# Salen–Cu(II) complex catalysed N-arylation of pyrazole under mild conditions

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Three inexpensive and air-/moisture-stable complexes (Salden)Cu (Salden = N, N'-bis(salicylidene)-1,2-dimethylethylenediamine), (Saldch)Cu (Saldch = N, N'-bis(salicylidene)-1,2-cyclohexenediamine), and (Salph)Cu (salph = N, N'-bis(salicylidene)-1,2-phenylenediamine) were synthesised and evaluated as catalysts for the *N*-arylation of pyrazole with aryl halides. A variety of aryl iodides and bromides underwent coupling with pyrazole, promoted by the (Saldch)Cu complex, in moderate to excellent yields without the protection by an inert gas.

Keywords: Salen-Cu complex, N-arylation; pyrazole, catalyse, C-N coupling

N-Aryl pyrazoles represent an interesting structural motif that is frequently found in agrochemical and pharmaceutical compounds.1 The development of convenient and efficient methods for the synthesis of N-aryl pyrazoles has attracted considerable attention. During the last few years, significant efforts have been devoted towards developing convenient approaches for the preparation of these compounds. Some methods describing copper-catalysed coupling reactions using various arylating reagents such as arylboronic acids and its derivatives,<sup>2</sup> aryllead triacetates,<sup>3</sup> aryltrimethylstannanes,<sup>4</sup> triarylbismuth diacetates5 or diaryliodonium salts6 have been reported. However, these processes suffer from an intrinsic limitation in terms of atom and step economy, because these arylating reagents often require time-consuming multi-step syntheses. As an alternative C-N bond-forming strategy, the direct arylation of pyrazoles with aryl halides catalysed by transition-metals represents a more efficient method because they are straightforward and attractive.<sup>7</sup> Despite these significant advances, more efficient, air stable and cheaper ligands or metal-complexes for facilitating these coupling reactions under relatively milder conditions are still in demand.

Recently, we reported Suzuki–Miyaura reactions catalysed by Salen and half-salen palladium(II) complexes.<sup>8</sup> Although Salen-Pd complexes showed low catalytic activity for C–C coupling reactions, we assumed that Salen–Cu complexes might be a class of effective catalysts for the C–N coupling reaction. Recently, Zhou *et al.* have developed Salen–Cu complexes for C–N coupling reaction of aryl halides with aqueous ammonia, aliphatic amines and imidazoles.<sup>9–11</sup> We now report Salen– Cu complexes as catalysts for the N-arylation of pyrazole. This system contains several advantages as following: (1) the complexes were easily synthesised from cheap starting materials, and stable in air and moisture; (2) the reaction conditions were relatively mild and did not require protection by an inert atmosphere; (3) the complexes worked well for aryl iodides, and bromides with moderate to excellent yields.



Fig. 1 List of complexes 1-3

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# **Results and discussion**

#### *Synthesis of complexes* **1–3**

Complexes 1-3 were synthesised by the literature methods (Fig. 1).<sup>12,13</sup>

Salen-Cu catalysed N-arylation reactions

Initially, the catalytic activity of the complexes 1-3 were evaluated by coupling 4-iodotoluene with 1H-pyrazole as a model reaction in the presence of NaOH at 100 °C for 12 h in DMSO. As expected, the three Salen-Cu complexes all exhibited good catalytic activity for this reaction, and gave the desired product in 77-95% isolated yields (Table 1, entries 1-3). The coupling reaction did not occur in the absence of any catalyst (Table 1, entry 4). Subsequently, we selected the complex 2 as the catalyst to further investigate the effects of other conditions on the N-arylation, including reaction temperature, bases, solvents, and catalyst loading. The results showed that lower temperature decelerated the rate of the reaction. For example, 88% yield was obtained when the reaction was carried out at 80 °C (Table 1, entry 5). Base also played an important role in the catalyst systems. Among the various bases examined, NaOH was the most effective, although K<sub>2</sub>PO<sub>4</sub>, KOH and Cs<sub>2</sub>CO<sub>2</sub> also promoted the coupling

Table 1 Optimisation of the reaction conditions<sup>a</sup>



Entry	Complex	Base	Solvent	Temp/°C	Yield/% <sup>b</sup>
1	1	NaOH	DMSO	100	77
2	2	NaOH	DMSO	100	95
3	3	NaOH	DMSO	100	92
4	_	NaOH	DMSO	100	0
5	2	NaOH	DMSO	80	84
6	2	Na <sub>2</sub> CO <sub>3</sub>	DMSO	100	0
7	2	K₃PO₄	DMSO	100	50
8	2	Cs,CO,	DMSO	100	88
9	2	Et <sub>3</sub> N	DMSO	100	0
10	2	KÕH	DMSO	100	91
11	2	NaOH	DMF	100	87
12	2	NaOH	DMA	100	84
13	2	NaOH	Toluene	100	0
14	2	NaOH	DMSO	100	73°

<sup>a</sup>Reaction conditions: 4-iodotoluene (0.5 mmol), 1*H*-pyrazole (1.0 mmol), complexes **1–3** (10 mol%), base (1.0 mmol), and solvent (1 mL), reaction time 12 h.

<sup>b</sup>lsolated yields.

°Complex 2 (5.0 mol%).

reaction and gave the corresponding product in 50–91% yields (Table 1, entries 7 and 8). However, Na<sub>2</sub>CO<sub>3</sub> and organic base NEt<sub>3</sub> were ineffective (Table 1, entries 6 and 9). Consequently, NaOH was used in the subsequent studies. Solvent was another important factor affecting catalysis. It was found that DMSO was the best solvent. Both DMF and DMA were not as good as DMSO (Table 1, entries 11 and 12). Toluene was not suitable as a solvent (Table 1, entry 13). Furthermore, decreasing the loading of the complex **2** from 10 mol% to 5 mol% led to a decrease in the yield (Table 1, entry 14). Finally, the combination of Salen–Cu complex **2** (10 mol%), NaOH (2 equiv.) at 100 °C for 12 h in DMSO was chosen as the optimum conditions for the *N*-arylation of 1*H*-pyrazole with 4-iodotoluene.

A range of substrates was then investigated with this catalytic system under the optimum reaction conditions. As shown in Table 2, most aryl iodides reacted with 1H-pyrazole smoothly to afford the desired products in moderate to excellent yields. Electronic effects seemed to have significant impact on the reaction. For example, aryl iodides with electron-donating substituents were be coupled with 1H-pyrazole to give the products in 88-93% yields (Table 2, entries 2 and 3), whilst aryl iodides with electron-withdrawing substituents including, 1-chloro-4-iodobenzene, 1-fluoro-4-iodobenzene, 1-bromo-4-iodobenzene and 1-iodo-4-nitrobenzene also afforded the corresponding arylated products in 75-87% yields (Table 2, entries 7, 9-11). However, when 1-(4-iodophenyl)ethanone and 4-iodophenol were used as coupling partners, the yields dropped to 21% and 39% respectively (Table 2, entries 6 and 13). Unfortunately, with 4-iodobenzonitrile as the substrate, the N-arylation reaction did not proceed smoothly (Table 2, entry 12). However, sterically demanding ortho substituents such as 1-iodo-2-methylbenzene and 1-iodo-2-methoxybenzene did not hamper the arylation reaction and gave 82% and 83% yields respectively (Table 2, entries 4 and 5). Next, we considered the possibility of using aryl bromides as coupling partners. However, low yields were obtained under the previously optimised reaction conditions (Table 2, entries 14 and 15).

#### Conclusions

In summary, we have developed a novel general catalytic method for N-arylation of 1H-pyrazole promoted by complex 2.

Table 2N-Arylation of 1H-pyrazole with aryl halides complex 2a

$R_{\parallel}^{\parallel}$ + $N_{N}^{N}$ complex 2						
	$\checkmark$	H 1	00 °C 12	2 h		
4 5						
Entry	R, X	Product	Yield/% <sup>b</sup>	M.p./°C		
				Found	Reported	
1	H, I ( <b>4b</b> )	5b	93	Colourless oil	Colourless oil <sup>1</sup>	
2	4-0Me, I ( <b>4c</b> )	5c	93	44-46	45 <sup>14</sup>	
3	2-Me, I ( <b>4d</b> )	5d	83	Yellow oil	Yellow oil <sup>2</sup>	
4	2-0Me, I ( <b>4e</b> )	5e	82	Colourless oil	Colourless oil <sup>1</sup>	
5	4-COMe, I (4f)	5f	21	110	109-11015	
6	4-NO <sub>2</sub> , I ( <b>4g</b> )	5g	75	169–170	17015	
7	4-Ph, I ( <b>4h</b> )	5h	89	124–125	126 <sup>16</sup>	
8	4-Cl, I ( <b>4i</b> )	5i	80	50-51	51 <sup>14</sup>	
9	4-Br, I ( <b>4j</b> )	5j	78	71	7015	
10	4-F, I ( <b>4k</b> )	5k	87	Yellow oil	Yellow oil <sup>14</sup>	
11	4-CN, I (41)	51	0	-	89-9115	
12	4-COMe, Br (4m)	5f	26	110	109-11015	
13	4-NO <sub>2</sub> , Br ( <b>4n</b> )	5g	61	169–170	170 <sup>15</sup>	

<sup>a</sup>Reaction conditions: aryl halide (0.5 mmol), 1*H*-pyrazole (1.0 mmol), complex **2** (10 mol%), NaOH (1.0 mmol), and DMSO (1 mL), 100 °C, 12 h. <sup>b</sup>Isolated yields. The system is effective in the coupling of 1H-pyrazole with ArX (X=I, Br) to give moderate to excellent yields. The easily availability of the catalyst, mild reaction conditions, experimental simplicity, and broad substrate scope are features of the catalytic method presented in the current paper. Further application of these copper(II) complexes catalysed organic reaction is currently on-going in our laboratory.

# Experimental

All reactions were carried out under air using magnetic stirring unless otherwise noted. <sup>1</sup>H NMR spectra were recorded on a Bruker DPX-400 spectrometers using TMS as internal standard and CDCl<sub>3</sub> as solvent. EI–Mass spectra were measured on a LC/Q–TOF MS (Micromass, England). All other reagents were of commercial analytical grade quality.

### N-Arylation of 1H-pyrazole; general procedure

Complex 2 (0.05 mmol) was added to a 5 mL of a sealed tube containing the aryl iodide or bromide (0.5 mmol), 1*H*-pyrazole (0.75 mmol), NaOH (1 mmol), and DMSO (1 mL). The mixture was stirred at 100 °C for 12 h. After being cooled to room temperature, the mixture was quenched with 10 mL H<sub>2</sub>O and extracted with EtOAc ( $3 \times 20$  mL). The combined EtOAc extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with PE/EtOAc (from 10:1 to 5:1) as the eluent to afford the pure products. All *N*-aryl pyrazoles reported here are known products and were characterised by <sup>1</sup>H NMR, and GC-MS.

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