*=9.0 Hz, 2H), 7.53 (d, *J*=8.8 Hz, 1H), 7.36 (d, *J*=3.3 Hz, 1H), 7.09 (d, *J*=2.4 Hz, 1H), 6.87-6.84 (dd, *J*=8.8 Hz, 2.4 Hz, 1H), 6.66 (d, *J*=3.2 Hz, 1H), 4.60 (br, 1H). ^{13}C {1H} NMR (400 MHz, DMSO-d_6): δ (ppm) 152.8, 145.2, 144.2, 131.5, 129.2, 128.6, 125.8, 122.8, 113.2, 111.9, 105.8, 105.7. MS (ESI^-): m/z 253.06 $[M-H]^-$. HRMS (ESI): $C_{14}H_9N_2O_3^-$ $[M-H]^-$ calcd for 253.0619; found: 253.0631.

1-(4-Methoxyphenyl)-1H-indole-2-carboxylic acid (3x). [31] According to the general procedure, the **3x** was obtained as white solid (0.18 g, 84%). m.p. 208-211 °C. ^1H NMR

(400 MHz, $CDCl_3$): δ (ppm) 7.74-7.72 (dt, *J*=8.0 Hz, 1.0 Hz, 1H), 7.54 (d, *J*=0.8 Hz, 1H), 7.31-7.26 (m, 2H), 7.24-7.23 (m, 1H), 7.21-7.17 (m,1 H), 7.09-7.06 (m, 1H), 7.03-6.99 (m, 2H), 3.90 (s, 3H). MS (ESI^-): m/z 266.09 $[M-H]^-$.

1-(3-Carboxyphenyl)-1H-indole-2-carboxylic acid (3y). [32]According to the general procedure, the **3y** was obtained as white solid (0.22 g, 98%). m.p. 245-246 °C. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.07-8.02 (m, 1H), 7.82-7.81 (m, 1H), 7.80-7.77 (dt, *J*=7.9 Hz, 1.1 Hz, 1H), 7.70-6.63 (m, 2H), 7.44 (d, *J*=0.6 Hz, 1H), 7.32-7.28 (m, 1H), 7.22-7.18 (m, 1H), 7.05-7.03 (m, 1H). ^{13}C {1H} NMR (400 MHz, DMSO-d_6): δ (ppm) 167.2, 162.3, 140.3, 138.9, 132.6, 132.3, 130.3, 129.9, 129.1, 128.7, 126.4, 126.0, 123.0, 121.8, 111.9, 111.4. MS (ESI^-): m/z 280.08 $[M-H]^-$. HRMS (ESI): $C_{16}H_{10}NO_4^-$ $[M-H]^-$ calcd for 280.0615; found: 280.0612.

1-(4-Nitrophenyl)-1H-indole-2-carboxylic acid (3z). [32] According to the general procedure, the **3z** was obtained as yellow solid (0.22 g, 98%). m.p. 243-244 °C (lit. 263-264 °C). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.02 (br, 1H), 8.40-8.36 (m, 2H), 7.81-7.79 (d, *J*=7.9 Hz, 1H), 7.74-7.70 (m, 2H), 7.50 (s, 1H), 7.36-7.32 (m, 1H), 7.24 (t, *J*=7.2 Hz, 1H), 7.19 (d, *J*=8.4 Hz, 1H). MS (ESI^-): m/z 281.07 $[M-H]^-$.

1-Phenyl-1H-imidazole (3aa). [33] According to the general procedure, the **3aa** was obtained as colorless liqud (0.10 g, 88%). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.28 (s, 1H), 7.77 (s, 1H), 7.67-7.64 (m, 2H), 7.54-7.50 (m, 2H), 7.37 (t, *J*=7.4 Hz, 1H), 7.14 (s, 1H). MS (ESI^+): m/z 145.04 $[M+H]^+$.

1-(4-Methoxyphenyl)-1H-imidazole (3ab). [28] According to the general procedure, the **3ab** was obtained as white solid (96 mg, 69%). m.p. 55-57 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (s, 1H), 7.30 (d, *J*=9.0 Hz, 2H), 7.20 (d, *J*=7.6 Hz, 2H),6.97 (t, *J*=6.8 Hz, 2H). MS (ESI^+): m/z 175.07 $[M+H]^+$.

1-(2-Methoxyphenyl)-1H-imidazole (3ac). [34] According to the general procedure, the **3ac** was obtained as colorless liqud (88 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78 (s, 1H), 7.37-7.33 (m, 1H), 7.28-7.26 (dd, J=7.7 Hz, 1.5 Hz, 1H), 7.20-7.16 (m, 2H), 7.06-7.01 (m, 2H), 3.84 (s, 3H). MS (ESI^+): m/z 175.06 $[M+H]^+$.

3-(1H-Imidazol-1-yl)aniline (3ad). [6a] According to the general procedure, the **3ad** was obtained as white solid (92 mg, 72%). m.p. 110-111 °C. ^1H NMR (400 MHz,

$CDCl_3$) δ (ppm): 7.82 (s, 3H), 7.26-7.17 (m, 3H), 6.67-6.74 (m, 1H), 6.68-6.64 (m, 2H), 3.66 (br, 2H). MS (ESI^+): m/z 160.05 $[M+H]^+$.

1-(2-(1H-Imidazol-1-yl)phenyl)ethan-1-one (3ae). [35] According to the general procedure, the **3ae** was obtained as white solid (0.13 g, 85%). m.p. 183-184 °C. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62-7.60 (dd, J=7.4 Hz, 0.4 Hz, 1H), 7.37-7.33 (m, 1H), 7.27-7.19 (m, 3H), 7.13 (s, 1H), 1.88 (s, 3H). MS (ESI^+): m/z 187.09 $[M+H]^+$.

1-(Thiophen-2-yl)-1H-imidazole (3af). [34] According to the general procedure, the **3af** was obtained as colorless liqud (97 mg, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (s, 3H), 7.19-7.11 (m, 3H), 7.00-6.96 (m, 2H). MS (ESI^+): m/z 151.03 $[M+H]^+$.

2-Methyl-1-phenyl-1H-benzo[d]imidazole (3ag). [36] According to the general procedure, the **3ag** was obtained as white solid (90 mg, 54%). m.p. 62-65 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (d, *J*=7.9 Hz, 1H), 7.60-7.56 (m, 2H), 7.54-7.49 (m, 1H), 7.38-7.35 (m, 2H), 7.29-7.24 (m, 1H), 7.21-7.17 (m, 1H), 7.14-7.12 (m, 1H), 2.51 (s, 3H). MS (ESI^+): m/z 209.11 $[M+H]^+$.

5-(4-Nitrophenoxy)-1-(4-nitrophenyl)-1H-indole (3ah). According to the general procedure, the **3ah** was obtained as yellow solid (0.16 g, 20%). m.p. 161-162 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.80-8.42 (m, 2H), 8.21-8.18 (m, 2H), 7.73-7.69 (m, 2H), 7.68 (d, *J*=8.9 Hz, 1H), 7.47-7.42 (dd, *J*=17.8 Hz, 3.3 Hz, 2H), 7.06-7.03 (dd, *J*=9.0 Hz, 2.4 Hz, 2H), 7.03-7.00 (m, 2H), 6.77 (d, *J*=3.2 Hz, 1H). ^{13}C {1H} NMR (400 MHz, $CDCl_3$): δ (ppm) 164.4, 149.3, 145.5, 144.8, 142.4, 133.0, 131.1, 128.8, 125.9, 125.6, 123.5, 116.9, 116.5, 113.1, 112.0, 106.1. HRMS (ESI): Not responding.

1,4-Di(1H-pyrazol-1-yl)benzene (3ai). [37] According to the general procedure, the **3ai** was obtained as white needle solid (0.13 g, 75%). m.p. 103-104 °C (lit. 180 °C). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, *J*=1.8 Hz, 2H), 7.80 (s, 4H), 7.75 (d, *J*=1.3 Hz, 2H), 6.50 (t, *J*=1.8 Hz, 2H). MS (ESI^+): m/z 211.13 $[M+H]^+$.

1-(4-(Trifluoromethyl)phenyl)-1H-pyrazole (3aj). [38] According to the general procedure, the **3aj** was obtained as white solid (0.12 g, 72%). m.p. 42-44 °C (lit. 93 °C). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 (br, 1H), 7.83 (d, *J*=8.5 Hz, 2H), 7.78 (br, 1H), 7.72 (d, *J*=8.4 Hz, 2H), 6.54 (br, 1H). MS (ESI^+): m/z 213.07 $[M+H]^+$.

3-(1H-Pyrazol-1-yl)benzonitrile (3ak). [39] According to the general procedure, the

3ak was obtained as yellow oil (0.11 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.20 (t, *J*=1.8 Hz, 1H), 8.02 (d, *J*=2.4 Hz, 1H), 7.90-7.88 (m, 1H), 7.77-7.73 (m, 2H), 7.55 (t, *J*=7.9 Hz, 1H), 6.52 (t, *J*=2.0 Hz, 1H). MS (ESI$^+$): m/z 170.06 $[M+H]^+$.

1-(3-Fluorophenyl)-1H-pyrazole (3al). [40] According to the general procedure, the **3al** was obtained as colorless oil (91 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (br, 1H), 7.75 (s, 1H), 7.50 (d, *J*=8.0 Hz, 2H), 7.44-7.38 (m, 1H), 7.01-6.97 (m, 1H), 6.52 (br, 1H). MS (ESI$^+$): m/z 163.07 $[M+H]^+$.

1,1'-(4-Nitro-1,2-phenylene)bis(1H-pyrazole) (3am). According to the general procedure, the **3am** was obtained as yellow solid (0.17 g, 81%). m.p. 65-66 ^{o}C (lit. 93 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.55 (d, *J*=2.5 Hz, 1H), 8.38-8.35 (dd, *J*=8.9 Hz, 2.6 Hz, 1H), 8.02 (d, *J*=9.0 Hz, 1H), 7.80-7.76 (dd, *J*=12.7 Hz, 1.6 Hz, 2H), 7.16 (d, *J*=2.4 Hz, 1H), 6.87 (d, *J*=2.5 Hz, 1H), 6.42 (t, *J*=2.2 Hz, 1H), 6.36 (t, *J*=2.4 Hz, 1H). ^{13}C {1H} NMR (400 MHz, $CDCl_3$): δ (ppm) 146.7, 142.5, 142.3, 139.4, 133.6, 130.7, 130.3, 127.0, 123.9, 123.4, 109.0, 108.6. MS (ESI$^+$): m/z 256.10 $[M+H]^+$. HRMS (ESI): $C_{12}H_9N_5O_2Na^+$ $[M+Na]^+$ calcd for 278.0648; found: 278.0663.

1-(4-Fluorophenyl)-1H-indole-2-carboxylic acid (3an). [41] According to the general procedure, the **3an** was obtained as white solid (0.16 g, 79%). m.p. 188-190 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75-7.73 (dt, *J*=8.4 Hz, 0.9 Hz, 1H), 7.56 (d, *J*=0.7 Hz 1H), 7.33-7.17 (m, 3H), 7.23-7.17 (m, 3H), 7.07-7.04 (m, 1H). MS (ESI$^-$): m/z 254.06 $[M-H]^-$.

1-(4-Carboxyphenyl)-1H-indole-2-carboxylic acid (3ao). According to the general procedure, the **3ao** was obtained as off-white solid (0.19 g, 85%). m.p. 185-186 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.29-8.26 (m, 2H), 7.71-7.63 (m, 4H), 7.40 (d, *J*=3.3 Hz, 1H), 7.30-7.28 (m, 1H), 7.23-7.19 (m, 1H), 6.75 (d, *J*=3.3 Hz, 1H). MS (ESI$^-$): m/z 280.07 $[M-H]^-$.

Ethyl 1-(2-cyanophenyl)-1H-pyrazole-4-carboxylate (3ap). According to the general procedure, the **3ap** was obtained as yellow solid (0.17 g, 90%). m.p. 68-70 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.54 (d, *J*=0.4 Hz, 1H), 8.19 (s, 1H), 7.84-7.81 (m, 1H), 7.78-7.72 (m, 2H), 7.54-7.50 (m, 1H), 4.38-4.33 (q, *J*=14.3 Hz, 7.1 Hz, 2H), 1.38 (t, *J*=7.1 Hz, 3H). ^{13}C {1H} NMR (400 MHz, $CDCl_3$): δ (ppm) 162.3, 143.1, 141.2,

134.6, 134.1, 132.8, 128.4, 124.7, 117.9, 116.2, 106.3, 60.7, 14.4. MS (ESI^+): m/z 242.09 $[M+H]^+$. HRMS (ESI): $C_{13}H_{11}N_3O_2Na^+$ $[M+Na]^+$ calcd for 264.0743; found: 264.0753.

4,4'-Dinitro-1,1'-biphenyl (3aq). [42] According to the general procedure, the **3aq** was obtained as yellow solid (59 mg, 30%). m.p. 237-238 °C (lit. 238-239 °C). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.23-8.19 (m, 4H), 7.51-7.48 (m, 4H).

1-(2-(Allyloxy)phenyl)-1H-pyrazole (3ar). [43] According to the general procedure, the **3ar** was obtained as colorless liquid (0.24 g, 30%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.09 (s, 1H), 7.77-7.74 (dd, *J*=7.9 Hz, 1.4 Hz, 1H), 7.73 (s, 1H), 7.30-7.25 (m, 1H), 7.10-7.03 (m, 2H), 6.44 (s, 1H), 6.06-5.96 (m, 1H), 5.39-5.33 (m, 1H), 5.29-5.25 (m, 1H), 4.61-4.59 (dt, *J*=5.1 Hz, 1.5 Hz, 2H). MS (ESI^+): m/z 201.12 $[M+H]^+$.

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Supporting Information

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^1H NMR and ESI-MS spectra for all products; ^1H NMR, ^{13}C NMR, ESI-MS and HRMS spectra for new products.

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Notes

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