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COMMUNICATION

Cyclometallation of arylimines and nitrogen-containing heterocycles *via* room-temperature C–H bond activation with arene ruthenium(II) acetate complexes†‡

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The reaction of $[RuCl_2(p\text{-cymene})]_2$ with arylimines and 4 equiv. of KOAc in methanol at room temperature produces stable (N^C)-cyclometallated ruthenium(II) complexes *via* C–H bond activation/deprotonation. This method can be applied also to nitrogen-containing molecules: *N*-phenylpyrazole, 2-phenyl-2-oxazoline and benzo[*h*]quinoline. *N*-Phenylpyrazole, $[RuCl_2(p\text{-cymene})]_2$ and diphenylacetylene directly lead to alkyne insertion into the metallacycle C–Ru bond.

Catalytic C–H bond activation and functionalisation of arenes with ruthenium(II) catalysts is a very fast developing area due to its success in direct arylation[1–3] and alkenylation[4] reactions. The regioselectivity of these catalytic reactions is usually controlled by a nitrogen-containing directing group such as a heterocycle[1–4] that is binding to the ruthenium(II) centre. The mechanism of ruthenium(II) catalysed sp^2C–H bond functionalisation involves as the initial step the easy formation of an (N,C)-cyclometallated intermediate *via ortho* C–H bond deprotonation that is favoured by a reversibly coordinating base such as carbonate[5] and especially carboxylate.[6,7] This C–Ru bond formation key step is followed by more energetic oxidative addition of arylhalides leading to arylation[6] or by insertion of alkenes en route to C–H alkenylation after β elimination.[8,9]

Although (N,C)-cyclometallated ruthenium(II) complexes were initially made by transmetallation from mercury salts,[10] they have been shown, especially by Pfeffer *et al.*[11,12] and Davies *et al.*,[13,14] to arise from *N*-containing functional arene derivatives by C–H bond deprotonation, such as from arylmethylamines,[10a,11c,12] 1-aminotetraline,[11d] phenylpyrrolidine,[11c] phenylpyridine,[11a,12,14] oxazolines,[13b,c] and pyrazole.[13c]

Surprisingly, whereas arylimines could be functionalized by catalytic arylation with ruthenium(II) catalysts,[15–17] their cyclometallation with ruthenium(II) complexes is not straightforward. Previously cationic ruthenium(II) cyclometallated imines were obtained from benzylideneanilines from $RuCl_2(PMe_3)(C_6Me_6)$,[18] and benzodiazepine offered its arylimine moiety to generate a ruthenacycle.[19] The positive influence of acetate to promote cyclometallation at room temperature was observed by Davies[13a] and two aldimines, containing an *N*-alkyl group, led to the (N,C)-cyclometallated product on reaction with RuCl(OAc)(*p*-cymene) but in the presence of benzaldehyde to reach good yields.[13] Whereas arylideneanilines did not lead readily to the cyclometallated ruthenium(II) complex,[13c] they easily led to rhodium or iridium cyclometallated derivatives.[13a,14,20] Cyclometallation of arylimines such as oxazolines appears less favorable than that of alkylimines and it often failed with ruthenium and rhodium complexes with respect to iridium promoted cyclometallation.[13c]

Aldimine cyclometallation with the ruthenium(II) complex was previously reported but surprisingly mostly with aldimine containing an *N*-alkyl group.[13a,18,19] By contrast, catalytic diarylation of *N*-arylimines with arylhalides in the presence of $[RuCl_2(p\text{-cymene})]_2$ **1** catalyst activated by KOAc and PPh_3 was recently shown to be successful in both NMP[16] and water[17] solvents. This reaction is expected to take place *via* initial formation of the cyclometallated intermediate that was not observed before and it motivated our search for imine cyclometallation with the same complex precursor.

We now report an easy method to directly produce stable cyclometallated ruthenium(II) complexes of arylimines with a $[RuCl_2(p\text{-cymene})]_2$ precursor, *via* C–H bond activation/deprotonation in the presence of KOAc at room temperature in methanol, a method that can be applied to related nitrogen-containing heterocyclic molecules. The same reaction in the presence of alkyne directly leads to alkyne insertion into the cyclometallated C–Ru bond.

Thus the ruthenium(II) complex **1** was reacted with 2 equiv. of aldimine **2a** in the presence of 2 equiv. of KOAc as it was also shown to be profitable for C–H bond activation by deprotonation on cooperative action of both the Ru(II) centre and the acetate base.[6,13] No reaction occurred in THF, but in methanol after only 5 h at room temperature, 36% of orange complex **3a** were isolated. The reaction was then performed in the presence of

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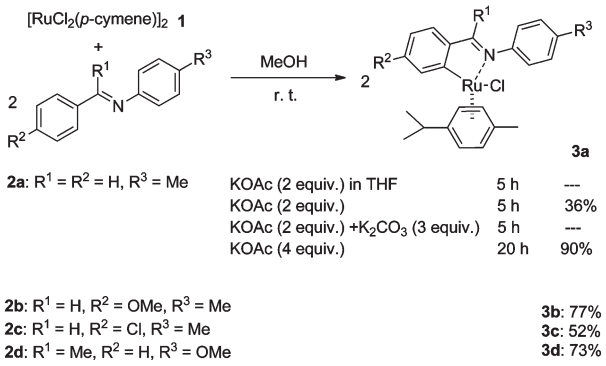
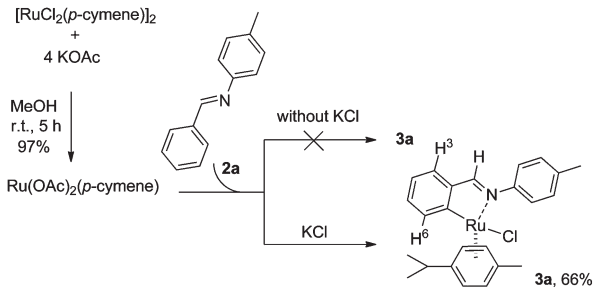
‡ Electronic supplementary information (ESI) available. CCDC 891360 and 891361. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2dt31401k



Scheme 1 Ruthenium(II) cyclometallation of arylimines.



Scheme 2

2 equiv. of KOAc and 3 equiv. of K_2CO_3 but no product was obtained. This result is consistent with the observation of Jutand *et al.*,[6] during the phenylpyridine cyclometallation with Ru(OAc)$_2$(arene): on addition of K_2CO_3 the C–H bond activation process and the cyclometallation were drastically slowed down, likely due to competitive coordination of carbonate on the ruthenium(II) centre.[21] This reaction of **1** and **2a** in methanol with 4 equiv. of KOAc at room temperature for 20 h led to the quantitative formation of **3a** that was isolated in 90% yield (Scheme 1).

The reactions of aryl aldimines **2a–c** and aryl ketimine **2d** with [RuCl$_2$(*p*-cymene)]$_2$ in the presence of 4 equiv. of KOAc per ruthenium dimer complex **1** took place at room temperature in methanol to generate the ruthenium complexes **3a–d** isolated in 52–90% yields (Scheme 1).

It is noteworthy that when complex **1** was reacted with 2 equiv. of KOAc per ruthenium atom, in the absence of aldimine but in methanol at r.t., the quantitative formation of Ru(OAc)$_2$(*p*-cymene)[3a,b] took place easily (Scheme 2). Thus in the presence of aldimine in methanol the quantitative metallacycle formation was fast, with respect to that of Ru(OAc)$_2$(*p*-cymene), and one chloride was retained in complex **3a**. Actually when this isolated complex Ru(OAc)$_2$(*p*-cymene) was formed in methanol, the addition of aldimine **2a** to the methanol solution did not give the metallacycle **3a**. However the reaction of isolated Ru(OAc)$_2$(*p*-cymene) with **2a** in the presence of 1 equiv. of KCl in methanol led to the formation of complex **3a** with 66% isolated yield (Scheme 2). This is consistent with a fast exchange of OAc^-/Cl^- in methanol to give the more stable complex **3a** containing chloride than acetate, and with Davies' observation of the crucial role of the RuCl(OAc)(arene) intermediate for cyclometallation.[13a]

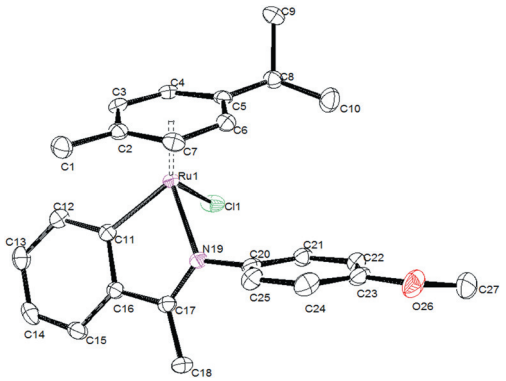
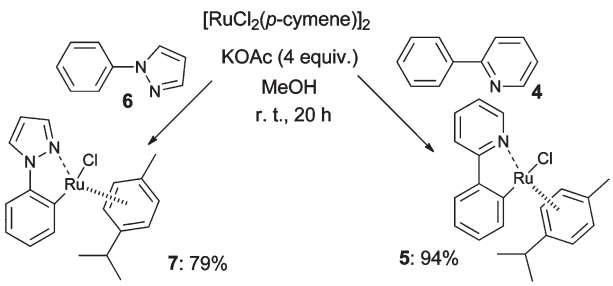


Fig. 1 X-ray structure of **3d** with 50% probability thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ru–C11 2.0411(17), Ru–N 2.0916(14), Ru–Cl 2.4149(5), C11–Ru–N 77.26(6), C11–Ru–Cl 86.87(5), Cl–Ru–N 88.27(4), C17–N19 1.302(2).



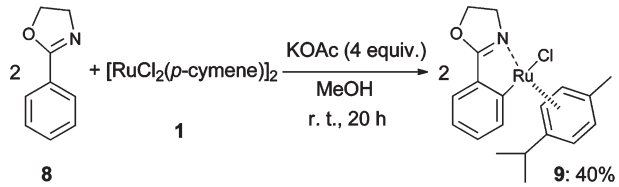
Scheme 3 Ruthenium(II) cyclometallation of 1-phenylpyrazole and 2-phenylpyridine.

The ^{1}H NMR spectrum of **3a** shows that the cyclometallated phenyl H^6 and H^3 protons are observed as two inequivalent doublets at δ = 8.19 ppm and δ = 7.54 ppm, respectively. The CH=N proton gives a singlet at δ = 8.10 ppm. The ^{1}H NMR data of *p*-cymene are consistent with a chiral metal centre. The ν(C=N) free imine absorption at 1621 cm^{-1} decreases to 1579 cm^{-1} as expected by coordination of the aryl aldimine nitrogen. In the ^{13}C NMR spectra, notably the phenylmetallated carbon atoms of ruthenium complexes **3a–3d** are observed at δ 188–192 ppm, respectively.[22]

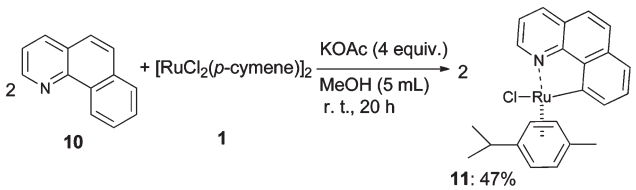
The molecular structure of the new complex **3d** was confirmed by X-ray crystallography. ORTEP drawings with the corresponding atom labelling are shown in Fig. 1. The structure shows a typical piano-stool type geometry.[13a,22]

This easy cyclometallation synthetic method for imines led us to apply this method in the synthesis of known cyclometallated Ru(II) complexes. The reaction of 2-phenylpyridine **4** with [RuCl$_2$(*p*-cymene)]$_2$ in the presence of 4 equiv. of KOAc led to the formation of ruthenium cyclometallated complex **5** in 94% yield after 20 h at room temperature (Scheme 3).[6,23] The reaction of 1-phenylpyrazole **6** with [RuCl$_2$(*p*-cymene)]$_2$ in the presence of 4 equiv. of KOAc gave after 20 h at room temperature complex **7**[13c] that was isolated in 79% yield.

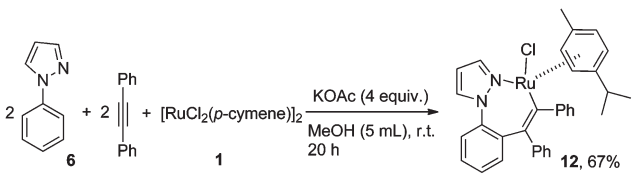
2-Phenyloxazoline **8**, that was not previously cyclometallated with the (arene)–ruthenium(II) complex, was reacted with [RuCl$_2$(*p*-cymene)]$_2$ in the presence of KOAc in methanol and



Scheme 4 Ruthenium(II) cyclometallation of 2-phenyloxazoline.



Scheme 5 Ruthenium(II) cyclometallation of benzo[*h*]quinoline.



Scheme 6 Ruthenium(II) cyclometallation of phenylpyrazole.

led to the formation of complex **9** isolated in 40% yield (Scheme 4). This low yield may be due to the weak coordinating ability of an oxazoline group to ruthenium(II) centres although it can efficiently direct C–H bond catalytic arylation of 2-oxazolyl benzene in water.[17]

The reaction of benzo[*h*]quinoline **10** with $[RuCl_2(p\text{-cymene})]_2$ in the presence of KOAc can be performed in methanol at r.t. and a new complex **11** was isolated in 47% yield (Scheme 5). In the ^{13}C NMR spectrum, the cyclometallated carbon atom is observed at δ 178.4 ppm.

These examples of cyclometallation of arenes containing a nitrogen functional directing group with $[RuCl_2(p\text{-cymene})]_2$/4KOAc in methanol show the crucial role of at least one chloride ligand and the inertness of $Ru(OAc)_2(p\text{-cymene})$ alone (Scheme 2). It is thus likely that the *ortho* C–H bond deprotonation of the coordinated ligand to the $Ru(Cl)(arene)^+$ moiety is achieved by external acetate as for phenylpyridine by $[Ru(OAc)(arene)]^+ OAc^-$.[6]

The reaction of phenylpyrazole **6** and complex **1** under the cyclometallation formation conditions (Scheme 1) but with 1 equiv. of diphenylacetylene led directly to the formation of complex **12** that was isolated in 67% yield after 20 h (Scheme 6). Complex **12** corresponds to the insertion product of alkyne into the cyclometallated C–Ru of intermediate **7**. The ^{13}C NMR spectrum of **12** shows for the new cyclometallated carbon atom=C(Ph)–Ru moiety a singlet at δ = 183.3 ppm, whereas the (C_1–Ru) carbon singlet in **7** is at δ 162.0 ppm.[24]

In conclusion, the above results show a general method to produce a variety of (N^C)-cyclometallated ruthenium(II) complexes on reaction of $[RuCl_2(p\text{-cymene})]_2$ with arylaldimines, arylketimine, but also with 2-phenylpyridine, *N*-phenyl-pyrazole, 2-phenyl-2-oxazoline and benzo[*h*]quinoline. The mild reaction conditions in methanol at room temperature and the action of 4 equiv. of KOAc per ruthenium dimer appear crucial, and are consistent with C–H bond activation/deprotonation by external acetate. It is shown that the imine cyclometallated complex is isolated in the presence of chloride, rather than with only acetate, and that *N*-phenylpyrazole and diphenylacetylene and the complex resulting from alkyne insertion into the metallocycle C–Ru bond can be obtained directly.

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22 Crystallographic data for compounds **3a** and **3d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 891360 and 891361.

23 Complex **5** was previously made from $[RuCl_2(p\text{-cymene})]_2$ by transmetallation with a mercury salt,[10*d*] and from phenylpyridine in the presence of 2.5 equiv. of NaOAc at r.t. in CH_2Cl_2 (64%),[14] and from KOAc in acetonitrile.[6]

24 This complex **12** was previously obtained by Davies by insertion of diphenylacetylene into complex **7** (42%).[13]