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### One-pot direct C–H arylation of arenes in water catalysed by RuCl<sub>3</sub>·*n*H<sub>2</sub>O–NaOAc in the presence of Zn<sup>†</sup>

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The inexpensive and commercially available catalytic system  $RuCl_3 \cdot nH_2O$ -NaOAc-Zn is active in water for the direct C-H arylation of arenes with aryl/heteroaryl chlorides. The reaction can be accelerated by the use of microwave irradiation and can also be scaled up to a multi-gram scale with excellent isolated yields.

Transition metal catalyzed direct arylation *via* direct activation– functionalization of C–H bonds has emerged as an efficient methodology for  $C(sp^2)-C(sp^2)$  bond forming reactions using organic halides as electrophiles and heterocyclic arenes as pronucleophilic substrates (Scheme 1). This synthetic route provides an appealing alternative to traditional cross-coupling processes using stoichiometric amounts of usual organometallic reagents (Li, Mg, Zn, B, and Sn), avoiding the generation of less toxic wastes since the acid HX is the unique by-product.

Although regioselective functionalization of arenes *via* C–H activation (mainly by rhodium and palladium catalysts) is well-documented,<sup>1</sup> ruthenium based versions have also shown excellent catalytic activity both in terms of efficiency and regioselectivity.<sup>2</sup> In this regard, catalytic systems generated from the ruthenium(II) dimers [RuCl<sub>2</sub>( $\eta^{6}$ -arene)]<sub>2</sub> (arene = *p*-cymene, benzene) associated with *N*-heterocyclic carbene, carboxylate, phosphine or phosphine



Scheme 1 Direct arylation reactions.

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‡ Present address: Departamento Química Inorgánica, Facultad de Química, Universidad de Santiago de Compostela, 15752, Santiago de Compostela, Spain. oxide ligands in the presence of  $M_2CO_3$ , have been widely used.<sup>3,4</sup> It is presently well known that the cooperative action of the carbonate and carboxylates or phosphine oxides as C–H bond activation partners of ruthenium(II) catalysts favours the formation of key intermediate cyclometallated species.<sup>5</sup>

The catalytic direct arylation procedure itself constitutes an important contribution to the processes in the context of green chemistry. However, the ruthenium catalysed processes proceed at high temperature and, hence, require the use of organic solvents with high boiling point, typically toluene or NMP (N-methyl-2-pyrrolidone). In the search for more benign solvents and reaction conditions, Dixneuf, Bruneau and co-workers, have recently reported that the  $[RuCl_2(\eta^6-p-cymene)]_2-4KO_2CR$  system in the presence of  $K_2CO_3$ catalyses the reaction of heteroarylbenzene derivatives with aryl and heteroaryl halides (2-phenylpyridine and phenylchloride) using water as the reaction medium.<sup>6</sup> Remarkably, it was found that the catalytic activity in water<sup>7</sup> is higher than in organic solvents (NMP) allowing the transformation to be performed even at room temperature.<sup>6</sup> When the ruthenium(II) complex [RuCl<sub>2</sub>(PPh<sub>3</sub>)(p-cymene)] is used as a catalyst, ortho-monoarylation derivatives are formed selectively.7b Following on from seminal contributions on the use of the commercially available RuCl<sub>3</sub> nH<sub>2</sub>O as a catalyst for the direct arylation of arenes,<sup>8</sup> herein we report the catalytic activity of the RuCl<sub>3</sub> nH<sub>2</sub>O-Zn-NaOAc system in the direct arylation of 2-phenylpyridine with aryl chlorides in water via C-H bond functionalization (Scheme 2). The following features of this catalytic system are remarkable: (i) this is the first example of a RuCl3 nH2O based catalytic system active with aryl chloride substrates in water,<sup>9</sup> (ii) a high regioselectivity is achieved giving rise to mono-/diarylated ratios up to 90/10%, (iii) it represents an easy, efficient and one-pot catalytic procedure using inexpensive aryl chlorides and a commercially available catalytic system.

Kinetic and mechanistic studies on autocatalytic C–H bond activation of 2-phenylpyridine *via* deprotonation with the acetate ligand, using [Ru(OAc)<sub>2</sub>( $\eta^6$ -arene)] as a catalyst precursor, establish the crucial role of coordinatively unsaturated Ru( $\pi$ )-acetate species which allows the C–H deprotonation to generate a metallacycle intermediate.<sup>5b</sup> Since the Ru( $\pi$ ) to Ru( $\pi$ ) reduction is readily achieved in water,<sup>10</sup> we envisaged that the Ru( $\pi$ )-acetate-aqua species might be formed directly from a mixture of RuCl<sub>3</sub>·*n*H<sub>2</sub>O and NaOAc with an

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appropriate reductant. In our initial studies, we investigated the phenylation of 2-phenyl pyridine with a slight excess of chlorobenzene (1.2 mmol) in order to reach the monoarylation, using 5 mol% of RuCl<sub>3</sub>·nH<sub>2</sub>O paired with a series of suitable reductants such as Zn, H<sub>3</sub>PO<sub>2</sub>, NaH<sub>2</sub>PO<sub>2</sub>, hydrazine or NaBH<sub>4</sub> in the presence of several deprotonating reagents i.e. NaOAc, Na(acac), NaOH, Na<sub>2</sub>CO<sub>3</sub> or Cs<sub>2</sub>CO<sub>3</sub> in water at 110 °C (see Table S1 in ESI<sup>+</sup>).<sup>11</sup> Good catalytic conversions (65-99%) are found when either Zn or H<sub>3</sub>PO<sub>2</sub> is used as a reductant in the presence of Na(acac) or NaOAc (Table 1, entries 2-5). The reactions exclusively gave the mono- and diarylated derivatives without formation of side-products. In the presence of the Brønsted bases, NaOH or carbonate salts, the reaction did not occur (Table 1; entries 6–9). It is also worth noting that the use of  $Cs_2CO_3$ inhibits the reaction even in the presence of the otherwise active NaOAc (Table 1; entry 4 vs. entry 9). This catalytic behaviour strongly contrasts with that shown for a wide series of Ru(II) catalysts reported to date, for which the presence of an excess of K<sub>2</sub>CO<sub>3</sub> is required for the reaction to occur.<sup>6,7b</sup> Among the suitable reductants tested (Zn and H<sub>3</sub>PO<sub>2</sub>), the latter is very sensitive to the stoichiometry when used in the presence of Na(acac) (see entries 5 and 6 in Table S1, ESI<sup>+</sup>) whereas Zn showed similar conversions and selectivities independent of the stoichiometric amount and the base used (see entries 3 and 7-9 in Table S1, ESI<sup>+</sup>). In order to stabilize the putative Ru(II) intermediate, water-soluble phosphines (PTA and TPPMS) were added to the resulting aqueous medium (Table 2; entries 1 and 2). However, lower conversions were found in the former case while the latter precludes the reaction. Apparently, these phosphines are prone to coordinate the ruthenium available sites vs. the binding ability of the substrates. Significantly, the C-H activation in water appears to be more efficient than in organic solvents such as toluene and THF, glycerol and ethanol (Table 1; entry 4 vs. Table 2 entries 5-8).

One of the optimised conditions (Table 1; entry 4) was used for the monoarylation of 2-phenylpyridine with a wide range of functionalized aryl chlorides. The results are summarized in Table 3. The catalytic system showed its reliability over a wide array of substrates

Table 1	Screening conditions for the reaction of 2-phenylpyridine with chlorobenzen

Entry	Base (eq.)	Reductant (eq.)	Conversion (m/d)
1	NaOAc (3)	_	0 (-/-)
2	Na(acac) (3)	Zn (0.25)	86 (89/11)
3	Na(acac) (3)	$H_{3}PO_{2}(0.1)$	87 (83/17)
4	NaOAc (3)	Zn (0.15)	82 (88/12)
5	NaOAc (3)	$H_{3}PO_{2}(0.1)$	65 (93/7)
6	NaOH (1.1)	Zn (0.25)	0 (-/-)
7	$Cs_2CO_3(1.1)$	Zn (0.25)	0 (–/–)
8	$Na_2CO_3(1.1)$	Zn (0.25)	0 (–/–)
9	$NaOAc(3) + Cs_2CO_3$ (1.1)	Zn (0.15)	0 (-/-)

Reaction conditions:  $RuCl_3 \cdot nH_2O$  (0.05 mmol, 5 mol%), 2-phenylpyridine (1 mmol), chlorobenzene (1.2 mmol), base, 110 °C for 16–20 h in 2 mL of water. <sup>*a*</sup> Conversion and product ratio determined by NMR.

 Table 2
 Additive and solvent effects in the reaction of 2-phenylpyridine with chlorobenzene

Entry	Additive (eq.)	Solvent	Conversion $(m/d)^b$
1	PTA (0.1)	Water	29 (80/20)
2	<b>TPPMS</b> (0.1)	Water	0 (-/-)
3 <sup><i>a</i></sup>	AcOH (1)	Water	31 (90/10)
4	$Cs_2CO_3$ (1.1)	Water	0 (-/-)
5	_	THF	70 (85/15)
6	_	Glycerol <sup>a</sup>	74 (81/19)
7	_	EtOH	17 (100/0)
8	_	Toluene	0 (90/10)
			. ,

Reaction conditions: RuCl<sub>3</sub> $\cdot n$ H<sub>2</sub>O (0.05 mmol, 5 mol%), 2-phenylpyridine (1 mmol), chlorobenzene (1.2 mmol), NaOAc (3 mmol), Zn (0.15 mmol), 110 °C for 16–20 h in 2 mL of solvent. <sup>*a*</sup> 200 °C. <sup>*b*</sup> Conversion and product ratio determined by NMR.

producing similar results independent of the electronic properties of the aryl halide. The lower conversion observed for substrates 4 and 5 is probably due to their poor solubility in water compared to the other substrates. On the other hand, the modest results observed with aryl halides 7 and 8 are the consequence of the steric hindrance produced by the presence of substituents ortho to the reactive chloride. From entries 9-13 (Table 3) we could observe that this catalytic system also shows good activity when heteroaryl halides are used, the only exception is substrate 13 where the presence of a methoxy substituent in the meta position erodes the yield observed (a decrease in selectivity is observed in this series of heterocyclic halides). This is due to the fact that when the first arylation takes place, the newly bonded heteroaryl group can itself act as a directing group thus competing with the incoming substrate for the formation of the diarylated product. To our delight, the effect of increasing the reaction temperature (140 °C) under microwave conditions12 notably decreases reaction times almost reaching a quantitative conversion (Table 3; method 2) after just 1 h, although also slightly increasing the formation of the diarylated product (d), apparently at the expense of the monoarylated (m) one (Table 3; method 2 vs. method 1). The use of microwave heating also allowed the use of the reductant NaH<sub>2</sub>PO<sub>2</sub>, otherwise inactive in the thermal version (see ESI<sup>+</sup> for details). Due to the high selectivity and straightforward workup/ purification of the reaction, mild reaction conditions and low catalyst loading, the method is highly amenable to scaling-up. The preparation of 1-(4-methoxyphenyl)-2-phenylbenzene (3m) in multi-gram quantities is a representative example (see ESI<sup>+</sup>). Insights into the nature of the Ru-containing species<sup>13</sup> in the catalytic RuCl<sub>3</sub>-Zn (or H<sub>3</sub>PO<sub>2</sub>)-NaOAc system in aqueous media were obtained from electrospray ionization mass spectrometry (ESI-MS).14 Either in the absence or in the presence of substrates, putative monomeric Ru(II) species were not observed by ESI-MS, being the dimeric  $[Ru_2(\mu-OAc)_4]^+$  cation being the only detectable Ru-containing species, which suggest that formally  $Ru(\pi)$ - $Ru(\pi)$   $[Ru_2]^{5+}$  species are initially formed (see Fig. S1 and S3, ESI<sup>+</sup>).<sup>15</sup> Further evidence for the presence of dimeric  $[Ru_2(\mu-OAc)_4]^+$  species as potential active catalysts has been assessed by performing the direct arylation of 2-phenylpyridine with chlorobenzene (1.2 mmol) using isolated  $[Ru_2(\mu-Cl)(\mu-OAc)_4]_x$  (2.5 mol%) as a catalyst precursor in the presence of either AgSbF<sub>6</sub> or AgNO<sub>3</sub> in water at 110 °C. Although low conversions are achieved after 3 h (18% and 23%, respectively) the reactions are totally selective towards the monoarylated product (m/d: 100/0). The  $Ru(\pi)$ - $Ru(\pi)$  catalyst is also active in THF showing

 Table 3
 Functionalization of 2-phenylpyridine with aryl chlorides and heteroaryl chlorides



Method 1: RuCl<sub>3</sub>·*n*H<sub>2</sub>O (0.05 mmol, 5 mol%), 2-phenylpyridine (1 mmol), aryl/heteroaryl halide (1.2 mmol), NaOAc (3 mmol), Zn (0.15 mmol), 110 °C for 20 h in 2 mL of water. Method 2: RuCl<sub>3</sub>·*n*H<sub>2</sub>O (0.05 mmol, 5 mol%), 2-phenylpyridine (1 mmol), aryl/heteroaryl halide (1.2 mmol), NaOAc (3 mmol), Zn (0.15 mmol), 140 °C under MW irradiation for 1 h in 2 mL of water. <sup>*a*</sup> Conversion and product ratio determined by NMR. <sup>*b*</sup> 0.25 eq. Zn, 1 eq. NaOAc, 1.5 eq. Ar–Cl. <sup>*c*</sup> 0.25 eq. Zn, 1 eq. NaOAc, 42 h a 110 °C. <sup>*d*</sup> 1.5 eq. Ar–Cl. <sup>*e*</sup> 180 °C, 1 h. <sup>*f*</sup> Homocoupling of 2-phenylpyridine instead of the diarylated product.

higher conversions and lower selectivity depending on the silver salts used (conversion; m/d values of 94; 67/33 and 68; 82/18% for AgSbF<sub>6</sub> and AgNO<sub>3</sub>, respectively). Remarkably, ESI(+)-MS analysis of the RuCl<sub>3</sub>-Zn (or H<sub>3</sub>PO<sub>2</sub>)-NaOAc catalytic system in THF solutions also revealed the presence of the dimeric  $[Ru_2(\mu-OAc)_4]^+$  cation (see ESI<sup>+</sup>).

In summary, in this work, we have shown that the  $RuCl_3 nH_2O$ -Zn-NaOAc catalytic system is active for the selective ortho monoarylation of 2-phenylpyridine and functionalized aryl chlorides in water.<sup>16</sup> Since it is formed from commercially available components, inexpensive aryl chloride substrates, and no further addition of  $K_2CO_3$  is needed, it can be used preferably to the ruthenium(II) catalysts  $[Ru(O_2CR)_2(\eta^6-p-cymene)]$  and  $[RuCl_2(PPh_3)(\eta^6-p-cymene)]$ .<sup>6,7b</sup> Since the reaction is also amenable on a multi-gram scale, the practical application of this methodology provides an attractive synthetic tool to conventional direct arylation methodologies via C-H bond activation-functionalization of arenes by N-containing heterocyclic directing groups. This is a further example of the ruthenium based catalytic system active in water which not only avoids the use of organic solvents but also reaches an enhanced catalytic activity.<sup>17</sup> Further synthetic applications of this catalytic methodology in aqueous media and mechanistic studies to gain insight into the active intermediate are presently under way.

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