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Ligand-tuned C-H bond activation/arylation of 2-arylpyridines over pyridine based *N,O/N,N* ligated ruthenium-arene complexes

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Abstract

Water soluble ruthenium(II)-arene complexes $[(\eta^6\text{-arene})Ru(\kappa^2\text{-L})]^{n+}$ (n = 0, 1) (**[Ru]-1** – **[Ru]-10**) containing pyridine based bischelating *N,O*/ *N,N* donor ligands (**L1** – **L5**) were synthesized and were employed for the catalytic C-H bond activation/ arylation of a wide range of 2-phenylpyridines and arylhalides in water, to afford corresponding mono and biarylated products. Exploring the reactivity of the synthesized complexes, our investigations including time dependent ^{1}H NMR studies with ruthenium-arene catalysts demonstrated a remarkable structure-activity relationship for the ligand-tuned C-H activation/ arylation of 2-phenylpyridine, where the complexes with bischelating *N,O* donor based ligands (acteylpyridine and picolinate) outperformed over those with *N,N* donor ligands (iminopyridine). Moreover, among *N,O* donor ligands a distinct effect of the nature of coordinating oxygen donor on the catalytic activity was also observed, where ruthenium-arene complexes having *N,O* donor ligands (acetylpyridine) with neutral oxygen donor atom exhibited enhanced catalytic activity over those with anionic oxygen donor (picolinate). The observed trend in the catalytic activity was attributed to the ligand promoted facile deprotonation and coordination-decoordination interconversion behavior. In addition, molecular structures for few of the representative complexes (**[Ru]-2**, **[Ru]-4** and **[Ru]-5**) were authenticated by single crystal X-ray diffraction studies.

Introduction

C-H bond activation and functionalization is a promising and efficient strategy to synthesize a wide range of organic compounds in a step economical way.[1] C-H bond activation/ functionalization reactions not only reduce time and efforts in long and tedious organic transformations, but also generate less waste and undesired side products. Therefore to serve this purpose, several methodologies have been developed to activate the otherwise un-reactive C-H bonds. Among these methodologies, the functional group directed C-H bond activation and functionalization has emerged as an efficient way to achieve tuned regioselectivity.[1-2] The key feature of this strategy is to exploit the Lewis basic site of substrate to bring the transition metal in the close proximity of the targeted C-H bond to facilitate deprotonation – *a concerted metalation and deprotonation mechanistic pathway*.[1-3] In recent years, reactions proceeded through the directed C-H bond activation have been illustrated by the formation of cyclometalated intermediates, an important intermediate of C-H bond activation reactions.[2-3] Along with a variety of transition metals including palladium,[4] iridium[5] and rhodium[6] which form cyclometalated species, ruthenium based complexes have also shown appreciable reactivity towards the formation of cyclometalated species.[7] Moreover, ruthenium complexes offers excellent water solubility which provides the opportunity to perform catalytic C-H bond activation/functionalization under environmentally benign condition using of water as a solvent.[8,9,12,13]

In particular, catalytic systems based on ruthenium-arene complexes for C-H bond activation/ functionalization of various heteroarenes have also been vastly explored, where the role of ligands was found to be a crucial factor.[7-14] For instance, bulky phosphines have been used to tune the selectivity of monoarylated product during the *ortho* arylation of heteroarenes by

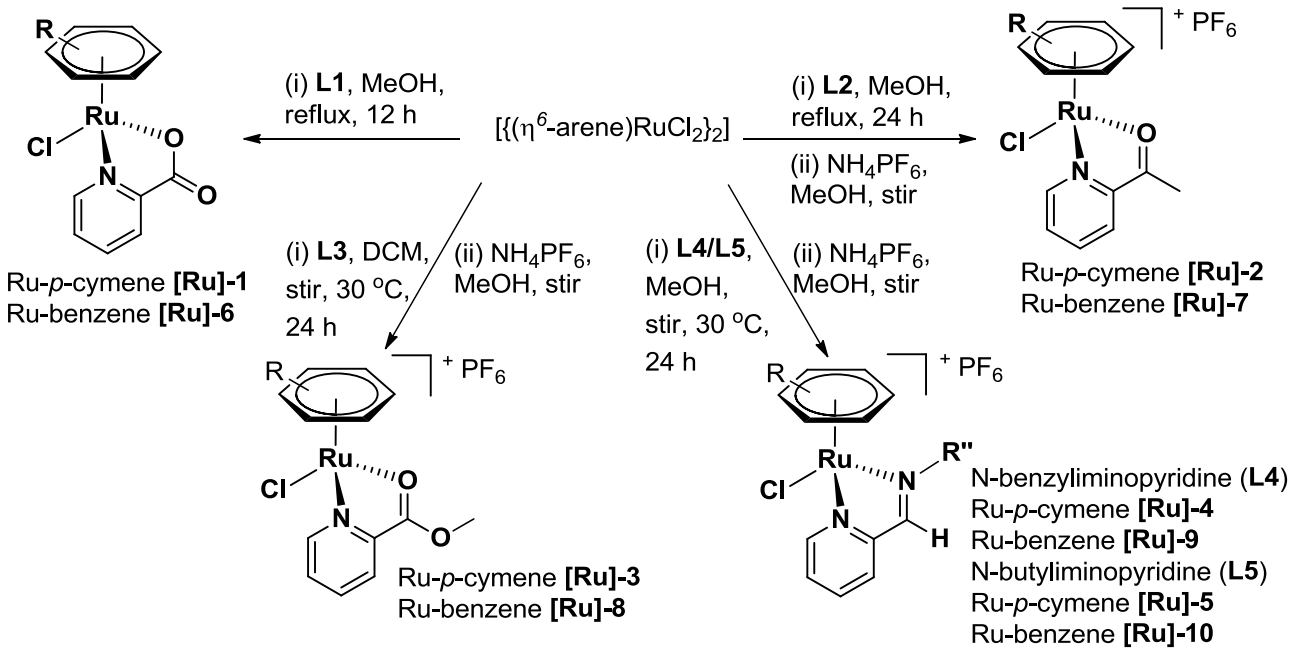
Inoue *et al*.[11a] Contrary to phosphine based ligands, carboxylates, as a ligand and deprotonating agent explored by various researchers and displayed high potential to achieve enhanced catalytic activity with tunable selectivity for ruthenium catalyzed C-H bond activation reaction.[12] Extensive kinetic studies by Jutand *et al.* also evidenced the active role of carboxylates as deprotonating agents, which enhances the catalytic efficiency of reaction by autocatalytic process.[12g] A remarkable example of robust ruthenium(II) catalyzed carboxylate assisted C-H arylation of amino acids and peptides has recently been reported by Ackermann *et al.* which also suggests the crucial role of carboxylates in C-H activation reaction.[12i] In our recent studies with ruthenium-arene complexes containing *O,O* and *O,N* donor tropolone/ aminotropolone ligands for C-H bond arylation of 2-phenylpyridine in water, we also investigated the interesting role of carboxylate additives, driven by steric bulkiness, in tuning the selectivity of C-H arylation products.[13] Later, we also explored aniline based ruthenium-arene complexes for C-H bond arylation in water, where the strength of aniline-ruthenium bond and the substitution on aniline ligand was found to be the crucial factors to tune the selectivity of mono v/s biarylated products during the reaction.[14]

Further, in our deliberate efforts to develop efficient catalytic system for C-H activation/ functionalization reactions,[13,14] herein we synthesized a series of ruthenium(II)-arene complexes containing pyridine based *N,O* and *N,N* donor ligands and systematically investigated their catalytic performance for *ortho* C-H bond activation/ arylation of 2-phenylpyridine with several arylhalides in water. Synthesized ruthenium-arene complexes were well characterized using NMR, mass spectral analysis and the molecular structure for few of the representative complexes were authenticated by single crystal X-ray diffraction studies. Attempts were also made to establish a relation between the pattern of bonding of ligands to the ruthenium metal center and

the observed catalytic activity of these complexes for *ortho* C-H bond activation/ arylation reaction using time-scaled ^{1}H NMR spectroscopy.

Results and Discussion

Synthesis of water-soluble ruthenium(II)-arene complexes [Ru]-1 to [Ru]-10: Water-soluble ruthenium-arene complexes (**[Ru]-1**−**[Ru]-10**) containing pyridine based *N,O* and *N,N* donor ligands were synthesized in good yield by reacting respective ruthenium(II)-arene dimer with the readily available *ortho* substituted pyridine based *N,O*/ *N,N* donor bidentate ligands with substituents ranging from carboxylic (pyridine-2-carboxylic acid (**L1**)), acetyl (2-acetylpyridine (**L2**)), ester (2-methylpicolinate (**L3**)) and imino groups (N-benzyl-pyridylimine (**L4**) and N-butyl-pyridylimine (**L5**)) as shown in the Scheme 1.



Scheme 1. Synthesis of ruthenium-arene complexes **[Ru]-1** – **[Ru]-10** containing pyridine based *N,O* and *N,N* donor ligands.

Ligand **L3** was prepared by acid catalyzed esterification of **L1** in methanol under refluxing condition.[15a] Iminopyridine ligands **L4** and **L5** were prepared by the condensation of pyridine-2-carboxyladehyde with benzylamine and *n*-butylamine respectively.[15b-15d] Identity and purity of the synthesized ligands **L3 – L5** were confirmed by ^{1}H and ^{13}C NMR.[15] Complexes **[Ru]-1 – [Ru]-2**, **[Ru]-4 – [Ru]-7**, **[Ru]-9** and **[Ru]-10**, with general formula [(η^6-arene)RuCl(κ^2-L)]$^{n+}$, where η^6-arene = C_6H_6 or $C_{10}H_{14}$, L = **L1 – L2**, **L4** and **L5** and n = 0, +1, were obtained by treating respective [{(η^6-arene)RuCl$_2$}$_2$] with ligands **L1 – L2**, **L4** and **L5** in methanol.[15d,16] Complexes **[Ru]-3** and **[Ru]-8** were obtained by stirring ligand **L3** with [{(η^6-arene)RuCl$_2$}$_2$] (η^6-arene = η^6-$C_{10}H_{14}$ and η^6-C_6H_6) in dichloromethane at room temperature. The synthesized complexes were well characterized by various spectro-analytical techniques, which further authenticated the proposed structure as shown in the Scheme 1.

^{1}H NMR spectra of the complexes **[Ru]-1** – **[Ru]-10** depicted an analogous trend, where a downfield shift in the chemical shifts of the protons associated with ligands was observed compared to the free ligands, suggesting the coordination of ligand to the ruthenium metal center. ^{1}H NMR resonances for protons corresponding to ruthenium coordinated η^6-arene ring were also observed in the expected region for all the complexes.[13,14,15-18] FTIR and UV-visible spectra recorded for the synthesized complexes were also in accordance with the previous reports.[16,18] The ESI mass spectra of the complexes **[Ru]-1** and **[Ru]-6** showed peaks corresponding to the [M-Cl]$^+$ ions, while rest of the cationic complexes displayed peaks for [M]$^+$ ions with the characteristic Ru isotopic patterns. Moreover, the synthesized complexes also exhibited appreciably good thermal stability (up to 250 ºC), as inferred from TGA studies (Figure S1).

Further, molecular structure of the representative complexes **[Ru]-2**, **[Ru]-4** and **[Ru]-5** was also confirmed by single crystal X-ray diffraction studies. Crystals suitable for X-ray

diffraction of the complexes **[Ru]-2**, **[Ru]-4** and **[Ru]-5** were grown by the diffusion of diethyl ether into the methanolic solution of these complexes at room temperature. Complexes **[Ru]-2** and **[Ru]-4** crystallized in monoclinic crystal system with P21/c space group, whereas **[Ru]-5** crystallized in triclinic crystal system with P-1 space group. The geometry around the ruthenium metal center was pseudo-octahedral, where the η^6-arene ring occupied the top of the *piano-stool*, and three legs were occupied by the bidentate *N,O* or *N,N* donor ligands and one chloride ligand. The η^6-arene ring centroid was displaced from the Ru(II) center by 1.671, 1.693 and 1.695 Å for the complexes **[Ru]-2**, **[Ru]-4** and **[Ru]-5** respectively, which is comparable to the similar arene-Ru(II) complexes.[16-18] For complex **[Ru]-2**, the ligand 2-acetylpyridine (**L2**) was coordinated with the ruthenium metal in bidentate fashion involving the nitrogen atom of pyridine ring and oxygen atom of acetyl. Similarly, for complexes **[Ru]-4** and **[Ru]-5**, iminopyridine ligands **L4** and **L5** were coordinated with the ruthenium metal in κ^2-mode through N_{py} and N_{imine}. Ru-N_{py}(1) and Ru-O(1) bond distances 2.107 and 2.117 Å respectively of complex **[Ru]-2** were within the permissible ranges for analogous ruthenium-arene complexes.[18] Angles between the legs of the complex, N(1)-Ru-Cl(1) and O(1)-Ru-Cl(1), were 83.9º and 83.8º respectively, whereas bond angle between the legs and the centroid of the η^6-arene ring (C_t) were in the range of 129.6 - 133.9º for complex **[Ru]-2**. The N(1)-Ru-O(1) bite angle was 76.2º for complex **[Ru]-2**. Ru-N_{py} and Ru-N_{imine} bond distances were 2.079 and 2.094 Å respectively for the complex **[Ru]-4** and those for **[Ru]-5** were 2.0871 and 2.0708 Å respectively. Bite angles N(1)-Ru-N(2) for the complexes **[Ru]-4** and **[Ru]-5** were 76.6º and 76.8º. Angles between legs of these *piano-stool* complexes were in the range of 83.3º-86.1º for complex **[Ru]-4** and 85.1º - 85.9º for complex **[Ru]-5**. The observed bond parameters are comparable to the previous reports for related complexes.[16,18] Detailed crystal refinement data , selected bond lengths and bond angles are given in the Table S1-S7.

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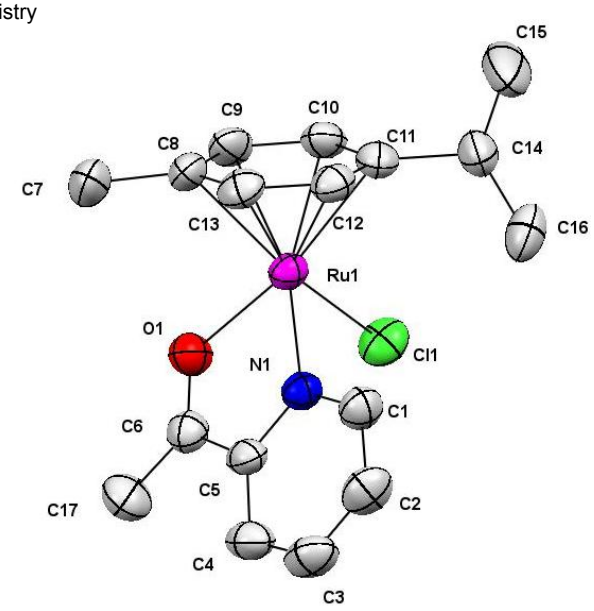


Figure 1. Single crystal X-ray structure of complex **[Ru]-2** with 50% probability of thermal ellipsoids. Counter ion PF_6 and all hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and selected bond angles (deg): Ru1-N1 2.107(4), Ru1-O1 2.117(4), Ru1-Cl1 2.391(14), Ru1-C_t 1.671, N1-Ru-Cl1 83.91(12), O1-Ru-Cl1 83.85(12), N1-Ru-O1 76.21(6).

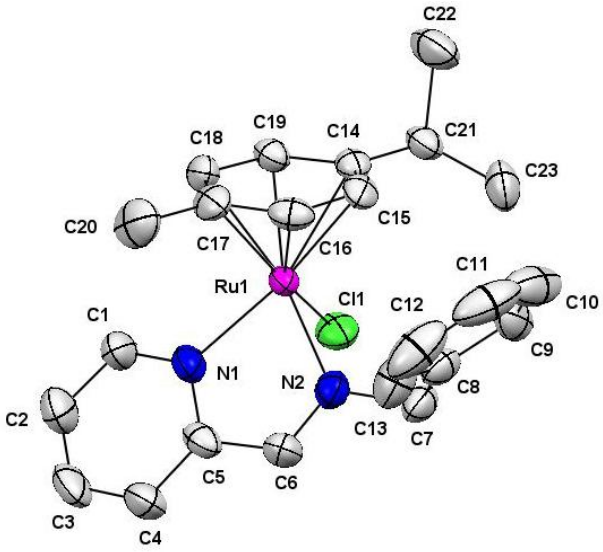


Figure 2. Single crystal X-ray structure of complex **[Ru]-4** with 50% probability of thermal ellipsoids. Counter ion PF_6 and all hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and selected bond angles (deg): Ru1-N1 2.079(5), Ru1-N2 2.094(5), Ru1-Cl1 2.398(15), Ru1-C_t 1.693, N1-Ru-Cl1 86.15(16), N2-Ru-Cl1 83.30(14), N1-Ru-N2 76.65(19).

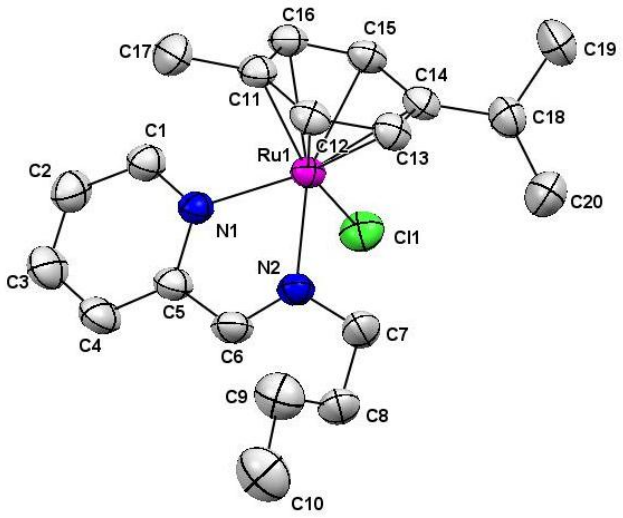
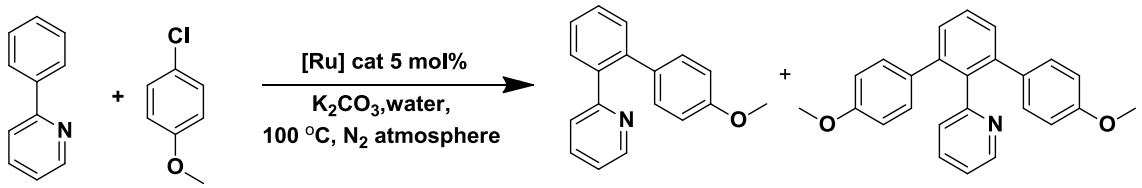


Figure 3. Single crystal X-ray structure of complex **[Ru]-5** with 50% probability of thermal ellipsoids. Counter ion PF_6 and all hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and selected bond angles (deg): Ru1-N1 2.0871(19), Ru1-N2 2.0708(19), Ru1-Cl1 2.3997(6), Ru1-C_t 1.695, N1-Ru-Cl1 85.10(6), N2-Ru-Cl1 85.93(6), N1-Ru-N2 76.80(8).

Ruthenium-arene catalyzed *ortho* C-H bond arylation of 2-phenylpyridines with arylhalides. At an outset, 2-phenylpyridine (**1a**) and 4-chloroanisole (**2a**) were chosen as model substrates for *ortho* C-H bond arylation over **[Ru]-1 – [Ru]-10** catalysts. The reaction of **1a** (0.5 mmol) and **2a** (1.25 mmol)[13,19] over **[Ru]-1** catalyst (5 mol %) in the presence of 3 equiv. of K_2CO_3 showed a conversion of 82% with 86% selectivity (63% yield) for the monoarylated product (**3aa**) in 8 h at 100 °C in water (Table 1, entry 1). Further, a remarkably high conversion of 98% was achieved over **[Ru]-2** with 73% selectivity for **3aa** (65% yield) in 8 h under analogous reaction conditions. Moreover, extending the catalytic reaction to 10 h, complete conversion of 2-phenylpyridine can be achieved over **[Ru]-2** catalyst. Notably, **[Ru]-3** catalyst also resulted in 93% conversion with 61% yield of **3aa** (Table 1, entry 3). In contrary to the higher catalytic activity of **[Ru]-1 – [Ru]-3** catalysts (ruthenium-arene with *N,O* donor ligands),

ruthenium-arene-iminopyridine complexes (**[Ru]-4 – [Ru]-5**) exhibited only moderate conversions (Table 1, entries 4 and 5).

Table 1. Catalytic activity of ruthenium-arene complexes for *ortho* C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**).[a]



1a 2a 3aa 4aa

Entry	Catalyst	Conv. (%)[d]	Sel. (%)[d] (**3aa/4aa**)	Yield (%) (**3aa**)	TON/TOF
1	[(η^6-*p*-cymene)Ru(κ^2-*N,O*-pyridine-2-carboxylate)Cl] **[Ru]-1**	82	86/14	63%	16.4/2.05
2	[(η^6-*p*-cymene)Ru(κ^2-*N,O*-2-acetylpyridine)Cl]PF_6 **[Ru]-2**	98 (100)[b]	73/27 (68/22)[b]	65% (60%)[c]	19.6/2.45
3	[(η^6-*p*-cymene)Ru(κ^2-*N,O*-2-methylpicolinate)Cl]PF_6 **[Ru]-3**	93	76/24	61%	18.6/2.32
4	[(η^6-*p*-cymene)Ru(κ^2-*N,N*-(N-benzyl-pyridylimine)Cl]PF_6 **[Ru]-4**	42	86/14	28%	8.4/1.05
5	[(η^6-*p*-cymene)Ru(κ^2-*N,N*-(N-butyl-pyridylimine)Cl]PF_6 **[Ru]-5**	45	88/12	33%	9.0/1.12
6	[(η^6-benzene)Ru(κ^2-*N,O*-pyridine-2-carboxylate)Cl] **[Ru]-6**	80	89/11	63%	16.0/2.0
7	[(η^6-benzene)Ru(κ^2-*N,O*-2-acetylpyridine)Cl]PF_6**[Ru]-7**	97	87/13	72%	19.4/2.42
8	[(η^6-benzene)Ru(κ^2-*N,O*-2-methylpicolinate)Cl]PF_6 **[Ru]-8**	88	84/16	65%	17.6/2.2
9	[(η^6-benzene)Ru(κ^2-*N,N*-(N-benzyl-pyridylimine)Cl]PF_6 **[Ru]-9**	62	80/20	40%	12.4/1.55
10	[(η^6-benzene)Ru(κ^2-*N,N*-(N-butyl-pyridylimine)Cl]PF_6 **[Ru]-10**	45	86/14	32%	9.0/1.12

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), K_2CO_3 (3 equiv.), [Ru] catalyst (5 mol%) in water (5 mL) at 100 °C for 8 h. [b]Reaction time = 10 h. [c]Isolated yield in 10 h. [d]Conversion and selectivity were determined by ^{1}H NMR. Yield (%) represents the isolated yield of the purified product (**3aa**). TON = Turn Over Number. TOF = Turn Over Frequency (h^{-1}).

Consistent with the higher catalytic activity observed with (η^6-*p*-cymene)Ru complexes (**[Ru]-1 – [Ru]-3**), analogous (η^6-benzene)Ru complexes (**[Ru]-6 – [Ru]-8**) also exhibited enhanced catalytic conversion, where the (η^6-benzene)Ru-acetylpyridine complex (**[Ru]-7**) showed 97% conversion of **1a** (Table 1, entry 6). Moreover, (η^6-benzene)Ru complexes containing iminopyridine based ligands (**[Ru]-9** and **[Ru]-10**) were also observed to be less active than the complexes with *N,O* donor ligands (Table 1, entries 9,10). Therefore, it is evident from the above results, that ruthenium-arene complexes with *N,O* donor pyridine based ligands displayed superior catalytic performance over those ligated with *N,N* donor ligands for the *ortho* C-H bond arylation of **1a**. Moreover, amongst *N,O* donor ligands, the ruthenium-arene complexes having *N,O* donor ligands with neutral oxygen donor group (acetylpyridine ligated ruthenium-arene complexes (**[Ru]-2**, **[Ru]-3**, **[Ru]-7** and **[Ru]-8**) outperformed over those coordinated with anionic oxygen donor group (picolinate ligated ruthenium-arene complexes **[Ru]-1** and **[Ru]-6**), under analogous reaction condition. The above results suggesting a crucial role of ligand in the observed trend in the catalytic C-H bond activation reaction. Moreover, most of the ionic ruthenium catalysts ([**Ru]-2**, **[Ru]-3**, **[Ru]-7** and **[Ru]-8**) exhibited superior catalytic activity than the electroneutral catalysts (**[Ru]-1** and **[Ru]-6**),[20] but the poor performance of other ionic catalysts (**[Ru]-4**, **[Ru]-5**, **[Ru]-9** and **[Ru]-10**) suggesting that presumably the effect of solvation was superseded by the dominating and crucial role of the ligands.

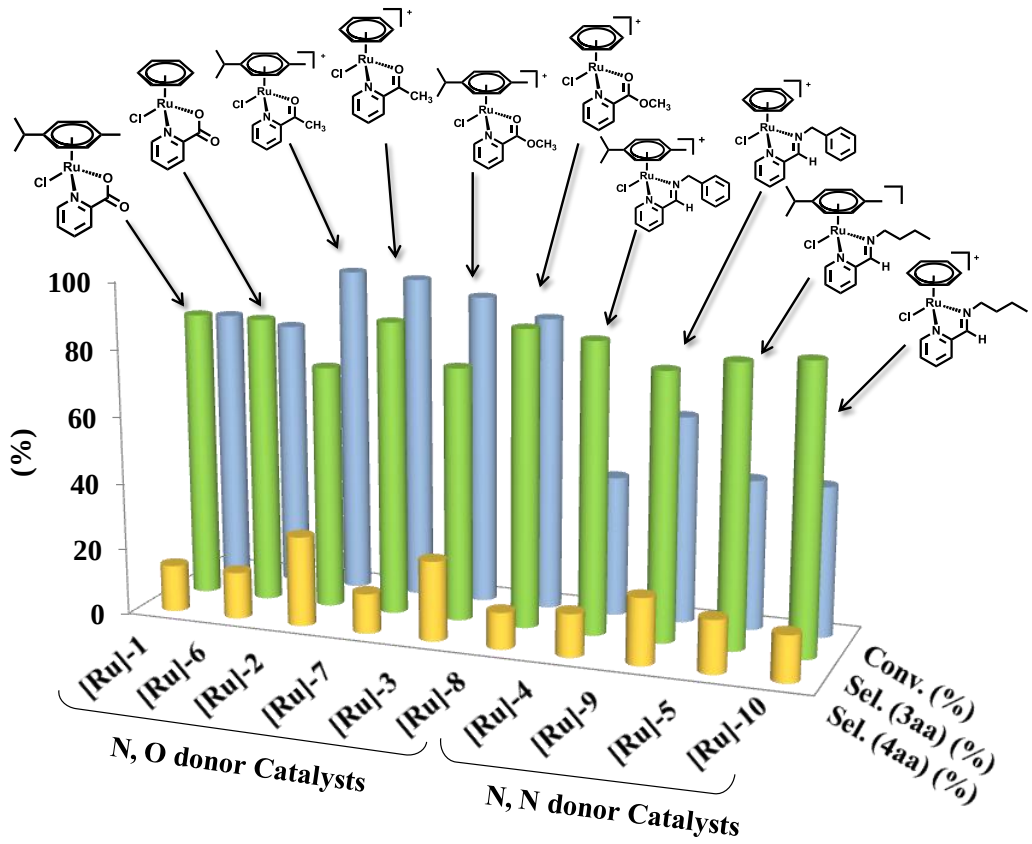


Figure 4. Structure-activity relationship for *ortho* C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over **[Ru]-1** – **[Ru]-10** catalysts.

Notably, carboxylate additives are considered as efficient deprotonating agents in C-H bond activation reactions, where its deprotonating properties increases with the increase in bulkiness/ basicity and on its availability in the solution.[12, 13] Therefore, the effect of carboxylate salts, with increasing bulkiness on α-carbon, were explored over the best catalyst (**[Ru]-2**) under the optimized reaction conditions: Cat. 5 mol%, 100 ºC, K_2CO_3 (3 equiv.) (Table 2). Results inferred that with the increase in bulkiness of the carboxylate salts (acetate → pivalate), a gradual decrease in the conversion of **1a** was observed over ruthenium-arene-acetylpyridine **[Ru]-2** catalyst (Table 2, entries 9-12). Interestingly, the ruthenium-arene picolinate catalyst **[Ru]-1** showed a reverse pattern, where an increase in the catalytic activity was observed with bulky carboxylates (acetate → pivalate) (Figure 5).

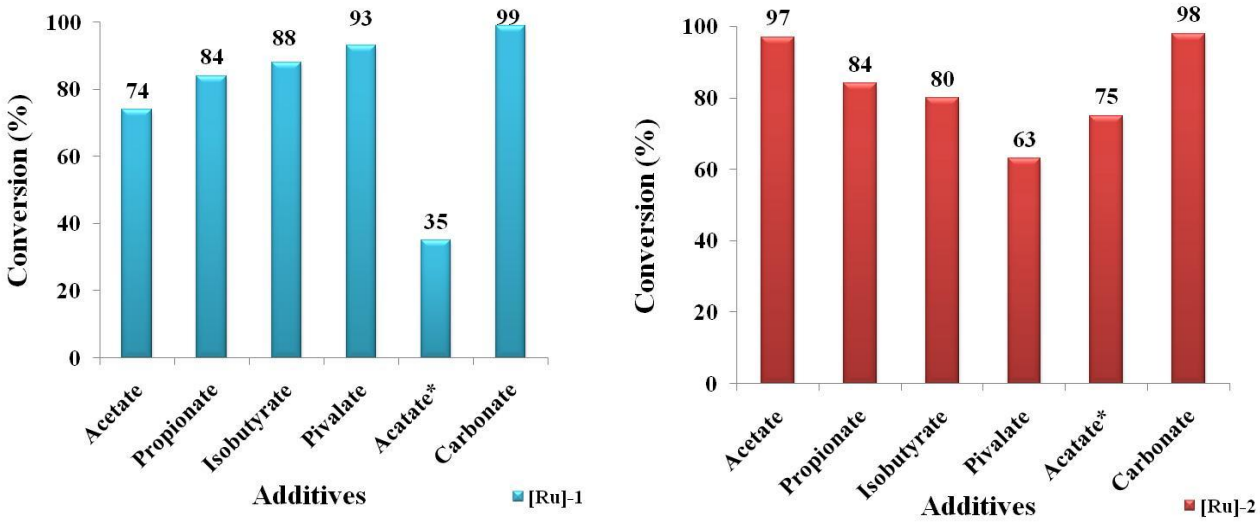
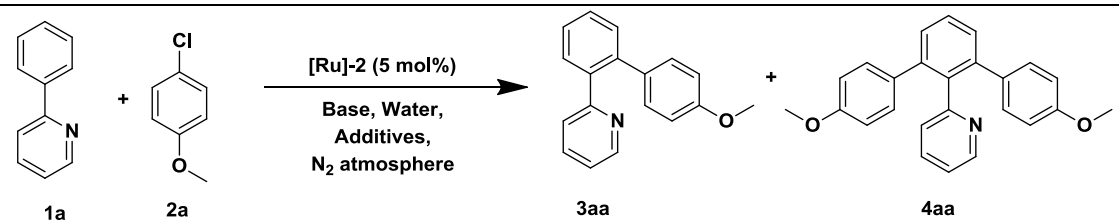


Figure 5. Effect of carboxylate additives on *ortho* C-H bond arylation of 2-phenylpyridine with 4-chloroanisole over **[Ru]-1** and **[Ru]-2** catalyst. * Reaction performed with KOAc in absence of K_2CO_3.

The observed trend can be attributed to the competitive coordination of the acetylpyridine/ picolinate and the carboxylate additives to the ruthenium center. The strong coordinating nature of pivalate compared to acetylpyridine, under catalytic reaction condition unless otherwise mentioned, resulted in the decreases in the availability of free carboxylate in the solution, whereas picolinate showed stronger coordination behavior than carboxylate additives and hence ensured greater availability of carboxylate additives in the solution. Though the observed conversion with a range of carboxylate salts (with or without K_2CO_3) was found to be lower than the conversion observed with only K_2CO_3 base (in the absence of any carboxylate additives) in case of both catalysts, the above observations are worth noting as it inferred the crucial role of the ligand in controlling the catalytic activity in the studied ruthenium-arene complexes. Therefore, further optimization experiments were performed using only K_2CO_3 base, without carboxylate additives. Notably, reaction could not occur in the absence of base or

catalyst (Table 2, entries 7-8). Moreover, performing the reaction at lower temperature < 100 ºC resulted in poor conversion over **[Ru]-2** catalyst (Table 2, entries 5-6).

Table 2. Optimization table for catalytic *ortho* C-H bond arylation of 2-phenylpyridine over complex **[Ru]-2**.[a]



Entry	Temp. (ºC)	Time (h)	Base	Additive	Conv. (%)	Sel. (%) (**3aa/4aa**)
1	100	2	K_2CO_3	-	33	>99/<1
2	100	4	K_2CO_3	-	86	83/17
3	100	6	K_2CO_3	-	92	75/25
4	100	8	K_2CO_3	-	98	73/27
5	70	8	K_2CO_3	-	12	>99/<1
6	80	8	K_2CO_3	-	37	>99/<1
7	100	8	-	-	n.r.	-
8[b]	100	8	K_2CO_3	-	n.r.	-
9	100	8	K_2CO_3	CH_3COOK	97	57/43
10	100	8	K_2CO_3	CH_3CH_2COOK	84	76/24
11	100	8	K_2CO_3	$(CH_3)_2CH_2COOK$	80	81/19
12	100	8	K_2CO_3	$(CH_3)_3CHCOOK$	63	89/11

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), base (3 equiv., 1.5 mmol), **[Ru]-2** (5 mol%), additives (0.05 mmol) in water (5 mL). Conversion and selectivity were determined by ^{1}H NMR.[b]without catalyst. n.r. = No reaction.

Further, time-dependent ^{1}H NMR experiments for C-H bond arylation reaction were conducted over the high performance **[Ru]-2** catalyst, and the results were compared with those of the analogous picolinate (**[Ru]-1**) and iminopyridine (**[Ru]-4**) complexes (Figure 6a). Among all the complexes studied, **[Ru]-2** exhibited higher rates (6.12×10^{-4} sec^{-1}) during the 0-8 hours of the catalytic reaction (Figure S2). Contrary to **[Ru]-2**, complexes **[Ru]-1** and **[Ru]-4** displayed relatively lower kinetics 3.50×10^{-5} sec^{-1} and 2.63×10^{-5} sec^{-1}, respectively (Figure S2). The above results clearly evidenced the crucial role of the coordination environment around the Ru

center, due to *N,O/ N,N* donor ligands, on the catalytic efficiency of the resulting ruthenium-arene complexes. Further, the time-dependent reaction profile over **[Ru]-2** catalyst showed >90% consumption of **1a** over a period of 6 h. Though the selectivity for monoarylated product (**3aa**) remains dominated throughout the reaction (2-10 h), the selectivity for the biarylated product (**4aa**) increases gradually with the increase in the reaction time, suggesting the consumption of **3aa** to form **4aa** (Figure 6b).

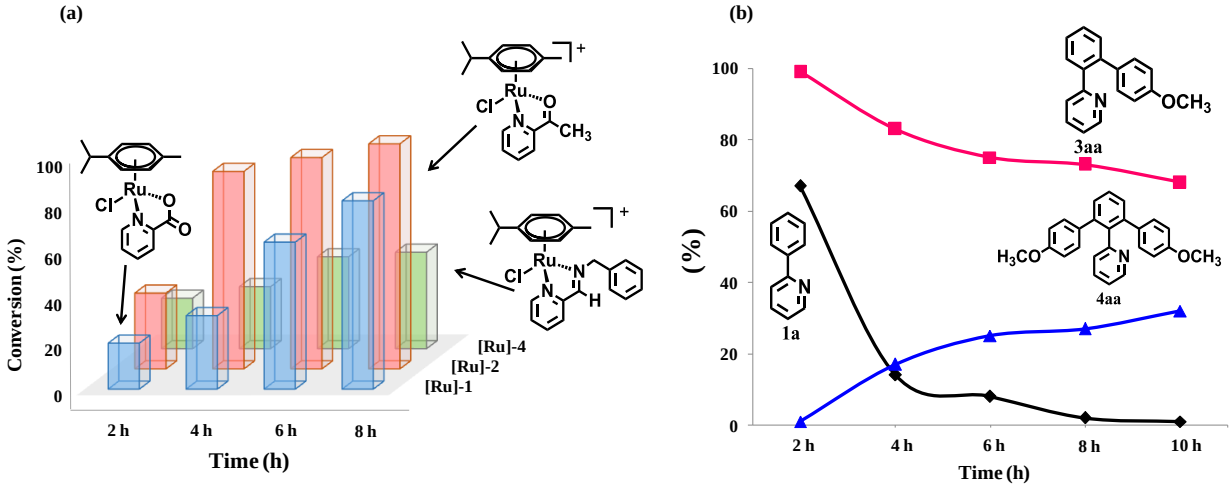
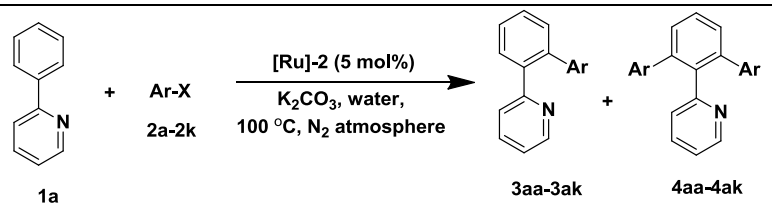


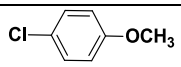
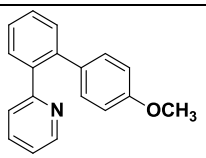
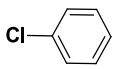
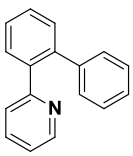
Figure 6. (a) Time dependent reaction profile with complexes complexes **[Ru]-1**, **[Ru]-2** and **[Ru]-4**, and **(b)** products, monoarylated (**3aa**) and biarylated (**4aa**), distribution over **[Ru]-2** for ortho C-H bond arylation of 2-phenylpyridine (1a) with 4-chloroanisole (**2a**) at 100 ºC in water.

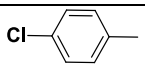
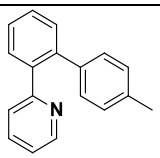
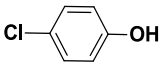
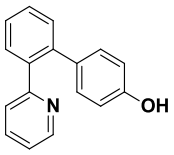
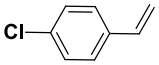
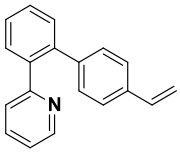
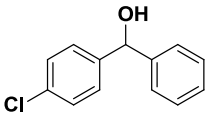
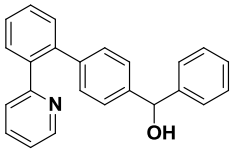
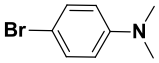
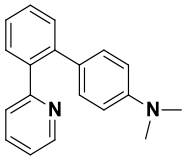
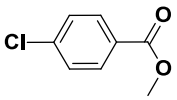
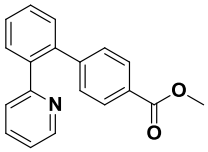
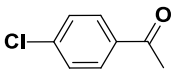
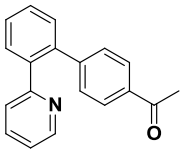
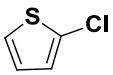
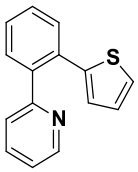
Further, the scope and generality for **[Ru]-2** catalyzed C-H bond arylation of 2-phenylpyridine (**1a**) using several arylhalides (**2a-2k**) was explored under the optimized reaction condition (Table 3). Notably, both electron donating and electron withdrawing arylhalides were proved to be efficient arylating agents for *ortho* C-H bond arylation of **1a** to afford corresponding monoarylated products (**3aa-3ak**) as major component, with moderate to high selectivity and yield in 8 h. The unsubstituted chlorobenzene (**2b**) afforded 82% conversion for the arylation of **1a** with 78% selectivity for the monoarylated product (**3ab**) (Table 3, entry 2).

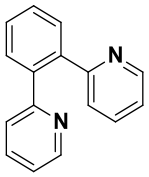
Analogous to 4-chloroanisole (**2a**), reaction with electron donating arylhalides, 4-chlorotoluene (**2c**) and 4-chlorophenol (**2d**), also afforded the respective monoarylated products with high selectivity, 70% for (**3ac**) and 75% for (**3ad**) (Table 3, entries 3-4). Notably, 4-chlorostyrene (**2e**) showed sluggish reaction, presumably due to the coordination of vinyl group to the catalyst and thus retarded the reaction progress. Nevertheless, 91% selectivity for the monoarylated product (**3ae**) was achieved with **2e** (Table 3, entry 5). Further, 4-chlorobenzhydrol (**2f**) and 4-bromo N,N-dimethylaniline (**2g**) also exhibited moderate conversion, but with high selectivity of 99% and 82% respectively for the monoarylated products (**3af**) and (**3ag**) (Table 3, entries 6,7). Electron withdrawing arylhalides, 4-chloromethylbenzoate (**2h**) and 4-chloroacetophenone (**2i**), also exhibited excellent conversion of 96% and 80%, respectively with selectivities of 45% and 80% for (**3ah**) and (**3ai**) (Table 3, entries 8,9). However, (hetero)arylhalides, 2-chlorothiophene (**2j**) and 2-bromopyridine (**2k**), showed only poor conversion, presumably due to the strong coordination of Lewis basic heteroatoms to the ruthenium center (Table 3, entries 10,11).[21]

Table 3. Catalytic *ortho*-C-H bond arylation of 2-phenylpyridine (**1a**) using various arylhalides (**2a-2k**).[a]



Entry	(Hetero)arylhalide	Conv. (%)/ Time (h)	Sel. (%)	Yield (%)
1	 **2a**	98 (8 h) >99 (10 h)	73/27 68/32 (**3aa**/**4aa**)	 **3aa** (63%)
2	 **2b**	82	78/22 (**3ab**/**4ab**)	 **3ab** (58%)

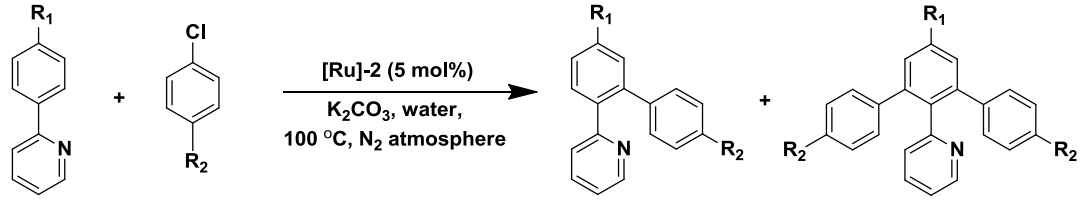
3	 **2c**	86	70/30 (**3ac**/**4ac**)	 **3ac** (53%)
4	 **2d**	>99	75/25 (**3ad**/**4ad**)	 **3ad** (63%)
5	 **2e**	52	91/9 (**3ae**/**4ae**)	 **3ae** (40%)
6	 **2f**	65	99/1 (**3af**/**4af**)	 **3af** (56%)
7	 **2g**	37	82/18 (**3ag**/**4ag**)	 **3ag** (20%)
8	 **2h**	96	45/55 (**3ah/4ah**)	 **3ah** (36%)
9	 **2i**	80	80/20 (**3ai/4ai**)	 **3ai** (58%)
10	 **2j**	40	80/20 (**3aj**/**4aj**)	 **3aj** (24%)

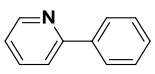
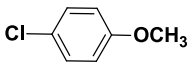
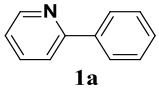
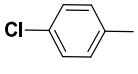
11	 **2k**	15	45/55 (**3ak**/**4ak**)	 **3ak** (nd)[b]

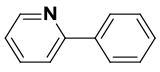
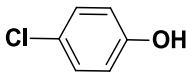
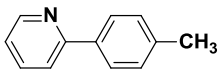
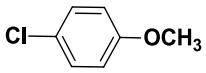
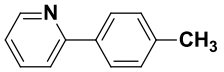
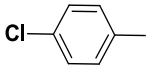
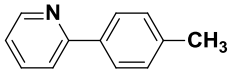
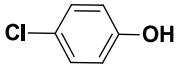
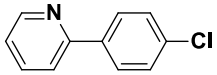
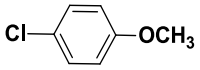
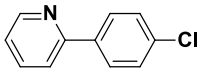
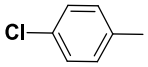
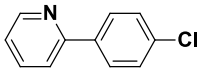
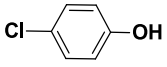
[a]Reaction conditions: **1a** (0.5 mmol), **2a-2k** (1.25 mmol), K_2CO_3 (3 equiv.), **[Ru]-2** (5 mol%) in water (5 mL) at 100 ºC for 8 h. Conversion and selectivity were determined by ^{1}H NMR. Yield (%) represents the isolated yield of the purified product. [b]nd = Not determined.

Moreover, the effect of the substituted 2-phenylpyridines (**1a-1c**) on *ortho* C-H bond arylation was also investigated (Table 4). Results inferred that having an electron donating substituent, 2-(*p*-tolyl)pyridine (**1b**) showed enhanced reactivity with >80% conversion and appreciably good selectivity for the monoarylated products was achieved (Table 4, entries 4-6). In contrary, 2-(4-chloro)phenylpyridine (**1c**) bearing electron withdrawing chloro substituent resulted in lower conversion for *ortho* C-H bond arylation (Table 4, entries 7-9). Nevertheless, monoarylated products remain the dominating product for all the reactions.

Table 4. Catalytic *ortho*-C-H bond arylation of substituted 2-phenylpyridines using selected arylhalides[a]



Entry	Phenylpyridine	Arylhalide	Conv. (%)	Sel. m/d (%) (Yield (%))
1	 **1a**	 **2a**	>99%[b]	68/22[b] (**3aa,** 60%)[c]
2	 **1a**	 **2c**	82%	78/22 (**3ac,** 58%)[c]

3	 **1a**	 **2d**	>99%	75/25 (**3ad,** 53%)[c]
4	 **1b**	 **2a**	98%	53/47 (**3ba,** 40%)[c]
5	 **1b**	 **2c**	95%	70/30 (**3bc,** 55%)[c]
6	 **1b**	 **2d**	>99%	68/32 (**3bd,** nd)[e]
7	 **1c**	 **2a**	62%	80/20 (**3ca,** 40%)[d]
8	 **1c**	 **2c**	39%	86/14 (**3cc,** 23%)[c]
9	 **1c**	 **2d**	55%	49/51 (**3cd,** 20%)[d]

[a]Reaction conditions: **1a-1c** (0.5 mmol), arylhalide (1.25 mmol), K_2CO_3 (3 equiv.), **[Ru]-2** (5 mol%) in water (5 mL) at 100 °C for 8 h. Conversion and selectivity for monoarylated (m) and biarylated product (d) were determined by ^{1}H NMR. [b]Time = 10 h. [c]Isolated yield. [d]Combined yield for monoarylated and biarylated product. [e]nd = Not determined.

To investigate and identify the possible organometallic species, which may be involved in one or many steps of the catalytic *ortho* C-H bond arylation reaction, several controlled experiments were performed. ^{1}H NMR analysis of the reaction mixture using the stoichiometric ratio of catalyst **[Ru]-2** and substrate (**1a**) (C:S = 1:5) after 3 h, showed the formation of 2-phenylpyridine coordinated cyclometallated species {(η^6-*p*-cymene)Ru(κ^2-*C*,*N*-phenylpyridine)}$^+$ **[Ru]-A**. Earlier reports inferred that such organometallic species **[Ru]-A** are indeed a crucial species involved in several ruthenium-arene catalyzed *ortho* C-H bond activation reactions.[8,12,14] The presence of cycloruthenated species (**[Ru]-A**) was also confirmed

by mass spectrometric investigation (m/z 390.1) of the stoichiometric reaction of complex **[Ru]-2** with 2-phenylpyridine (**1a**), even in the absence of base K_2CO_3 (Figure 7), suggesting the possible role of the ruthenium coordinated 2-acetylpyridine in C-H activation reaction. Therefore, the above NMR and mass spectral investigations along with the reaction kinetics and carboxylate effect experiments substantially accounted for the observed superior catalytic activity of *N,O* donor ligated ruthenium-arene complexes over those with *N,N* donor ligands,[21] and the order of catalytic activity of the studied complexes was found as (η^6-arene)Ru(κ^2-*N,O*-2-acetypyridine) > (η^6-arene)Ru(κ^2-*N,O*-2-methylpicolinate) > (η^6-arene)Ru(κ^2-*N,O*-picolinate) >> (η^6-arene)Ru(κ^2-*N,N*-iminopyridine). The observed trend is indeed in accordance with the previous studies, which evidenced the crucial role of bis-chelating ligands in tuning the catalytic C-H activation reaction pathway *via* coordination/decoordination mechanism and by participating in deprotonation step.[22,23] For instance, the crucial role of Pd-coordinated picolinate in the deprotonation of arene was reported over a Pd-catalyzed C-H acetoxylation of arenes, where interestingly, picolinate/picolinic acid remains coordinated to the Pd during this deprotonation step.[23a] Moreover, compared to the picolinate ligated metal complexes, those having N,N donor ligands exhibited lower activity.[23b] In contrary to the picolinate and N,N donor ligands, studies revealed that the acetyl group participated actively in the deprotonation of the C-H bond activation, while remain uncoordinated.[22] Moreover, literature also revealed that proton abstraction by a carbonate base requires less energy (-13.7 kcal/mol) and comparatively favorable over hydride abstraction pathway (+28.2 kcal/mol).[24]. Hence, we anticipated that the remarkable catalytic activity of acetylpyridine ligated ruthenium-arene complexes for C-H activation/ arylation is presumably due to the active participation of the ligand in facile deprotonation of C-H bond and efficient coordination-decoordination interconversion process

(Figure 7). On the basis of above experimental observations a plausible reaction pathway for the *ortho*-C-H bond arylation of 2-phenylpyridine is illustrated in Scheme S1.

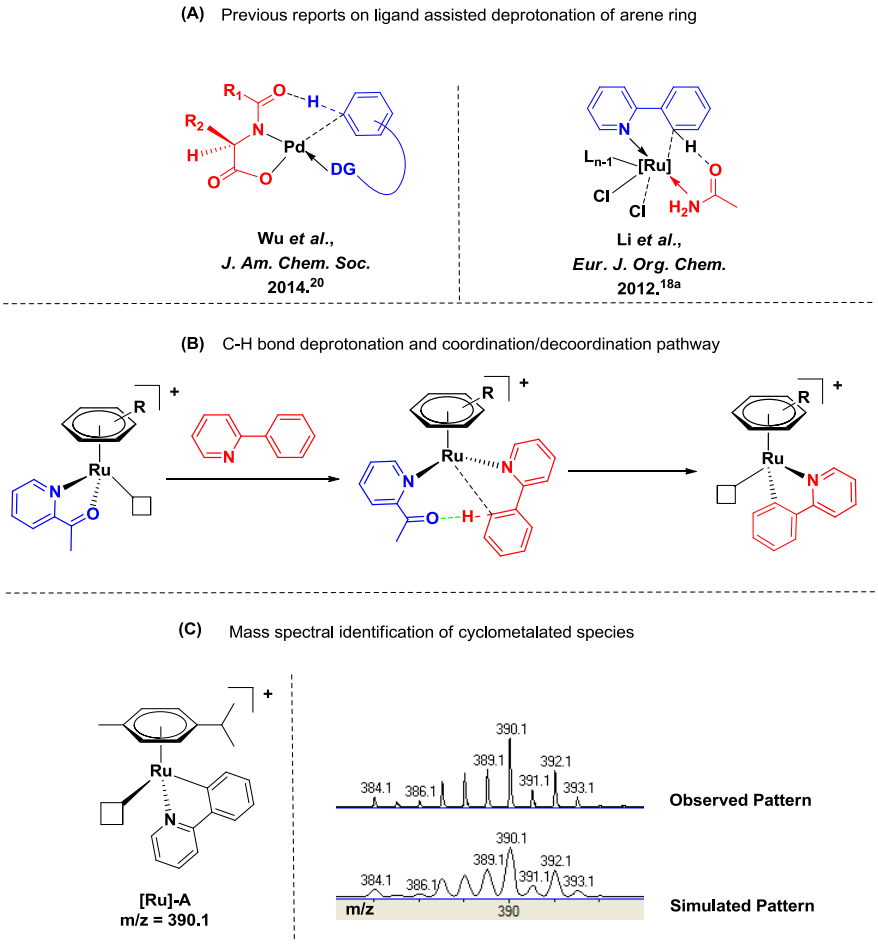


Figure 7. (A) Ligand assisted remote C-H bond deprotonation of various arene rings with transition metal (Ref. 18a, 20) **(B)** C-H bond deprotonation of 2-phenylpyridine and coordination and decoordination of carbonyl oxygen of *N,O* donor ligand for the formation of deprotonated cycloruthenated species. **(C)** Mass spectral identification of cycloruthenated species for the reaction of **[Ru]-2** with 2-phenylpyridine (with 1:5 molar ratio) in absence of base.

Conclusions

To summarize, we systematically investigated the ligand-tuned catalytic performance of ruthenium(II)-arene complexes ligated with *N,O* and N,N donor pyridine based ligands for the *ortho* C-H bond arylation of phenylpyridine with a variety of arylhalides in water. Our findings demonstrated that among all the synthesized complexes, ruthenium-arene complexes ligated with *N,O* donor pyridine ligands, **[Ru]-1** – **[Ru]-3** and **[Ru]-6** – **[Ru]-8**, outperformed with good to moderate yields (61-77%) for the C-H bond arylated products, over those containing N,N donor pyridine ligands (28-40%). Moreover, the time-dependent ^{1}H NMR studies inferred higher rate constant for **[Ru]-2** (ruthenium-acetylpyridine) ($k = 6.12 \times 10^{-4}$ sec^{-1}) over **[Ru]-3** (ruthenium-picolinate) ($k = 3.50 \times 10^{-5}$ sec^{-1}) and **[Ru]-4** (ruthenium-iminopyridine) ($k = 2.63 \times 10^{-5}$ sec^{-1}). The observed trend in the ligand-tuned catalytic performance of the studied complexes inferred the crucial role of the coordinating ligands (nitrogen *vs* oxygen and neutral *vs* anionic) to establish the structure-activity relationship for the catalytic C-H activation/ arylation reactions, where the facile ligand to Ru center coordination-decoordination interconversion and deprotonation of C-H bond played crucial role in the observed trend. Moreover, the mass spectral and ^{1}H NMR studies showed the formation of the crucial cycloruthenated species, {(η^6-arene)Ru(κ^2-*C,N*-phenylpyridine)}$^{+}$ (**[Ru]-A**) during the C-H bond activation of 2-phenylpyridine. In addition, molecular structures for few of the representative complexes, **[Ru]-2**, **[Ru]-4** and **[Ru]-5**, were also authenticated by single crystal X-ray diffraction studies. Specifically, we demonstrated ligand-tuned efficient ruthenium catalyzed C-H activation/ arylation reactions, which will be helpful in exploring new possibilities in this field.

Experimental Section

Materials and instrumentation. All the reactions for catalyst preparation were performed without inert gas protection and all the catalytic reactions for C-H bond arylation of 2-phenylpyridine with arylhalides were performed under N_2 atmosphere using chemicals of high purity purchased from Sigma Aldrich and Alfa Aesar. Ruthenium-arene precursors [{(η^6-C_6H_6)$RuCl_2$}$_2$]and [{(η^6-$C_{10}H_{14}$)$RuCl_2$}$_2$] were synthesized according to the literature procedures. [25, 26] ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{31}P NMR (161.98 MHz) spectra were recorded at 298 K using $CDCl_3$, Acetone-d_6 or DMSO-d_6 as the solvent on a Bruker Avance 400 spectrometer. The chemical shifts in ppm are reported relative to the center of the singlet at 7.26 ppm for $CDCl_3$, 2.04 ppm for Acetone-d_6 and 2.49 ppm for DMSO-d_6 in ^{1}H NMR and to the center of the triplet at 77.0 ppm for $CDCl_3$, singlet at 206.0 ppm for Acetone-d_6 and multiplet at 39.50 ppm for DMSO-d_6 in ^{13}C NMR. Coupling constants, J values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; sept, septet. Single-crystal X-ray structural studies of complexes were carried out using Agilent Technologies Supernova CCD system. FTIR for complexes was recorded on Perkin Elmer STD10 FTIR spectrometer and UV-visible spectra of all the complexes was recorded in methanol at room temperature on Carry-60 UV-visible spectrophotometer with concentration of 5×10^{-5} M. Elemental analysis was carried out using a Thermo Scientific FLASH 200 elemental analyzer. High-resolution mass spectra (HRMS) were recorded on amicrOTF-Q II mass spectrometer. Thermal gravimetric analyses (TGA) were performed on the Mettler Toledo thermal analysis system. CCDC deposition numbers of the complexes **[Ru]-2, [Ru]-4** and **[Ru]-5** are **1515543**, **1518468** and **1515545** respectively.

Procedure for the synthesis of arene-Ru(II) complexes ([Ru]-1-[Ru]-10) containing pyridine based ligands.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,O-pyridine-2-carboxylate)Cl] ([Ru]-1). Complex **[Ru]-1** was prepared by the modified procedure.[16] [{(η^6-*p*-cymene)$RuCl_2$}$_2$] (0.306 g, 0.5 mmol) was suspended in methanol (25 mL) and stirred for 30 minute at room temperature, and was added pyridine-2-carboxylic acid (0.135, 1.1 mmol). After refluxing the reaction mixture for 12 h, all volatiles were removed on rotavaporator and the residue obtained was dissolved in a minimum amount of dichloromethane. Upon addition of excess of diethyl ether in the above dichloromethane solution, yellow solid was precipitated out. Yield: 85% (0.260 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.99 (d, 1H, *J* = 8.0 Hz), 7.98-7.94 (m, 2H), 7.59 (d, 1H, *J* = 8.0 Hz), 5.63 (d, 2H, *J* = 4.0 Hz), 5.47 (d, 2H, *J* = 8.0 Hz), 2.88 (m, 1H), 2.28 (s, 3H), 1.23 (d, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =171.2, 153.1 151.1, 139.4, 128.4, 127.0, 102.6, 98.6, 83.2, 83.0, 82.1, 81.1, 31.1, 22.5, 22.49, 19.1. IR (cm^{-1}) = 1634 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 252 (5400), 320 (2400), 410 (400). MS (ESI) m/z calculated: 358.02 $[M\text{-}Cl]^+$ $[C_{16}H_{18}NO_2Ru]$, Found: 358.03 $[M\text{-}Cl]^+$ $[C_{16}H_{18}NO_2Ru]$.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,O-2-acetylpyridine)Cl]PF_6 ([Ru]-2). Complex **[Ru]-2** was synthesized following modified procedure,[16] by refluxing [{(η^6-*p*-cymene)$RuCl_2$}$_2$] (0.306 g, 0.5 mmol) and 2-acetylpyridine (124 µL, 1.1 mmol) in methanol (25 mL) for 24 h. Upon cooling to room temperature, 3 equiv. of NH_4PF_6 (0.489 g) was added and the solution was stirred for 4 h at room temperature. Then, solvent was removed on rotavapour and the obtained residue was dissolved in a minimum amount of dichloromethane. To the filtered dichloromethane solution, excess of diethyl ether was added to precipitate out a green solid. Yield: 89% (0.272 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.26 (d, 1H, *J* = 8.0 Hz), 8.25 (d, 1H, *J* = 8.0 Hz), 8.20-8.16 (m,

1H), 7.90-7.86 (m, 1H), 6.02 (d, 1H, *J* = 8.0 Hz), 5.90 (d, 1H, *J* = 4.0 Hz), 5.82 (d, 1H, *J* = 8.0 Hz), 5.76 (d, 1H, *J* = 8.0 Hz), 3.02-2.97 (sept, 1H, *J* = 8.0 Hz), 2.95 (s, 3H), 2.31 (s, 3H), 1.39 (d, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 211.0, 154.4, 151.1, 140.2, 131.9, 130.4, 103.7, 99.4, 85.7, 83.4, 83.3, 82.5, 31.3, 30.9, 22.5, 22.1, 18.3. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -144.6. IR (cm^{-1}) = 1615 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 270 (4800), 370 (1400), 437 (1100). MS (ESI) m/z calculated: 392.03 $[M]^+$ $[C_{17}H_{21}ClNORu]$, Found: 392.03 $[M]^+$ $[C_{17}H_{21}ClNORu]$.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,O-2-methylpicolinate)Cl]PF_6 ([Ru]-3). Complex **[Ru]-3** was synthesized by stirring $[\{(\eta^6\text{-}p\text{-cymene})RuCl_2\}_2]$ (0.306 g, 0.5 mmol) and 2-methylpicolinate (0.150 mg, 1.1 mmol) in dichloromethane (25 mL) at room temperature for 24 h. Volume was then reduced and 10 mL methanol was added followed by the addition of 3 equiv. of NH_4PF_6 (0.489 g). The resulting mixture was stirred for 4 h at room temperature. Volume of solution was again reduced to 5 mL under vacuum and complex was dissolved in minimum amount of dichloromethane. An excess of NH_4PF_6 was removed and complex was precipitated out with excess of diethyl ether as an orange colored solid. Yield: 80% (0.244 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.21 (d, 1H, *J* = 8.0 Hz), 8.12-8.09 (m, 2H), 7.92-7.89 (m, 1H), 6.04 (d, 1H, *J* = 8.0 Hz), 5.89 (d, 1H, *J* = 4.0 Hz), 5.83 (d, 2H, *J* = 4.0 Hz), 4.30 (s, 3H), 3.00-2.96 (sept, 1H, *J* = 8.0 Hz), 2.30 (s, 3H), 1.38 (d, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 202.0, 152.8, 145.1, 139.4, 128.7, 127.1, 102.6, 98.7, 82.7, 82.5, 81.7, 80.7, 31.0, 29.6, 22.23, 22.21, 18.6. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -144.6. IR (cm^{-1}) = 1599 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 250 (5000), 316 (2600), 415 (600). MS (ESI) m/z calculated: 408.03 $[M]^+$ $[C_{17}H_{21}ClNO_2Ru]$, Found: 408.03 $[M]^+$ $[C_{17}H_{21}ClNO_2Ru]$.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,N-(N-benzyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-4). Complex **[Ru]-4** was synthesized following the analogous procedure as used for complex **[Ru]-2**, by stirring [{(η^6-*p*-cymene)$RuCl_2$}$_2$] (0.306 g, 0.5 mmol) and N-benzyl-pyridylmethyleneamine (0.215 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 89% (0.272 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.32 (d, 1H, J = 8.0 Hz), 8.04 (s, 1H), 7.99-7.95 (m, 1H), 7.82 (d, 1H, J = 8.0 Hz) 7.67-7.63 (m, 1H), 7.47 (s, 5H), 5.84 (d, 1H, J = 4.0 Hz), 5.68-5.64 (m, 2H), 5.60 (d, 1H, J = 4.0 Hz), 2.74-2.67 (sept, 1H, J = 8.0 Hz), 2.13 (s, 2H), 1.59 (s, 3H), 1.15-1.07 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 166.0, 155.6, 154.3, 139.3, 133.2, 130.1, 129.6, 129.5, 129.0, 128.6, 106.9, 102.1, 86.1, 85.3, 85.0, 84.7, 69.5, 31.1, 22.1, 21.8, 18.4. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -149.3. IR (cm^{-1}) = 1598 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 264 (3600), 330 (2200), 427 (1000). MS (ESI) m/z calculated: 467.08 $[M]^+$ $[C_{23}H_{26}ClN_2Ru]$, Found: 467.08 $[M]^+$ $[C_{23}H_{26}ClN_2Ru]$.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,N-(N-butyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-5). **Ru]-5** was synthesized following the above procedure as used for complex **[Ru]-2** by stirring [{(η^6-*p*-cymene)$RuCl_2$}$_2$] (0.306 g, 0.5 mmol) and N-butyl-pyridylmethyleneamine (0.178 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 85% (0.260 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.26 (d,1H, J = 8.0 Hz), 8.37 (s, 1H), 8.03-7.99 (m, 1H), 7.94 (d, 1H, J = 8.0 Hz), 7.65-7.63 (m, 1H), 5.83 (d, 1H, J = 4.0 Hz), 5.79 (d, 1H, J = 8.0 Hz), 5.70 (d, 1H, J = 4.0 Hz), 5.62 (d, 1H, J = 4.0 Hz), 4.45-4.31 (m, 2H), 2.76-2.73 (sept, 1H, J = 8.0 Hz), 2.21 (s, 3H), 1.09-1.96 (m, 2H), 1.44-1.41 (m, 2H), 1.15 (d, 3H, J = 8.0 Hz), 1.10 (d, 3H, J = 8.0 Hz), 0.99-0.96 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 165.8, 155.4, 154.4, 139.4, 128.6, 128.5, 106.9, 102.1, 86.2, 85.4, 85.3, 84.9, 67.0, 31.3, 31.1, 22.0, 21.9, 20.0, 18.5,

13.6. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -149.4. IR (cm^{-1}) = 1599 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) ($\varepsilon_{max}/M^{-1}\ cm^{-1}$) = 272 (6400), 357 (2400), 415 (1800). MS (ESI) m/z calculated: 433.09 $[M]^+$ $[C_{20}H_{28}ClN_2Ru]$, Found: 433.10 $[M]^+$ $[C_{20}H_{28}ClN_2Ru]$.

Synthesis of [(η^6-benzene)Ru(κ^2-N,O-pyridine-2-carboxylate)Cl] ([Ru]-6). Complex **[Ru]-6** was synthesized by following the analogous procedure used for the synthesis of complex **[Ru]-1** by refluxing [{(η^6-benzene)$RuCl_2$}$_2$] (0.250 g, 0.5 mmol) and pyridine-2-carboxylic acid (0.135, 1.1 mmol) in methanol (25 mL) for 12 h. Brown solid. Yield: 80% (0.200 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.38 (d, 1H, J = 4.0 Hz), 8.08 (d, 1H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz), 5.93 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 170.3, 154.1, 150.3, 139.7, 127.9, 125.3, 83.2. IR (cm^{-1}) = 1655 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) ($\varepsilon_{max}/M^{-1}\ cm^{-1}$) = 250 (2200), 312 (1000), 391 (200). MS (ESI) m/z calculated: 301.97 $[M\text{-}Cl]^+$ $[C_{12}H_{10}NO_2Ru]$, Found: 301.97 $[M\text{-}Cl]^+$ $[C_{12}H_{10}NO_2Ru]$.

Synthesis of [(η^6-benzene)Ru(κ^2-N,O-2-acetylpyridine)Cl]PF_6 ([Ru]-7). Complex **[Ru]-7** was synthesized by following the analogous procedure used for the synthesis of complex **[Ru]-2** by refluxing [{(η^6-benzene)$RuCl_2$}$_2$] (0.250 g, 0.5 mmol) and 2-acetylpyridine (124 μL, 1.1 mmol) in methanol (25 mL) for 24 h. Green solid. Yield: 87% (0.217 g). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 8.96 (d, 1H, J = 8.0 Hz), 7.91 (d, 1H, J = 8.0 Hz), 7.69-7.65 (m, 1H), 7.31-7.28 (m, 1H), 5.48 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ (ppm) = 213.0, 157.2, 152.0, 142.2, 133.2, 132.2, 86.4, 30.4. ^{31}P NMR (161.97 MHz, Acetone-d_6) δ (ppm) = -139.9. IR (cm^{-1}) = 1567 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) ($\varepsilon_{max}/M^{-1}\ cm^{-1}$) = 268 (3000), 380 (600), 435 (400). MS (ESI) m/z calculated: 335.97 $[M]^+$ $[C_{13}H_{13}ClNORu]$, Found: 335.97 $[M]^+$ $[C_{13}H_{13}ClNORu]$.

Synthesis of [(η^6-benzene)Ru(κ^2-N,O-2-methylpicolinate)Cl]PF_6 ([Ru]-8). Complex **[Ru]-8** was synthesized by following the analogous procedure used for the synthesis of complex **[Ru]-3** by stirring [{(η^6-benzene)$RuCl_2$}$_2$] (0.250 g, 0.5 mmol) and 2-methylpicolinate (0.150 mg, 1.1 mmol) in dichloromethane (25 mL) at room temperature for 24 h. Orange solid. Yield: 83% (0.207 g). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 8.70 (d, 1H, J = 4.0 Hz), 7.45-7.41(m, 1H), 7.31 (d, 1H, J = 8.0 Hz), 7.13-7.10 (m, 1H), 5.30 (s, 6H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ (ppm) = 206.8, 157.1, 145.7, 142.2, 133.0, 129.0, 85.2, 58.3. ^{31}P NMR (161.97 MHz, Acetone-d_6) δ (ppm) = -144.6. IR (cm^{-1}) = 1596 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 260 (5000), 320 (1600), 394 (600). MS (ESI) m/z calculated: 351.96 $[M]^+$ [$C_{13}H_{13}ClNO_2Ru$], Found: 351.97 $[M]^+$ [$C_{13}H_{13}ClNO_2Ru$].

Synthesis of [(η^6-benzene)Ru(κ^2-N,N-(N-benzyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-9). Complex **[Ru]-9** was synthesized following a modified procedure,[15d] analogous to that used for synthesis of complex **[Ru]-4** by stirring [{(η^6-benzene)$RuCl_2$}$_2$] (0.250 g, 0.5 mmol) and N-benzyl-pyridylmethyleneamine (0.215 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 88% (0.220 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.62 (d, 1H, J = 8.0 Hz), 8.38 (s, 1H), 8.19 (d, 2H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.49-7.44 (m, 5H), 6.10 (s, 6H), 3.31 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 167.2, 156.0, 154.5, 139.7, 134.4, 129.7, 129.1, 128.7, 128.3, 121.9, 87.8, 68.5. ^{31}P NMR (161.97 MHz, DMSO-d_6) δ (ppm) = -148.9. IR (cm^{-1}) = 1601 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 270 (4600), 350 (1600), 576 (40). MS (ESI) m/z calculated: 411.01 $[M]^+$ [$C_{19}H_{18}ClN_2Ru$], Found: 411.03 $[M]^+$ [$C_{19}H_{18}ClN_2Ru$].

Synthesis of [(η^6-benzene)Ru(κ^2-N,N-(N-butyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-10). Complex **[Ru]-10** was synthesized by following the analogous procedure used for synthesis of

complex **[Ru]-5** by stirring [{(η^6-benzene)$RuCl_2$}$_2$] (0.250 g, 0.5 mmol) and N-butyl-pyridylmethyleneamine (0.178 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 82% (0.205 g). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 9.63 (d, 1H, J = 8.0 Hz), 8.76 (s, 1H), 8.26 (d, 1H, J = 8.0 Hz), 8.21 (d, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 4.0 Hz), 6.23 (s, 6H), 4.75-4.71 (m, 1H), 4.49-4.43 (m, 1H), 2.03-1.97 (m, 2H), 1.44-1.40 (m, 2H), 0.96-0.92 (m, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ (ppm) = 168.2, 157.3, 156.4, 141.1, 130.0, 129.3, 88.6, 68.1, 32.8, 21.2, 14.3. ^{31}P NMR (161.97 MHz, Acetone-d_6) δ (ppm) = -144.2. IR (cm^{-1}) = 1634 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 272 (5200), 348 (2200), 410 (1200). MS (ESI) m/z calculated: 377.03 $[M]^+$ [$C_{16}H_{20}ClN_2Ru$], Found: 377.04 $[M]^+$ [$C_{16}H_{20}ClN_2Ru$].

General procedure for catalytic ortho C−H bond arylation of 2-phenylpyridine with arylhalides.

All the reactions were carried out under N_2 atmosphere. *Ortho* C-H bond arylation reactions of 2-phenylpyridine were performed in a two necked round bottom flask. Flask was charged with ruthenium catalyst (5 mol %, 0.025 mmol) and K_2CO_3 (3 equiv., 1.5 mmol, 0.207 g) with distilled water (5 mL). Solution was stirred for 15 minutes and then added 2-phenylpyridine (0.5 mmol) and arylhalide (1.25 mmol). The reaction was continued to stir at 100 ºC for specified duration and then cooled down to room temperature. Further, the reaction mixture was extracted with ethyl acetate (3×10 mL) and the combine organic fractions was washed with 10 mL of brine solution and dried over Na_2SO_4. All the volatiles were removed under vacuum to obtain the crude product. Conversion and selectivity of the mono and biarylated products were determined by ^{1}H NMR. Products were purified and isolated from the crude reaction mixture by using column chromatography on silica gel with ethyl acetate/*n*-hexane as eluents.

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(Table of Content)

Catalytic C-H bond activation/ arylation of 2-phenylpyridine with a variety of arylhalides in water was achieved over a series of water-soluble ruthenium-arene complexes ligated with pyridine based *N,O* or *N,N* ligands, where a ligand-tuned structure-activity relationship for the catalytic C-H activation reaction was established by exploring carboxylate effect, time-dependent ^{1}H NMR and mass studies.