DOI: 10.1002/adsc.201000049

(η^6-Arene)ruthenium(N-heterocyclic carbene) Complexes for the Chelation-Assisted Arylation and Deuteration of Arylpyridines: Catalytic Studies and Mechanistic Insights

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Received: January 20, 2010; Published online: April 26, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000049.

Abstract: A series of (η^6-arene)ruthenium complexes have been tested in the arylation of arylpyridines. One (η^6-*p*-cymene)ruthenium(N-heterocyclic carbene) complex (labelled as **1** in the text) was found to be the most effective, being capable of arylating a wide set of substantially different arylpyridines. Complex **1** is also able to promote the regioselective deuteration of a series of arylated N-heterocycles, *via* a nitrogen-directed mechanism. Two of the deuterated amines were used to measure the kinetic isotope effect (KIE) in the arylation process. The detection of an inverse KIE, together with the observation that the C–H activation process does not require the addition of a base, suggest that the rate-limiting step in the arylation process may be different to that of previously reported studies.

Keywords: arylation of pyridines; chelation-assisted catalysis; deuteration; isotope effect; ruthenium

Introduction

Ruthenium-catalyzed C–C bond formation processes through C–H activation have emerged as valuable alternatives to traditional cross-coupling reactions using organometallic reagents and highly reactive electrophiles.[1] Among the Ru catalysts used, those containing η^6-arene[2] and N-heterocyclic carbene (NHC)[3] ligands, have shown an extraordinary catalytic versatility that has been used in a wide set of non-metathetical transformations applied to the production of advanced materials.[4] Because biaryl compounds are important motifs in organic synthesis and medicinal chemistry,[5] following the pioneering works of Oi and co-workers,[6] many efforts are currently being made to generate efficient ruthenium catalysts for the direct arylation of arenes.[6–11]

We recently described a series of '(η^6-*p*-cymene)Ru(NHC)' complexes that were applied to several hydrogen-borrowing catalytic reactions.[12] Being aware of the extraordinary ability of these complexes to promote C–H activation processes, we now have decided to extend their use to the arylation of pyridines with aryl halides. The easy access to'(η^6-arene)Ru(NHC)' complexes allowed us to prepare compounds **1**–**6** shown in Scheme 1. The use of three different η^6-arene ligands (hexamethylbenzene, *p*-cymene and methyl benzoate), and different NHC (and one phosphine) ligands seemed a good choice for the tuning of the electronic and steric properties of the metal centre. From this study, we have obtained a highly active catalyst for the effective arylation of a wide set of pyridines. Remarkably, the same catalyst is able to regioselectively deuterate the 2-positions of the aryl groups bound to a series of N-heterocycles. The deuteration of these positions affords an excellent possibility to study the kinetic isotope effect in the arylation of arylpyridines, and compare

1, arene = *p*-cymene, R = *n*-Bu
2, arene = hexamethylbenzene, R = *n*-Bu
3, arene = methyl benzoate, R = *n*-Bu
4, arene = *p*-cymene, R = Me
5, arene = hexamethylbenzene, R = Me
6, arene = *p*-cymene, R = *n*-Oct

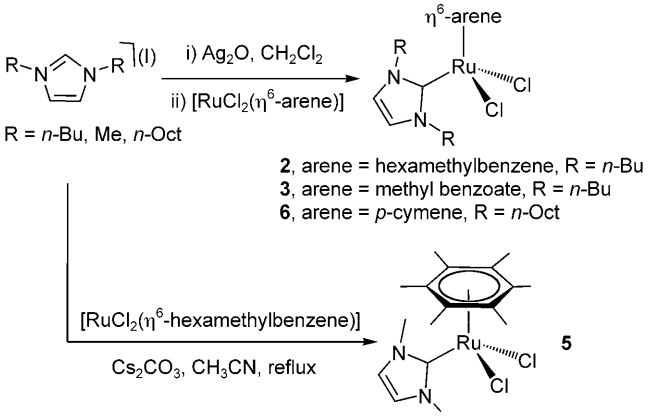
8 $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$
9 $[RuCl_2(\eta^6\text{-CMe})_6]_2$

Scheme 1. Ruthenium catalysts employed in this paper.

the results with previously reported mechanistic proposals for this reaction.[6,7,13]

Results and Discussion

Compounds **1**,[14] **4**[15] and **7**[16] were synthesized according to literature methods. Compounds **2**, **3** and **6** were prepared following the transmetallation from a pre-formed Ag(I)-NHC complex. The preparation of compound **5** was better achieved by deprotonating the imidazolium salt with Cs_2CO_3 (Scheme 2). All the



Scheme 2. Synthesis of compounds **2**, **3**, **5** and **6**.

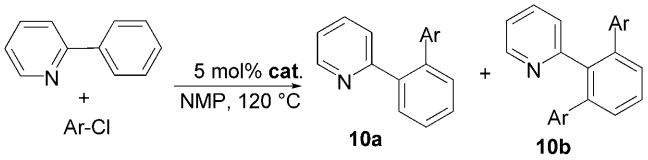
details concerning the characterization of these new complexes are described in the Experimental Section.

We first studied the different activities of complexes **1–9** in the arylation of 2-phenylpyridine with chlorobenzene (Table 1). For the study of this standard reaction we used the previously described reaction conditions (120 °C in NMP)[6–9] and a catalyst loading of 5 mol%. The optimization of the amount and type of bases added was carried out with catalyst **1**, for which the best catalytic performances were found when using a mixture of KOAc and K_2CO_3. Under these reaction conditions, the arylation of 2-phenylpyridine was studied for all compounds. As can be seen from the data shown in Table 1 (entries 6–17), the best performances were provided by **1**, which achieved full conversion to the bisarylated product **10b** in 5 h. In fact, we previously showed that the NHCs with *n*-Bu wingtips provided excellent activities in C–H activation processes promoted by 'Cp*Ir(NHC)' species, although we still do not have a satisfactory explanation for this observation.[17]

In general, it is observed that the introduction of the NHC ligands provides better performances than those provided by the metal precursors without this ligand (entries 16 and 17) or with a phosphine (entry 15). The arene ligand has also a clear influence in the catalytic outcome of the system, with the *p*-cymene ligand providing the best results. This observation is difficult to justify if we consider that the release of the coordinated arene ligand is necessary for the catalytic activity of these species, because this would imply that the methyl benzoate ligand (more weakly bound to the metal) should have provided the best outcomes. The change of the nature of the N-alkyl group at the NHC ligand also provides changes in the catalytic activity of the complexes under study. Complex **4** (N–Me), provides good activity although the formation of the bisarylated product is rather poor compared to the monoarylated one (entry 11), implying that the reaction may not have been fully completed after 5 h. In addition, complex **6** (N–*n*-Oct) shows similar activity to **1** after 5 h (entry 13), but the outcome after 3 h is significantly lower (entry 14).

Once we confirmed that catalyst **1** was the most active one in the arylation of 2-phenylpyridine, we decided to extend its use to other substrates. Table 2 shows the catalytic results when compound **1** was

Table 1. Catalyst screening in the arylation of 2-phenylpyridine.[a]



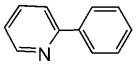
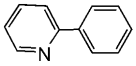
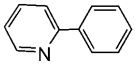
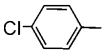
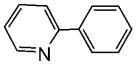
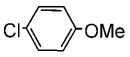
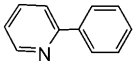
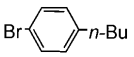
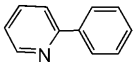
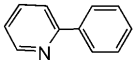
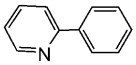
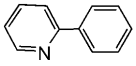
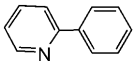
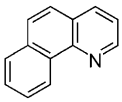
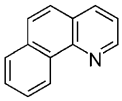
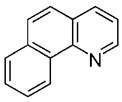
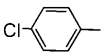
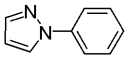
Entry	cat.	Conditions	*t* [h]	**10a** [%][b]	**10b** [%][b]
1	**1**	$NaOAc/Na_2CO_3$	20	15	1
2	none	$NaOAc/Na_2CO_3$	20	–	–
3	**2**	$NaOAc/Na_2CO_3$	20	–	–
4	**1**	$NaOAc/K_2CO_3$	5	25	5
5	**1**	$NaOAc/K_2CO_3$	18	–	>95 (91)
6	**1**	$KOAc/K_2CO_3$	5	–	>95 (92)
7	**1**	$KOAc/K_2CO_3$	3	25	70
8[c]	**1**	$KOAc/K_2CO_3$	7	60	22
9	**2**	$KOAc/K_2CO_3$	5	4	1
10	**3**	$KOAc/K_2CO_3$	5	25	40
11	**4**	$KOAc/K_2CO_3$	5	10	89
12	**5**	$KOAc/K_2CO_3$	5	–	–
13	**6**	$KOAc/K_2CO_3$	5	–	>95
14	**6**	$KOAc/K_2CO_3$	3	25	60
15	**7**	$KOAc/K_2CO_3$	5	68	10
16	**8**	$KOAc/K_2CO_3$	5	20	10
17	**9**	$KOAc/K_2CO_3$	5	9	42
18	none	$KOAc/K_2CO_3$	20	–	–

[a] *Reaction conditions:* NaOAc or KOAc (0.05 mmol), catalyst (0.025 mmol), 2 mL of NMP as solvent, room temperature for 1 h, then 2-phenylpyridine (0.5 mmol), PhCl (1.25 mmol), Na_2CO_3 or K_2CO_3 (1.5 mmol), 120 °C.

[b] Yields and ratios determined by GC (internal standard: anisole) and by ^1H NMR. Isolated yields in parenthesis.

[c] Using 2 mL of toluene as solvent instead of NMP.

Table 2. Arylation of pyridines using catalyst 1.[a]

	Pyridine	Ar-X	*t* [h]	**a** [%][b] Monoarylated	**b** [%][b] Bisarylated
1			4	–	>95 (92) (**10b**)
2			4	1 (**10a**)	90 (**10b**)
3			4	–	>95 (90) (**11b**)
4			5	25 (**12a**)	60 (**12b**)
5			5	–	>95 (91) (**13b**)
6			24	80 (**14a**)	6 (**14b**)
7			24	4 (**14a**)	90 (**14b**)
8			24	45 (**15a**)	2 (**15b**)
9			24	15 (**15a**)	<5 (**15b**)
10			24	15 (**15a**)	5 (**15b**)
11			5	94 (89) (**16a**)	
12			12	50 (**16a**)	
13			6	92 (**17a**)	
14			5	–	95 (81) (**18b**)

[a] *Reaction conditions:* KOAc (0.05 mmol), catalyst **1** (0.025 mmol), 2 mL of NMP as solvent, room temperature for 1 h, then substrate (0.5 mmol), Ar-X (1.25 mmol or 0.75 mmol), K_2CO_3 (1.5 mmol), 120 °C.

[b] Yields and ratios determined by GC (internal standard: anisole) and by ^{1}H NMR. Isolated yields in parenthesis.

used in the arylation of 2-phenylpyridine, benzo[*h*]-quinoline and *N*-phenylpyrazole with different arylating agents. Interestingly, the catalyst is capable of providing good results for all three substrates, a feature that illustrates its wide applicability. For the reactions with 2-phenylpyridine, **1** provides higher activity than previously reported ruthenium catalysts that generally need longer reaction times (>10 h) to achieve lower product yields[6–8] and compares well with the most efficient catalytic systems reported for this process.[13,18] In general, it seems that the use of chloroarenes provides higher conversions than iodo- and bromoarenes, a trend that is also observed in the arylation of benzo[*h*]quinoline (compare entries 11 and 12).

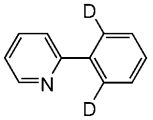
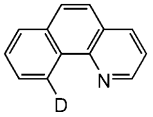
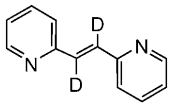
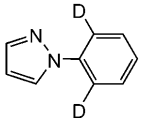
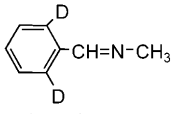
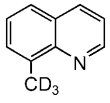
Hydrogen/deuterium exchange processes are powerful methods to evaluate the potential of a catalyst for the cleavage and formation of C–H bonds.[19] Since the mechanism of the arylation of arylpyridines implies the regioselective C–H activation at the 2-position of the aromatic rings of 2-substituted pyridines, we thought that it may be possible to use catalyst **1** for the N-directed regioselective deuteration of C–H bonds of different pyridines. The process seemed even more plausible after the recent description of the selective deuteration of benzo[*h*]quinoline at the C-10 position using a dirhodium(II) complex, although in this case the reaction needed a stoichiometric amount of the dimetallic species (the reaction is

not catalytic) and base.[20] Table 3 shows the selective deuteration of five different pyridines in the presence of MeOH-d_4 at 120 °C with 5 mol% of catalyst. It is important to point out that this reaction can be easily monitored by ^{1}H NMR, for which a growth of the resonance of the CH_3OH proton is concomitant with the deuteration of the pyridine. This observation suggests a C–D rather than O–D activation in the functioning of the deuterium source in the catalytic cycle, a fact that is confirmed by the absence of reaction when CH_3OD is used instead of MeOH-d_4. As an example of the monitoring of the process, Figure 1 shows two ^{1}H NMR spectra of the deuteration of *N*-phenylpyrazole at $t=0$ h and $t=10$ h, that clearly illustrates that the signals due to the protons at the 2-position of the phenyl ring disappear after 10 h of reaction.

As can be seen from the results shown above, the selective deuteration proceeds in an almost quantitative manner, without the need of addition of any additive such as a base, except for the imine and 8-methylquinoline, for which KOAc is needed (entries 5 and 6). Remarkably, the deuteration of the sp^3 C–H bonds at the methyl group of 8-methylquinoline is also almost quantitative. To the best of our knowledge, this is the first time that this selective deuteration of arylpyridines has been described.

In general, the search of catalysts able to selectively deuterate organic molecules is a matter of continuous interest because deuterium labelled compounds can be used in a wide range of applications such as the study of biologically active systems, solvents for NMR spectroscopy, and the study of reaction mechanisms.[21] In our case, the possibility to selectively deuterate pyridines provides an excellent opportunity for the experimental study of the reaction mechanism of the arylation of these substrates. In this sense, the time-course monitoring of the arylation of 2-phenylpyridine-d_2 and 2-phenylpyridine, allowed us to determine a kinetic isotope effect (KIE) of $k_H/k_D=0.46$ (based on the determination of $t_{1/2}$ values at 120 °C). For the reaction carried out with benzo[*h*]quinoline-*d*, a similar substantial inverse KIE of $k_H/k_D=0.43$ was determined. This inverse KIE is different from the normal (positive) KIEs found for other related hydrogen abstraction processes,[20,22] implying that a different mechanism should be at play or, at least that a different transition state is determining the kinetics of the process. Those processes implying the metal-mediated activation of C–H bonds are believed to occur *via* transient σ-C–H (agostic) complexes. On the basis of computational calculations applied to the ruthenium-catalyzed arylation of 2-phenylpyridine, Maseras and Dixneuf found that this agostic intermediate pre-

Table 3. Deuteration of pyridines in MeOH-d_4 using **1**.[a]

Entry	Substrate	Product	*t* [h]	Conversion [%][b]
1	2-phenylpyridine		7	92 (89)
2	benzo[*h*]quinoline		5	90(82)
3	1,2-bis(2-pyridyl)ethylene		10	>95
4	*N*-phenylpyrazole		10	>95
5	methylbenzylimine		10[c]	>95
6	8-methylquinoline		10[c]	80

[a] *Reaction conditions:* catalyst **1** (0.025 mmol), substrate (0.5 mmol), 4 mL of MeOH-d_4, 120 °C.
[b] Conversion determined by ^{1}H NMR. Isolated yields in parenthesis.
[c] Using KOAc (0.05 mmol).

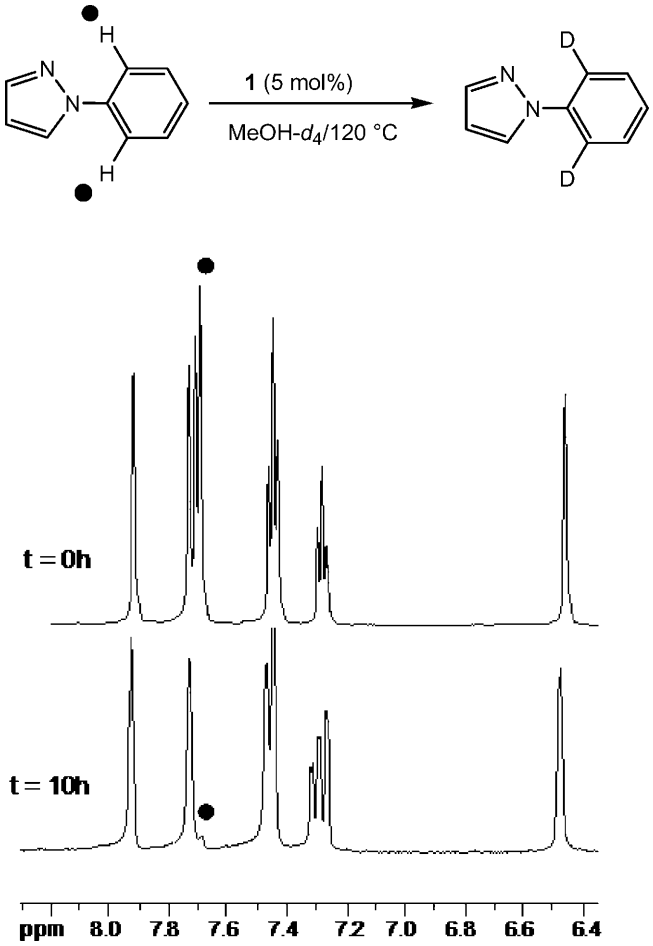


Figure 1. ^{1}H NMR spectra of the Ru-mediated deuteration of *N*-phenylpyrazole after 0 h and 10 h of reaction.

ferred the C–H cleavage through proton abstraction over a C–H oxidative addition generating an Ru(IV) with a hydride ligand.[7] However, this group did not report calculations in order to determine the transition state responsible for the rate-limiting step of the overall reaction. While a single-step reaction is almost invariably characterized by a normal primary KIE, the observation of an inverse KIE in a C–H activation process is commonly taken to imply an intermediate in a multistep reaction prior to the determining step.[23] In our case, the inverse KIE may imply that the C–H abstraction is not the rate-limiting step in the catalytic cycle,[23,24] probably indicating that the agostic intermediate has an intact, strong C–H or C–D bond.[23] It is important to recall that, for our Ru-catalyzed deuteration reactions, the results indicate that the C–H activation is a metal-mediated process that takes place in the absence of a base, which also supports the idea that the rate-limiting step of the catalytic reaction does not imply the proton abstraction from the phenyl ring of the arylpyridine compound.

Conclusions

In conclusion, we have obtained a series of highly effective catalysts for the chelation-assisted direct arylation of a wide series of pyridines, which clearly illustrates the wide applicability of the catalysts used.

Remarkably, catalyst **1** also resulted an efficient catalyst for the N-directed regioselective deuteration of sp^2 and sp^3 C–H bonds, a process that is unprecedented in the literature. Most substrates undergo this C–H activation process in the absence of a base, although methylbenzylimine and 8-methylquinoline required catalytic amounts of KOAc in order to accomplish their deuteration.

The easy access to selective deuterated arylpyridines allowed the determination of the kinetic isotope effect in the direct arylation of arylpyridines, which being inverse suggests that the reaction mechanism proceeds *via* a different mechanism than those proposed for other related hydrogen abstraction processes.[20,22] Our results suggest that, contrary to what has been proposed for other catalysts, the rate-limiting step for this ruthenium-catalyzed process does not imply the C–H proton abstraction. Calculations in order to determine the rate-limiting transition state of this catalytic process may be an interesting task to develop in the next future.

Experimental Section

General Remarks

The metal complexes $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$,[16] $[RuCl_2(\eta^6\text{-}CMe)_6]_2$,[25] $[RuCl_2(\eta^6\text{-methyl benzoate})]_2$,[26] **1**,[14] **4**[15] and **7**[16] and the ligand precursors 1,3-di-*n*-butylimidazolium iodide and 1,3-dimethylimidazolium iodide[27] were prepared according to literature procedures. All other reagents were used as received from commercial suppliers and used without further purification. NMR spectra were recorded on a Varian Innova 300 MHz and 500 MHz, using $CDCl_3$ and DMSO-d_6 as solvents. Electrospray mass spectra (ESI-MS) were recorded on a Micromass Quatro LC instrument; nitrogen was employed as drying and nebulizing gas. Elemental analyses were carried out on a EuroEA3000 Eurovector Analyser.

Synthesis of the Metal Complexes

1,2-Di-n-octylimidazolium iodide: To a round-bottom flask were added imidazole (480 mg, 7 mmol), NaOH (420 mg, 10.5 mmol), TBABr (50 mg, 0.15 mmol), and a few drops of water. The mixture was stirred at room temperature for 1 h, and then iodooctane (1.3 mL, 7 mmol) was added. After 48 h at room temperature, the reaction mixture was extracted with CH_2Cl_2/H_2O and the organic extracts were collected and dried over Na_2SO_4. Evaporation of the solvent under vacuum gave an oil which was further reacted with iodooctane (1.3 mL, 7 mmol). The mixture was refluxed overnight to give the desired product; yield: 2.6 g (90%). ^{1}H NMR

(300 MHz, $CDCl_3$): $\delta = 10.22$ (s, 1H, NC*H*N), 7.41 (s, 2H, C$H_{imidazole}$), 4.34 (t, $^3J_{H,H} = 7.35$ Hz, 4H, NC$H_{2\ n\text{-}Oct}$), 1.92 (m, 4H, C$H_{2\ n\text{-}Oct}$), 1.31 (m, 20H, C$H_{2\ n\text{-}Oct}$), 0.85 (t, $^3J_{H,H} = 6.00$ Hz, 6H, C$H_{3\ n\text{-}Oct}$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta =$ 136.7 (N*C*HN), 122.7 (*C*H$_{imidazole}$), 50.4 (N*C*H$_{2\ n\text{-}Oct}$), 31.8 (*C*H$_{2\ n\text{-}Oct}$), 30.4 (*C*H$_{2\ n\text{-}Oct}$), 29.1 (*C*H$_{2\ n\text{-}Oct}$), 29.0 (*C*H$_{2\ n\text{-}Oct}$), 26.3 (*C*H$_{2\ n\text{-}Oct}$), 22.7 (*C*H$_{2\ n\text{-}Oct}$), 14.1 (*C*H$_{3\ n\text{-}Oct}$); electrospray MS (15 V): *m/z* (fragment) = 293.3 $[M-I]^+$; anal. calcd. for $C_{19}N_2H_{37}I$ (mol. wt. 420.41): C 54.28, H 8.87, N 6.66; found: C 54.56, H 8.78, N 6.59.

Synthesis of 2: Silver oxide (58 mg, 0.25 mmol) was added to a solution of 1,3-di-*n*-butylimidazolium iodide (154 mg, 0.50 mmol) in CH_2Cl_2. The suspension was stirred at room temperature for 1 h, and $[RuCl_2(\eta^6\text{-}CMe)_6]_2$ (167 mg, 0.25 mmol) was then added. The mixture was refluxed for 2 h under the exclusion of light. The suspension was filtered through Celite and the solvent was evaporated under reduced pressure. The crude solid was purified by column chromatography. Elution with a mixture of CH_2Cl_2/acetone (4:1) afforded the separation of an orange band containing compound **2**. Compound **2** was obtained as an orange solid by precipitation with diethyl ether; yield: 160 mg (62%). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.04$ (s, 2H, C$H_{imidazole}$), 4.55 (td, $^3J_{H,H} = 11.87$ Hz, $^2J_{H,H} = 4.83$ Hz, 2H, NC$H_{2\ n\text{-}Bu}$), 3.66 (td, $^3J_{H,H} = 11.75$ Hz, $^2J_{H,H} = 4.83$ Hz, 2H, NC$H_{2\ n\text{-}Bu}$), 1.99 [s, 18H, $(CH_3)_6$], 1.63 (m, 2H, C$H_{2\ n\text{-}Bu}$), 1.51 (m, 2H, C$H_{2\ n\text{-}Bu}$), 1.38 (m, 4H, C$H_{2\ n\text{-}Bu}$), 0.98 (t, $^3J_{H,H} = 7.25$ Hz, 6H, C$H_{3\ n\text{-}Bu}$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 176.1$ ($C_{carbene}$-Ru) 121.8 (*C*H$_{imidazole}$), 93.6 $[(CCH_3)_6]$, 51.2 4 (N*C*H$_{2\ n\text{-}Bu}$), 34.0 (*C*H$_{2\ n\text{-}Bu}$), 20.4 (*C*H$_{2\ n\text{-}Bu}$), 15.6 $[(CCH_3)_6]$, 14.1 (*C*H$_{3\ n\text{-}Bu}$); electrospray MS (15 V): *m/z* (fragment) = 479.2 $[M-Cl]^+$; anal. calcd. for $C_{23}H_{38}Cl_2N_2Ru$ (mol. wt. 514.54): C 53.69, H 7.44, N 5.44; found: C 53.75, H 7.47, N 5.41.

Synthesis of 3: Silver oxide (37.5 mg, 0.162 mmol) was added to a solution of 1,3-di-*n*-butylimidazolium iodide (100 mg, 0.324 mmol) in CH_2Cl_2. The suspension was stirred at room temperature for 1 h, and $[RuCl_2(\eta^6$-methyl benzoate$)]_2$ (100 mg, 0.162 mmol) was then added. The mixture was refluxed overnight under the exclusion of light. The crude mixture was filtered through Celite and the solvent removed under reduced pressure. Complex **3** was obtained as a moderately unstable red solid by precipitation from CH_2Cl_2/diethyl ether; yield: 99 mg (62%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.06$ (s, 2H, C$H_{imidazole}$), 6.27 (d, $^3J_{H,H} = 6.00$ Hz, 2H, C$H_{ortho\text{-}benzoate}$), 5.84 (t, $^3J_{H,H} = 5.50$ Hz, 1H, C$H_{para\text{-}benzoate}$), 5.71 (t, $^3J_{H,H} = 5.80$ Hz, 2H, C$H_{meta\text{-}benzoate}$), 4.40 (br, 2H, N-C$H_{2\ n\text{-}Bu}$), 3.98 (br, 2H, N-C$H_{2\ n\text{-}Bu}$), 3.89 (s, 3H, -COOCH_3), 1.89 (br, 2H, C$H_{2\ n\text{-}Bu}$), 1.65 (br, 2H, C$H_{2\ n\text{-}Bu}$), 1.41 (m, 4H, C$H_{2\ n\text{-}Bu}$), 0.97 (t, $^3J_{H,H} = 7.20$ Hz, 6H, C$H_{3\ n\text{-}Bu}$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ0168.4 ($C_{carbene}$-Ru), 166.4 (*C*OOCH$_3$), 122.1 (*C*H$_{imidazole}$), 90.9 (*C*q $_{benzoate}$), 88.3, (*C*H$_{benzoate}$), 86.7 (*C*H$_{benzoate}$), 82.5 (*C*q $_{benzoate}$), 53.4 (COO*C*H$_3$), 51.4 (N*C*H$_{2\ n\text{-}Bu}$), 34.0 (*C*H$_{2\ n\text{-}Bu}$), 20.3 (*C*H$_{2\ n\text{-}Bu}$), 14.1 (*C*H$_{3\ n\text{-}Bu}$); electrospray MS (15 V): *m/z* (fragment) = 453.5 $[M-Cl]^+$; FT-IR (KBr): $\nu = 1723$ cm^{-1} ($\nu_{(C=O)}$).

Synthesis of 5: A mixture of $[RuCl_2(\eta^6\text{-}CMe)_6]_2$ (200 mg, 0.30 mmol), 1,3-di-*n*-methylimidazolium iodide (150 mg, 0.67 mmol), and Cs_2CO_3 (1.5 g, 4.70 mmol) in CH_3CN was refluxed for 6 h. The mixture was filtered, the solvent was evaporated and the crude solid was purified by column chromatography. Elution with CH_2Cl_2/acetone (9:1) afforded the separation of a yellow band that contained compound **5**. Compound **5** was obtained as a yellow solid by precipitation with diethyl ether; yield: 215 mg (50%). ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.88$ (s, 2H, C$H_{imidazole}$), 3.64 (s, 6H, NCH_3), 2.10 [s, 18H, $(CH_3)_6$]; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta =$ 181.9 ($C_{carbene}$-Ru), 123.4 (*C*H$_{imidazole}$), 92.8 $[(CCH_3)_6]$, 37.2 (N*C*H$_3$), 15.7 $[(CCH_3)_6]$; electrospray MS (15 V): *m/z* (fragment) = 395.4 $[M-Cl]^+$; anal. calcd. for $C_{17}H_{26}Cl_2N_2Ru$ (mol. wt. 430.38): C 47.44, H 6.09, N 6.51; found: C 47.56, H 6.05, N 6.42.

Synthesis of 6: Silver oxide (76 mg, 0.33 mmol) was added to a solution of 1,3-di-*n*-octylimidazolium iodide (138 mg, 0.33 mmol) in CH_2Cl_2. The solution was stirred at room temperature for 1 h, and $[RuCl_2(\eta^6$-*p*-cymene$)]_2$ (100 mg, 0.16 mmol) was then added. The mixture was refluxed for 3 h under the exclusion of light, the suspension was filtered through Celite and the solvent was evaporated under reduce pressure. The crude solid was purified by column chromatography. Elution with a mixture of CH_2Cl_2/acetone (9:1) afforded the separation of an orange band that contained compound **6**. Compound **6** was obtained as an orange solid by precipitation with ether; yield: 105 g (53%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.05$ (s, 2H, C$H_{imidazole}$), 5.37 (d, $^3J_{H,H} = 6.00$ Hz, 2H, C$H_{p\text{-}cym}$), 5.06 (d, $^3J_{H,H} = 5.70$ Hz, 2H, C$H_{p\text{-}cym}$), 4.56 (br, 2H, NC$H_{2\ n\text{-}Oct}$), 3.97 (br, 2H, NC$H_{2\ n\text{-}Oct}$), 2.91 (sept, $^3J_{H,H} = 6.90$ Hz, 1H, C$H_{isop\ p\text{-}cym}$), 2.03 (s, 3H, C$H_{3p\text{-}cym}$), 1.97 (br, 2H, C$H_{2\ n\text{-}Oct}$), 1.67 (br, 2H, C$H_{2\ n\text{-}Oct}$), 1.30 (br, 20H, C$H_{2\ n\text{-}Oct}$), 1.25 (d, $^3J_{H,H} = 7.20$ Hz, 6H, C$H_{3isop\ p\text{-}cym}$), 0.87 (t, $^3J_{H,H} = 6.60$ Hz, 6H, C$H_{3\ n\text{-}Oct}$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 173.4$ ($C_{carbene}$-Ru) 121.7 (*C*H$_{imidazole}$), 108.0 (*C*H$_{isop\ p\text{-}cym}$), 99.3 (*C*q$_{p\text{-}cym}$), 85.3 (*C*H$_{p\text{-}cym}$), 83.0 (*C*H$_{p\text{-}cym}$), 51.7 (N*C*H$_2$), 32.0 (*C*H$_{2\ n\text{-}Oct}$), 30.9 (*C*H$_{isop\ p\text{-}cym}$), 29.6 (*C*H$_{2\ n\text{-}Oct}$), 29.3 (*C*H$_{2\ n\text{-}Oct}$), 27.1 (*C*H$_{3isop\ p\text{-}cym}$), 22.8 (*C*H$_{2\ n\text{-}Oct}$), 22.7 (*C*H$_{2\ n\text{-}Oct}$), 18.8 (*C*H$_{3isop\ p\text{-}cym}$), 14.2 (*C*H$_{3\ n\text{-}Oct}$); electrospray MS (15 V): *m/z* (fragment) = 563.3 $[M-Cl]^+$; anal. calcd. for $RuCl_2C_{29}H_{50}N_2$ (mol. wt. 598.70): C 58.18, H 8.42, N 4.68; found: C 57.96, H 8.47, N 4.67.

Catalytic Experiments

Arylation of 2-phenylpyridine: The ruthenium complex (**1**–**9**) (0.025 mmol) and KOAc (0.05 mmol) were stirred in NMP (2 mL) at room temperature in a thick-walled glass tube for 1 h. Then 2-phenylpyridine (0.5 mmol), Ar-X (1.25 mmol) and K_2CO_3 (1.50 mmol) were added. The resulting mixture was stirred at 120 °C. H_2O and EtOAc were added to the cold reaction mixture. The organic phase was dried with Na_2SO_4 and concentrated under vacuum. The remaining residue was purified by column chromatography on silica gel (hexanes/EtOAc mixture) to yield the corresponding *ortho*-arylated products. Yields and ratios were determined by ^1H NMR spectroscopy and by GC analyses using anisole (0.5 mmol) as internal standard. According to previously reported spectroscopic data, products were identified as **10a**,[6] **10b**,[6] **11b**,[6] **12a**,[28] **12b**[28] **14a**,[11] **14b**,[11] **15a**[6] and **15b**.[6]

2-(4,4''-Dibutyl-1,1':3',1''-terphenyl-2'yl)pyridine (13b) (Table 2, entry 5): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.31$ (d, $^3J_{H,H} = 4.50$ Hz, 1H), 7.44 (m, 3H), 7.29 (m, 1H), 6.97 (m, 8H), 6.88 (m, 2H), 2.53 (t, $^3J_{H,H} = 7.65$ Hz, 4H), 1.55 (m, 4H), 1.31 (m, 4H), 0.91 (t, $^3J_{H,H} = 7.35$ Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 148.6$ (CH), 142.1 (Cq), 141.0 (Cq), 139.1 (CH), 134.5(CH), 129.7 (CH), 129.5 (CH), 128.3

(Cq), 127.9 (CH), 127.1 (Cq), 120.9 (Cq), 35.4 (CH_2), 33.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3).

Arylation of benzo[h]quinoline: KOAc (0.05 mmol) and catalyst **1** (0.025 mmol) were stirred in NMP (2 mL) at room temperature in a thick-walled glass tube for 1 h. Then benzo[*h*]quinoline (0.5 mmol), Ar-X (0.75 mmol) and K_2CO_3 (1 mmol) were added. The resulting mixture was stirred at 120 °C. H_2O and EtOAc were added to the cold reaction mixture. The organic phase was dried with Na_2SO_4 and concentrated under vacuum. The remaining residue was purified by column chromatography on silica gel (hexanes/EtOAc mixture) to yield the monoarylated product. Yields and ratios were determined by ^{1}H NMR spectroscopy and by GC analyses using anisole (0.5 mmol) as internal standard. According to previously reported spectroscopic data, products were identified as **16a**[6] and **17a**.[6]

Arylation of N-phenylpyrazole: KOAc (0.05 mmol) and catalyst **1** (0.025 mmol) were stirred in NMP (2 mL) at room temperature in thick-walled glass tube for 1 h. Then *N*-phenylpyrazole (0.5 mmol), chlorobenzene (1.25 mmol) and K_2CO_3 (1.50 mmol) were added. The resulting mixture was stirred at 120 °C. The purification of the arylated product was carried out as explained above. Conversions were determined by ^{1}H NMR spectroscopy and by GC analyses using anisole (0.5 mmol) as internal standard. According to previously reported spectroscopic data, product was identified as **18b**.[20]

Deuteration of pyridines in MeOH-d_4: A mixture of the substrate (0.5 mmol) and catalyst **1** (0.025 mmol) in MeOH-d_4, was heated at 120 °C in a thick-walled glass tube fitted with a Teflon cap. At the desired reaction times, aliquots were extracted from the reaction vessel and added to an NMR tube with 0.5 mL of $CDCl_3$.

Acknowledgements

We gratefully acknowledge financial support from MEC of Spain (CTQ2008-04460) and Bancaixa (P1.1B2007-04; P1.1A2008-02). We also like to thank the Ramon y Cajal program (M.P.). A.P. thanks the Ministerio de Ciencia e Innovación for a fellowship. The authors are grateful to the Serveis Centrals d'Instrumentació Científica (SCIC) of the Universitat Jaume I for providing us with spectroscopic facilities. We also wish to thank Prof. Feliu Maseras from the ICIQ for his useful comments on the mechanism of the reactions under study.

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