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Mechanistic Insight into Ruthenium Catalysed Meta-Sulfonation of 2-Phenylpyridine

Patricia Marcé, a Andrew J. Paterson, b Mary F. Mahon  a and Christopher G. Frost* a

The catalytic meta-functionalization of arenes has emerged as an important synthetic methodology in the last decade. We report herein structural and mechanistic studies of the meta-sulfonation of phenylpyridine using ruthenium complexes. Furthermore, we disclose that the catalytically active species does not require the presence of a meta-arene ligand. Furthermore, the novel cycloruthenated phenylpyridine complex tosylated at the para position to the metal has been isolated and fully characterised. Protodemetalation studies suggest that a concerted C-H activation-demetalation process may be involved. Overall, this study provides fundamental insight into the meta-sulfonation phenylpyridine reaction pathway and uncovers new reaction intermediates that will guide the design of new catalytic systems for remote meta-functionalization.

Introduction

The functionalization of arenes catalysed by a metal complex via C-H activation has attracted great attention in the last decade.1,2 This transformation requires the presence of a directing group (DG) that coordinates to the metal centre to facilitate the C-H activation at the ortho position to form a metallacycle. Once the metallacycle is formed, the introduction of a functional group can be achieved at the ortho1,2 and meta positions.3 The ortho-functionalization of arenes has been widely studied and there are many transformations reported in the literature such as arylation,4 alkylations,5 olefination6 and amidations7 among others.1,2 Despite the great achievements in this area, the direct introduction of a functional group at the meta position remains a challenge. We reported the first example of catalytic meta-functionalization by remote electronic activation using ruthenium catalysis.8,9 This important switch of regioselectivity in the sulfonation of phenylpyridines from the ortho10 to the meta position was realised by changing the catalyst from Pd(II) to Ru(II). The innovative template assisted direct meta-C–H bond activation first reported by Yu et al. involves the use of a removable tethered directing group capable of coordinating to the catalyst and directing it to the meta position.11 Other strategies involve transient mediators such as a carboxylic acid12 or norborne13 that direct ortho but reveal meta-arylated products after their removal (Scheme 1a). Recently, new examples of meta selective catalytic C-H functionalization controlled by the catalyst have been achieved using secondary14 or tertiary15,16 alkyl halides and bromination reagents.17 To account for the switch in regioselectivity in the meta-sulfonation, we hypothesized that the chelating group facilitates the formation of a stable Ru-Caryl σ-bond that induces a strong para directing effect.8 Although the α-activation of aromatics has been studied for a range of stoichiometric processes such as electrophilic halogenation,18 acylation,19 and nitration,18b,18c,20 a catalytic α-activation process invokes a novel mechanistic pathway for C-H functionalization processes.15 Recent studies have revealed that the meta-functionalization of arenes via cycloruthenated complexes may follow a radical pathway.14,15,16 Herein, we present mechanistic studies to establish important steps and intermediates in the meta-sulfonation of phenylpyridines. We also demonstrate that the presence of a p-cymene ligand is not essential for catalytic turnover. Moreover, this is the first time that the cycloruthenated tosylpyridine complex has been isolated and fully characterised confirming the α-activation pathway in the catalytic meta-sulfonation.
process (Scheme 1b). This study provides fundamental insight into the reaction pathway and contributes to the broader understanding needed to design future catalytic processes for meta-selective C-H functionalization.

Results and discussion

The catalytic species. The C-H activation step of heteroarenes is crucial for further functionalization at the ortho position\textsuperscript{21} and has been thoroughly investigated.\textsuperscript{22} Recent studies carried out by Dixneuf and Jutand have revealed that C-H activation is an autocatalytic process which goes through a S\textsubscript{x}3 mechanism when [Ru(O\textsubscript{2}CR)(p-cymene)] complexes are employed.\textsuperscript{23,24} In contrast, DFT calculations carried out by Dixneuf and Maseras postulated that the C-H activation with Ru(II)-NHC complexes goes through a concerted metalation-deprotonation (CMD) mechanism.\textsuperscript{25}

Intrigued by the nature of the active species involved in the catalytic cycle for meta-functionalization, a number of ruthenium complexes were synthesised. Based on previous studies in which ruthenium cyclometallated complexes were shown to be key intermediates, complexes 3, 4 and 5 were initially investigated (Table 1).\textsuperscript{23,24,26} As we have previously reported, complex 3 selectively delivered the sulfonated phenylpyridine in good yield.\textsuperscript{8} Preformed cationic complex 4 was also found to perform competitively. Remarkably, Ru(II) complex 5 with no p-cymene coordinated was also catalytically competent. This is in contrast to the work of Jutand et al. who showed that this ligand was essential for catalytic turnover in ortho arylation reactions catalysed by Ru(II).\textsuperscript{24} It is worth noting that ortho arylation employing Ru(III) and Ru(IV) complexes did not require the presence p-cymene ligand to achieve high reaction conversions.\textsuperscript{27}

In order to observe the evolution of the ruthenium intermediates during the catalytic process, a series of reactions were followed by in situ \textsuperscript{1}H-NMR. [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2} as well as complexes 3 and 4 were employed as the precatalysts. When [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2} was used, it was converted into cyclometallated complex 4 within 40 min at 393 K (Figure 1). The presence of a new doublet at 9.22 ppm (J = 5.82 Hz, H12) along with two doublets at 0.95 ppm and 0.92 ppm (J = 6.93 Hz, H17, H18) confirmed the formation of complex 4. A new doublet at 1.23 ppm (J = 6.93 Hz, H17, H18) was also observed and assigned to free p-cymene (6). After 2 h, signals from complex 4 and free p-cymene (6) were also identified along with characteristic signals from the tosylated phenylpyridine (2). After 4 h, only traces of ruthenium complex 4 remained with a significant increase in the signals corresponding to free p-cymene. The fact that complex 4 was detected along with the formation of the final product indicates that the Ru(II) species 4 is not involved in the catalytic cycle. Additionally, the increase of the signals of the free p-cymene together with the formation of the final product suggests that the active catalytic species does not contain p-cymene as ligand. Similar behaviour was observed when complex 3 was employed. In this case, in the initial stages of the reaction the characteristic signals of 3 appeared at 9.32 ppm (d, J = 5.79 Hz, H12), 0.92 ppm and 0.82 ppm (d, J = 6.92, H17, H18).

After 40 min at 393 K these signals disappeared to give new peaks which were assigned to complex 4 and free p-cymene (Figure S2, see ESI'). When the reaction was performed with complex 4, no changes in the ruthenium complex were observed after 1 h at 393 K (Figure S3, see ESI'). These results were consistent with previous observations.

In order to know whether the chloride anion was involved in a coordination-discoordination equilibrium, complex 4 was treated with 15 equivalents of KCl in CD\textsubscript{3}CN and heated at 363 K overnight. Changes in the \textsuperscript{1}H-NMR splitting pattern showed the formation of 5 along with the dissociation of the p-cymene, but no evidence for the formation of 3 was detected. This experiment supported the fact that when the chloride dissociates from the metal centre it is very unlikely to re- coordinate under these reaction conditions (Figure S4, see ESI').

In recent work published by Dixneuf and Jutand,\textsuperscript{22} the attempt to isolate [Ru(O\textsubscript{2}CR)(PhPy)(p-cymene)] by flash chromatography using a chloroform as eluent failed and gave 3 instead, showing that chloride is a better ligand for the Ru(II) centre than acetate. Although under Dixneuf conditions the re-coordination of the chloride was evident, the ruthenium species detected by \textsuperscript{1}H-NMR in our experiment confirms that the ruthenium precatalyst does not contain chloride as ligand.
**Tosylation step.** The tosylation step was also subjected to investigation. The cycloruthenated complex 3 was placed in a NMR tube and treated with 1.5 equivalents of p-toluenesulfonyl chloride (TsCl) in CD$_3$CN at 373 K (Scheme 2). Interestingly, after heating the reaction overnight only the formation of 5 was observed. Taking into account that during the tosylation step a proton has to be abstracted, the presence of a base would favour the substitution. Thus, complex 3 was treated with TsCl and 2 equivalents of K$_2$CO$_3$. When the NMR tube was heated at 373 K the dissociation of the p-cymene ligand started taking place and, after 2 h the formation of a new complex was observed.

The appearance of a new doublet at 8.92 ppm with a coupling constant of 5.5 Hz and a new doublet at 8.14 ppm with a small coupling constant of 1.8 Hz prompted us to think that the formation of the cycloruthenated tosylpyridine complex 7 was occurring. An analogous stoichiometric experiment was also performed on complex 4 and similar reactivity to 3 was observed (Scheme 2). The treatment of 4 with TsCl afforded complex 5 with concomitant dissociation of the p-cymene. Subsequent addition of K$_2$CO$_3$ was also necessary to detect the formation of the new ruthenium complex observed previously. To prove that this new ruthenium complex was indeed 7, the tosylation on 5 was carried out under the same reaction conditions. After purification of the reaction mixture and full spectroscopic and X-ray analysis of the product, compound 7 was unequivocally assigned to the tosylated phenylpyridine complex with the tosyl group located at the para position to the Ru(II) (Figure 2). In light of these results, it could be confirmed that the meta-tosylation reaction proceeds by the activation of the para position to the Ru(II). This evidence corroborates the
role of Ru(II) acting as a para directing group.\textsuperscript{28} Finally, complex 7 was also used as precatalyst in the sulfonation reaction.

![Scheme 2](image)

**Scheme 2**

Dissociation of p-cymene. In all previous experiments it was impossible to detect the tosylated Ru(II) complex with the p-cymene coordinated. This indicated that the dissociation of the p-cymene is faster than the tosylation reaction under stoichiometric conditions. At this point, we decided to investigate the nature of the p-cymene dissociation. In order to study the stability of the cyclometallated Ru complex 3, a NMR tube was charged with 3 in CD$_3$CN. The sample was heated at 343 K for one hour, showing no modification of the splitting pattern. Then, 1.5 equivalents of tosyl chloride were added and the sample was kept at 343 K. After 24 min the dissociation of p-cymene was observed showing that TsCl promotes the dissociation of the p-cymene ligand. The mechanism of this process is still uncertain. However, it is worth noting that the dissociation of p-cymene can be accomplished by a thermal process but longer reaction times are required.\textsuperscript{31}

**Nature of the meta-functionalization.** Having confirmed that sulfonation occurs at the para position to the newly installed C-Ru bond, we became intrigued by the nature of this process. We had previously proposed that cyclometallation increases the electron density of the aromatic ring, activating it for S_Ar type reactivity. However, recent studies have shown the likelihood of a radical mechanism in meta-selective alkylation reactions.\textsuperscript{14,15,16}

In order to investigate a possible the S_Ar pathway, the effect of various sulfonating reagents were subjected to study (Table 2). Sulfonating reagents more susceptible to react with nucleophiles such as tosylimidazole, TsOBt and p-toluenesulfonic anhydride were employed in this transformation. Analysis of the crude reaction mixture did not show any evidence for the formation of 2 indicating that a simple S_Ar pathway was doubtful. We also noted that the use of the radical scavenger TEMPO caused a detrimental effect on the reaction conversions (see ESI\textsuperscript{†}). Other mechanistic studies carried out on meta-functionalization catalysed by ruthenium have also shown inhibition when TEMPO was employed as radical scavenger.\textsuperscript{14,15}

In this context, we have previously proposed a mechanism involving a distinct Ru(II)/Ru(III)Cl redox cycle whereby a Ru(II) species can cause homolytic cleavage of a C-X bond to generate reactive radical species. Upon site selective addition to the aromatic substrate, the newly formed Ru(III)Cl species can reoxidise the resulting cyclohexadienyl radical intermediate. This proposal was independently supported by Ackermann in analogous meta-selective alkylation reactions.\textsuperscript{16} It is therefore possible that the meta-selective sulfonation reaction follows analogous reactivity. This is supported by the precedence for the generation of sulfonyl radicals throughout the literature, including those promoted by ruthenium complexes.\textsuperscript{32}

Gratifyingly, it was found to be catalytically active, indicating the likelihood of sulfonated complexes involved in the catalytic cycle (Scheme 2). Interestingly, it has recently been demonstrated that similar ruthenium complexes such as [Ru(BuCN)$_2$][BF$_4$] can catalyse the C-H arylation of fluoroarenes and arenes with directing groups.\textsuperscript{30}

![Figure 2](image)

**Figure 2** Single crystal X-ray structure of the cation in complex 7.\textsuperscript{29} Ellipsoids are represented at 30% of probability.
Deuterium labelled experiments. In order to determine the C-H bonds involved in kinetically relevant steps, deuterium labelled experiments were performed. Competitive reaction of [D6]-1 and [D6]-1 showed a kinetic preference to react with unlabelled [D6]-1 (Scheme 3a) similar to that demonstrated in previous studies. In order to ascertain whether it was the ortho or meta C-H protons causing this effect, [D6]-1 and [D6]-1 were studied. A competitive reaction between [D6]-1 and 1 was carried out and the mixed product fraction was analysed. This revealed a product ratio of almost 1:1 of the deuterated and non-deuterated 2 when the H2 protons were considered. This is consistent with no kinetically relevant ortho C-H bond cleavage. Comparison of H2 and H6 in [D6]-2 showed a different ratio of deuterium incorporation. This may reflect the involvement of 2 in a reversible C-H activation reaction which could cause this proton enrichment at the less hindered position. In contrast, the competitive reaction between [D6]-1 and 1 showed a higher percentage of the non-labelled product indicating a clear isotopic effect (Scheme 3c).

Table 3 Study of the protodemetalation of the TsPhPy from the metal centre.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>2 (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>10 equiv KHCO3</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>1 equiv MesCO2H</td>
<td>2 equiv KHCO3</td>
</tr>
<tr>
<td>3</td>
<td>1.5 equiv MesCO2H</td>
<td>--</td>
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<td>1 equiv PhPy</td>
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<td>6</td>
<td>1.5 equiv p-TSA</td>
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<td>4.5 equiv TsCl</td>
<td>2 equiv KHCO3</td>
</tr>
<tr>
<td>8</td>
<td>10 equiv PhPy</td>
<td>2 equiv KHCO3</td>
</tr>
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a) Demetallation of the sulfone was observed but the pyridyl moiety was still coordinated to the Ru. b) 1.5 equivalents of tosyl chloride were added for the formation of the sulfone. The reaction was performed at 363 K in an NMR tube.
**Single Turnover Experiment.** To provide further insight into the mechanism of catalyst turnover, a stoichiometric experiment was performed using an isotopically labelled ruthenium complex $[D_4]-4$ and unlabelled 2-phenylpyridine. The deuterium incorporation of the resulting organic and inorganic components was then analysed by $^1$H-NMR (Scheme 4). In recovered fractions $[D_n]-1$, $[D_n]-2$ and $[D_n]-7$, 50% deuteration was observed at the meta and para positions to the pyridine ring. These results indicate that 1 and the labelled phenylpyridine ligand exchange multiple times before a slower tosylation step. Analysis of the ortho positions in $[D_n]-1$ and $[D_n]-2$ also revealed proton enrichment at the less hindered positions. This evidence supports the fact that tosylphenylpyridine is also involved in a reversible C-H activation.

We propose that the catalytic cycle starts by the breaking of the dimer followed by C-H activation of phenylpyridine with concomitant dissociation of the chloride to give complex 4. Once complex 4 is formed, the presence of CH$_3$CN favours the dissociation of the p-cymene ligand generating 5 which is the active Ru(II) species involved in the catalytic cycle. This cycloruthenated species 5 activates the phenyl ring from the phenylpyridine towards a radical addition of tosyl chloride at the para position. The tosylation step has been determined as a kinetically relevant step.

**Conclusions**

The mechanism of the meta-sulfonation catalysed by Ru(II) complexes has been subjected to study. This is the first time in which the meta-sulfonlated Ru(II) complex 7 has been isolated and fully characterized. This proves that this new catalytic C-H functionalization goes unequivocally via the activation of the para position to the Ru(II) complex. It has also been demonstrated that complexes 5 and 7 are the active catalytic species which has been shown to be inactive in other catalytic processes. This study reveals that the presence of a p-cymene ligand is not crucial for the meta-sulfonation of phenylpyridines and it is postulated that the meta-sulfonation follows a radical mechanism.

**Experimental**

**General Considerations**

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade acetonitrile (CH$_3$CN),
and diethyl ether were dried using a solvent purification system (PS-400-71). 1H and 13C NMR spectra were recorded on Bruker, AV 300, AV 400 or AV 500 spectrometers spectrometer in CD3CN as solvent, with chemical shifts (δ) were referenced internally to residual protic solvent signal for CD3CN (1.94 ppm 1H (q), 1.39 ppm 13C (sept)). 2D correlation spectra (gCOSY, gHSQC, gHMBC) were recorded to fully characterise the non-reported ruthenium complexes. Multiplicities are presented as: singlet (s), broad singlet (br s), doublet (d), apparent doublet (app d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), triplet of doublets (td), doublet doublet of doublets (dddt), triplet of triplets (ttt), quartet (q), quintet (quint.), and multiplet (m). Coupling constants, (J) were expressed in Hertz (Hz).

ESI MS were run on an Agilent® 1200 Series LC/MSD. Elemental analysis (C, H, N, S) was run in London Metropolitan University. Analytical thin layer chromatography (TLC) was performed on Merck® silica gel 60 F254 glass or aluminium plates. Organic compounds were visualized by UV (254 nm) irradiation. Flash column chromatography was carried out using forced flow or by gravity of the indicated solvent on Fluka® silica gel 60 (230-400 mesh) or on Acros® neutral aluminium oxide (50-200 μm, 60 Å). All complexes were synthesised using standard Schlenck techniques under nitrogen atmosphere. The precursor catalyst [RuCl2(p-cymene)] was purchased from Strem Chemicals and used without further purification. [RuCl(PhPy)(p-cymene)]23,26 [Ru(PhPy)(p-cymene)]23,27 [Ru(PhPy)(CH3CN)]PF6,23 [Ru(PhPy)(CH3CN)]PF6,23 D5-2-phenylpyridine14, 1H-benzo[d][1,2,3]triazol-1-yl 4-methylbenzenesulphonate37 and 1-tosyl-1H-imidazole38 were prepared according literature methods.

Experimental procedures for the NMR experiments, full characterisation data for all new compounds and crystallographic data (CIF) can be found in the supporting information.

Preparation of [Ru(TsPhPy)(CH3CN)]PF6 (7). A dried Schlenck tube under argon was charged with molecular sieves 4 Å, complex 5 (0.1 g, 0.18 mmol) and dry CH3CN (1.8 mL). Then, p-toluenesulfonyl chloride (67 mg, 0.35 mmol) and oven-dried K2CO3 (61 mg, 0.44 mmol) were added. After stirring the reaction mixture overnight at 120 °C, the reaction crude was purified through oven-dried neutral alumina (Al2O3) and eluted with CH3CN. The solution was concentrated under reduced pressure and precipitated with diethyl ether. After filtration and drying, complex 7 was obtained as green solid (66 mg, 52%). Crystals of 7 were grown by vapour diffusion using CH3CN–Et2O.

1H NMR (500 MHz, CD3CN) δ 8.92 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.81 (td, J = 8.0, 1.5 Hz, 1H), 7.49 (dd, J = 8.0, 1.9 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 6.5 Hz, 1H), 2.50 (s, 3H, CH3CN), 2.38 (s, 3H), 2.14 (s, 16H, CH3CN), 1.97 (s, 5H, CH3CN), 1.96 (s, 3H, CH3CN). 13C NMR (126 MHz, CD3CN) δ 201.76, 167.73, 153.96, 149.45, 145.40, 141.64, 140.55, 137.92, 135.27, 131.35, 128.44, 125.52, 123.74, 121.56, 120.02, 118.69, 21.89, 4.75 (CH3CN), 4.50 (CH3CN). HRMS-ESI Calcd for C24H23F3N4O2RuS: 533.0585 [M+CH3CN]+. Found 533.0573. Anal. Calcd for C24H23F3N4O2PuRuS: C, 43.46; H, 3.65; N, 9.75; Found: C, 43.35; H, 3.75; N, 9.67.

Catalytic reactions. To a nitrogen-purged ampule, [RuCl2(p-cymene)]; (21 mg, 5 mol%), [RuCl(PhPy)(p-cymene)]; (30 mg, 10 mol%) or [Ru(PhPy)(p-cymene)](CH3CN)]PF6 (40 mg, 10 mol%) was dissolved in dry CH3CN (4 mL). Then, phenylpyridine (0.1 mL, 0.70 mmol), K2CO3 (0.193 g, 1.4 mmol) and tosyl chloride (0.4 g, 2.1 mmol) were added and the reaction mixture was heated at 120 °C in an oil bath overnight. The reaction crude was filtered over celite using EtOAc as eluent and the resulting mixture was purified by flash chromatography (from 20% EtOAc/hexane to 40% EtOAc) affording 2 as yellowish solid (0.11 g, 50%).

General procedure for the competitive experiments. A nitrogen-purged ampule, [RuCl2(p-cymene)]; (11 mg, 5 mol%) was dissolved in dry CH3CN (4 mL). Then, phenylpyridine (50 μL, 0.35 mmol), [D3]-1 (56 mg, 0.35 mmol), [D1]-1 (51 mg, 0.35 mmol) or [D1]-1 (55 mg, 0.35 mmol) along with K2CO3 (97 mg, 0.7 mmol) and tosyl chloride (0.2 g, 1 mmol) were added. The reaction mixture was heated at 120 °C in an oil bath. The reaction mixture was filtered through a pad of celite and the crude was purified by flash chromatography on silica gel (from 20% EtOAc:hexane to 40% EtOAc).

References


The crude reaction mixture was fully analysed by LC-MS to determine all possible by-products formed in this transformation. In all cases, traces of heterodimer and homodimer were detected.


Graphical Abstract

Mechanistic Insight into Ruthenium Catalysed *Meta*-Sulfonation of 2-Phenylpyridine

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The mechanism of the ruthenium catalysed *meta*-sulfonation has been studied and a novel cycloruthenated phenylpyridine complex tosylated at the *para* position to the metal has been structurally characterised.