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Biomass Derived Ligands Accelerated Ruthenium-Catalyzed C-H Bond Activation/ Arylation

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Abstract

A variety of ligands are being explored extensively to achieve enhanced performance for ligand assisted C-H bond activation/functionalization reactions. We explored here, several readily available biomass-derived ligands as effective additives to significantly enhance the catalytic activity of arene-Ru(II) dimer for *ortho* C-H bond arylation in a water-based catalytic reaction. We achieved almost 7-fold enhancement in the catalytic activity with $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ catalyst in the presence of levulinic acid ligand at 80 °C. Mass investigations revealed the *in-situ* formation of a ruthenium-levulinate complex, which presumably plays a crucial role in the formation of the important cycloruthenated intermediate by facilitating the initial activation of *ortho* C-H bond of 2-phenylpyridine. Density functional theoretical studies also inferred that the ligand assisted route is energetically more favorable, where acetyl group is found to be involved in the deprotonation step.

Keywords: C-H activation; biomass; platform chemicals; ligand tuned activity; DFT studies

Introduction

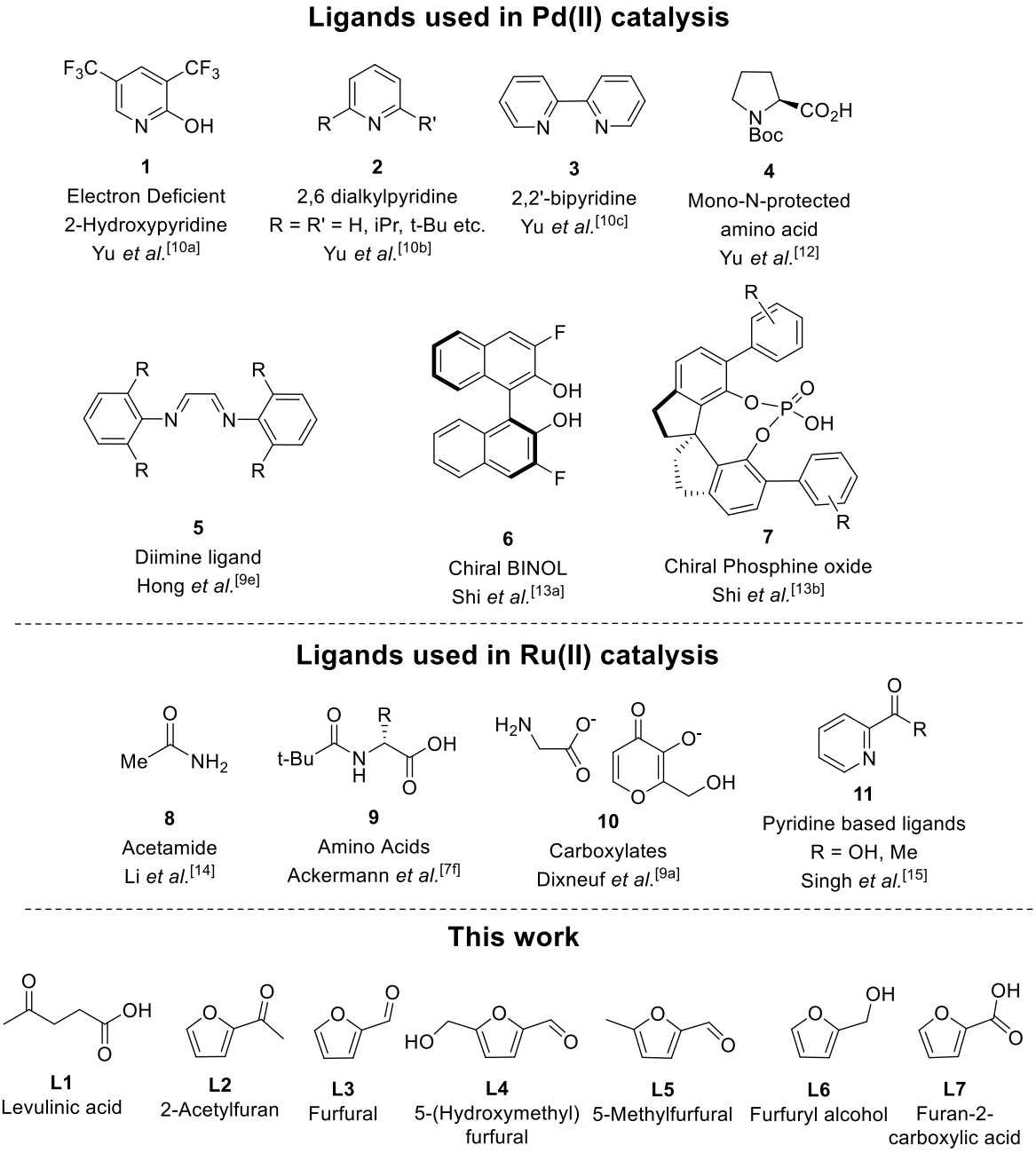
Metal catalyzed C-H bond activation and functionalization methodologies are of significant importance in the field of synthetic organic transformations.[1] It is evident that several metal catalysts based on Rh,[2] Pd,[3] Ir,[4] and Ru[5] have been extensively explored for C-H bond functionalization reactions. With further advancement in the field, the earth abundant 3d transition metals (Mn, Co, Fe) are also seeking attention as active catalysts for C-H bond activation and functionalization reactions in a very efficient, selective and cost-effective manner.[6] Among the various metals explored for C-H activation/functionalization reactions, the ruthenium-based catalysts, particularly arene-Ru(II) complexes have shown several advantages over others due to its non-toxic nature, stability in air and water, high aqueous solubility and therefore these catalysts are considered as one of the most promising catalytic system for C-H activation/functionalization reactions. Among several strategies, designing and utilizing efficient ligand to induce accelerated C-H bond activation reactions has contributed remarkably to enhance the practical usability of C-H activation/functionalization reactions. In this context, a variety of ligands such as carboxylates,[7] phosphorus-based ligands[8] and several *N,O*/ *O,O* donor ligands,[9] either as additives or pre-coordinated with the metal center, have been extensively studied to achieve enhanced catalytic activity. In general, carboxylate additives facilitate the initial deprotonation of *ortho* C-H bond while phosphine-based ligands play crucial role in stabilizing the active catalytic species.

The other set of ligands, which are rather weakly coordinating, also found to significantly tune the catalytic activity in C-H bond functionalization reactions. For instance, Yu *et al*. employed bulky pyridine ligands for the challenging C-H activation of electron deficient arenes catalyzed on Pd catalyst.[10] They showed that sterically bulky 2,6-dialkylpyridines induced a significant enhancement in the catalytic activity, which was attributed to the facile replacement of bulky pyridine by reactant. We also observed an

accelerated Ru(II) catalyzed C-H bond arylation in the presence of weakly coordinating electron deficient aniline ligands.[11] Apart from several monodentate ligands, various bidentate ligands have also been explored to achieve enhance catalytic activity. For instance, Pd(II) catalyzed *ortho* C-H bond alkylation was accelerated by N-protected amino acid ligands, where it was proposed that the coordination/de-coordination mode of one of the coordinating group of these ligands presumably tune the catalytic activity.[12] However, no direct role of these ligands in deprotonation step was observed. The designing and development of various chiral ligands for enantioselective Pd(II) catalyzed C-H bond activation/functionalization has also revolutionized the synthesis of several chiral organic compounds with excellent enantioselectivity.[13] Furthermore, accelerated Ru(II) catalyzed C-H bond arylation has also been achieved in the presence of acetamide ligand where the pendent acyl group of Ru-coordinated acetamide facilitated the deprotonation of C-H bond.[14] In a recent report, we have also explored several pyridine based bidentate ligands and observed that 2-acetylpyridine ligand greatly enhanced the catalytic activity for C-H bond arylation reaction.[15] The observed ligand-induced enhancement in the catalytic activity was attributed to the involvement of acetyl group in the deprotonation step due to its close proximity to the *ortho* C-H bond of 2-phenylpyridine (Scheme 1).

Envisioned by the recent advancement and our continuous efforts towards ligand assisted C-H bond activation reaction, herein we investigated in detail a wide range of ligands, which can be readily derived from biomass, for arene-Ru(II) catalyzed C-H bond arylation in water-based reaction condition (Scheme 1). As these ligands such as levulinic acid (**L1**), 2,5-hexanedione and other furan-based ligands, contain acetyl, formyl or carboxylate groups, these groups may play an important role in accelerating the catalytic activity for C-H bond arylation of 2-phenylpyridine with several aryl chlorides over arene-Ru(II) catalyst. We also probed mass investigations to elucidate the involvement of these ligands in the C-H bond activation

reactions by identifying reaction intermediates such as ligand coordinated Ru species and cyclometalated species under the catalytic and controlled reaction conditions. Density functional theoretical (DFT) calculations provided substantial support to our experimental findings and the active role of the studied ligands in accelerating the catalytic activity for C-H activation reactions.



Scheme 1. Various ligands explored for C-H bond activation reactions.

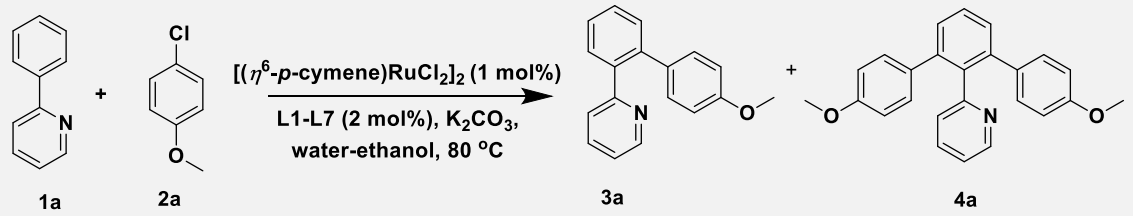
Results and discussion

At an outset, we evaluated the ligands **L1-L7** (2 mol%) for C-H arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**), as model substrates, catalyzed by $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (1 mol%) catalyst at 80°C in water-ethanol (9:1 v/v) solution. After evaluating various biomass-derived ligands (**L1-L7**), we found that levulinic acid (**L1**), greatly accelerated the catalytic activity with 70% yield of monoarylated product (**3a**) in 4 h (**3a**/**4a** selectivity = 93/7) (Table 1, entry 2). Yield for **3a** was further improved to 87% by extending the reaction for 8 h under analogous reaction condition. The remarkable activity shown by Ru(II) catalyst in the presence of the acyclic ligand **L1**, can be attributed to the conformational freedom of **L1** which further facilitated its orientation to promote the deprotonation of *ortho* C-H bond of 2-phenylpyridine.

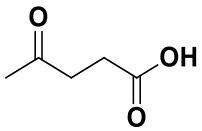
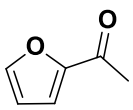
In contrary to the excellent activity achieved in the presence of levulinic acid (**L1**) ligand, other furan-based ligands (**L2-L7**) showed relatively lower activity for the product **3a** (35-75% conv.) (Table 1). After levulinic acid (**L1**), 2-acetylfuran (**L2**) showed the highest yield (65%) for **3a**, (Table 1, entry 3) while furfural (**L3**), 5-HMF (**L4**), 5-methylfurfural (**L5**), furfuryl alcohol (**L6**) and furan-2-carboxylic acid (**L7**) could not efficiently accelerated the catalytic activity of ruthenium catalyzed C-H arylation reaction (Table 1, entries 4-8). It is noteworthy to mention here that comparatively lower temperature, shorter reaction duration or using aryl halide as a limiting agent may favor higher selectivity for monoarylation over biarylation of 2-phenylpyridine.[7g][8g][16] It is also evident from the previous reports that using excess of aryl halide (>2 equiv.) resulted in the higher selectivity of biarylated product.[8c] Hence we optimized the reactions with slight excess of 2-phenylpyridine (1.1 equiv.) at 80 °C for 4 h to achieve higher selectively for the monoarylated product. As a result, high selectivity for monoarylated product (**3a**) over biarylated product (**4a**) was maintained for all the conducted reactions. The lower activity for ruthenium catalyzed C-H bond arylation of **1a** in the presence of furan-based ligands can be attributed to the tendency of these ligands to

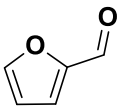
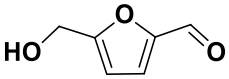
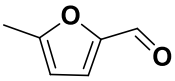
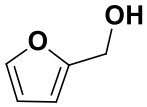
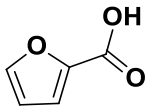
polymerize in aqueous solvent.[17] Reports also revealed that the polymerization of 5-HMF (**L4**) is lower than the furfuryl alcohol (**L6**), which is in line with the lower yield for **3a** observed with **L6** (38%) as compared to the moderate yield (53%) achieved with **L4**. It is evident from the results that *O,O* donor furan-based ligands having neutral oxygen donor groups (**L2-L6**) outperformed over furan-2-carboxylic acid (**L7**) with anionic oxygen donor (Table 1). These findings can be attributed to the strong coordination behavior of **L7** with the Ru(II) metal center. Previous studies also demonstrated enhanced catalytic activity for C-H bond arylation reaction over 2-acetylpyridine ligated Ru(II) complex as compared to 2-picolinate ligated Ru(II) complex.[15] Notably, carboxylate additives, such as acetates and pivalates are well explored for the Ru(II) catalyzed C-H bond activation reactions,[7][18] where these carboxylates facilitated the deprotonation of C-H bond by coordinating with the Ru center.

Table 1. Catalytic *ortho* C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ catalyst in the presence of various biomass-derived ligands[a]



1a 2a 3a 4a

Entry	Ligand	Conv. (%)	Sel. (%) (3a/4a)	Yield[c] (%) (3a)
1	**ligand free**	12%	93/7	n.d.
2	 **(L1)**	83% >99%[b]	93/7 90/10[b]	70% 87%[b]
3	 **(L2)**	75%	94/6	65%

4	 **(L3)**	70%	91/9	58%
5	 **(L4)**	65%	94/6	53%
6	 **(L5)**	52%	93/7	42%
7	 **(L6)**	44%	96/7	38%
8	 **(L7)**	35%	90/10	27%

[a] **Reaction Condition:** [(η^6-*p*-cymene)$RuCl_2$]$_2$ (1 mol%), **L1-L7** (2 mol %.), K_2CO_3 (3 equiv.), 2-phenylpyridine (**1a**) (0.6 mmol), 4-chloroanisole (**2a**) (0.5 mmol), water-ethanol (9:1 v/v, 2 mL), 80 ºC, 4 h, N_2 atmosphere, [b] time = 8 h, [c] isolated yield, conversion and selectivity were determined by ^{1}H NMR, n.d. = not determined.

Based on the above findings, levulinic acid (**L1**) was identified as the best performing ligand to induce 7-fold enhancement in the catalytic activity of [(η^6-*p*-cymene)$RuCl_2$]$_2$ catalyst. Notably, in the absence of the ligand, [(η^6-*p*-cymene)$RuCl_2$]$_2$ displayed only poor catalytic conversion under analogous reaction condition (Table 1, entry 1). Further, optimization of reaction condition inferred that performing the catalytic reaction with lower amount of K_2CO_3 base (3 equiv.) significantly deteriorated the conversion. Moreover, reaction could not proceed in the absence of base or performing the catalytic reaction at lower temperature (Table S1).

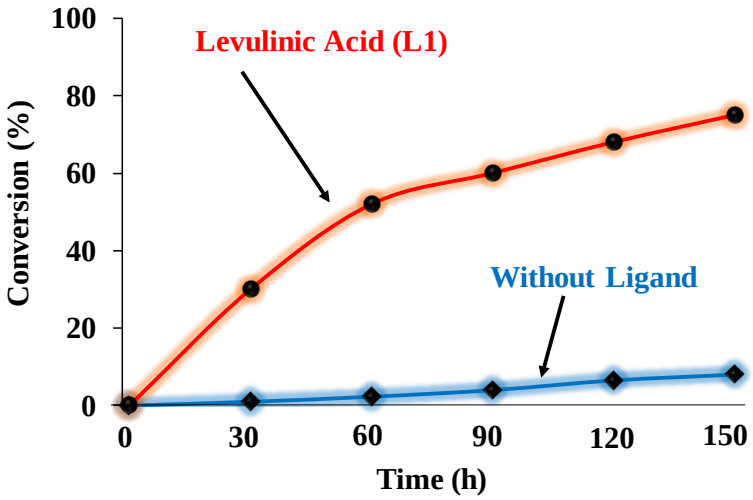


Figure 1. Time dependent reaction profile for C-H arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ catalyst in ligand-free condition and in the presence of ligand **L1** under the optimized reaction condition.

As evident from the time dependent reaction profile (Figure 1), when reaction was performed in the absence of any ligand, very slow reaction rate (4.89×10^{-4} sec^{-1}) was observed. Contrary to the base-free condition, significantly increased kinetics with relatively very high rate constant (1.02×10^{2} sec^{-1}) was observed in the presence of levulinic acid (**L1**) (Figure 1 and Figure S1), suggesting that the enhancement in the catalytic reaction was probably due to the involvement of levulinic acid (**L1**) in the C-H bond cleavage step. To further support this hypothesis, we probed mass investigations, under the catalytic and controlled reaction condition, to identify possible reaction intermediates for the Ru(II) catalyzed *ortho* C-H bond arylation of **1a** with **2a** in the presence of the ligand **L1** (Figure 2). Notably, levulinate coordinated arene-Ru species (**[Ru]-A**, m/z = 351, [M]-Cl) was observed upon the treatment of $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ with levulinic acid (Ru:**L1** = 1:1) in water-ethanol (9:1 v/v) in the presence of K_2CO_3 at 80 ºC for 1.5 h (Figure S2). Further, upon addition of 2-phenylpyridine (**1a**) (Ru:**1a** = 1:5), mass peak corresponding to the crucial cyclometalated species [Ru(η^6-*p*-cymene)(κ^2-*C*,*N*-2-phenylpyridine)Cl] (**[Ru]-B**, m/z = 390, [M]-Cl) was appeared as prominent peak (Figure S3). The ligand coordinated arene-Ru species **[Ru]-A**, was also observed under

the base free condition, which was possibly formed *via* an initial aqua-coordinated arene-Ru species ([(η^6-*p*-cymene)Ru(OH_2)Cl_2] (m/z = 288, [M]-Cl) (Figure S4). Notably, presence of the prominent mass peak at m/z 390 corresponding to the cyclometalated species **[Ru-B]** under base free condition upon the treatment of [(η^6-*p*-cymene)RuCl_2]$_2$ with 2-phenylpyridine (Ru:**1a** = 1:5) in the presence of levulinic acid (**L1**) at 80 ºC, substantiate the crucial role of levulinic acid (**L1**) in achieving high catalytic activity. Earlier reports also inferred the presence of analogous cyclometalated species **[Ru-B]** as one of the key intermediate in several Ru(II) catalyzed C-H bond activation reactions.[19] Further to investigate the role of acetyl and carboxylate groups, we performed the catalytic reaction by replacing levulinic acid (**L1**) with dicarbonyl compounds (2,5-hexanedione (**L8**) and 2,3-butanedione (**L9**)) and aliphatic carboxylic acids (1-butanoic acid (**L10**), 1-hexanoic acid (**L11**), 1,6-hexanedioic acid (**L12**)) (Scheme S1). Results inferred that the dicarbonyl ligands (**L8** and **L9**) could not enhance the catalytic performance, attributed to their poor coordination with the metal center and hence could not efficiently participated in the ligand assisted deprotonation step. Moreover, controlled experiments performed using aliphatic carboxylic acid (**L10 – L12**) also inferred no significant enhancement in the catalytic reaction, presumably due to the strong coordination behavior of these ligands with the metal center.

The above findings inferred that the facile coordination of the ligand **L1** in a bidentate manner with the ruthenium center *via* acetyl and carboxylate-O^- groups, as also evidenced by the presence of levulinate coordinated arene-Ru species (**[Ru]-A**) (m/z = 351, [M]-Cl) during mass studies, is presumably responsible for the observed accelerated catalytic activity. In this context, previous studies also revealed that analogous bis-chelating ligands may display coordination/de-coordination behavior during the catalytic reaction and hence significantly tune the catalytic reactivity (Scheme S2).[14][15][20] It is also evident from the literature that the enhanced catalytic activity in Ru-picolinate systems was due to the involvement of acetyl group

in C-H deprotonation, while remain coordinated with metal center with strongly coordinating pyridine.[15]

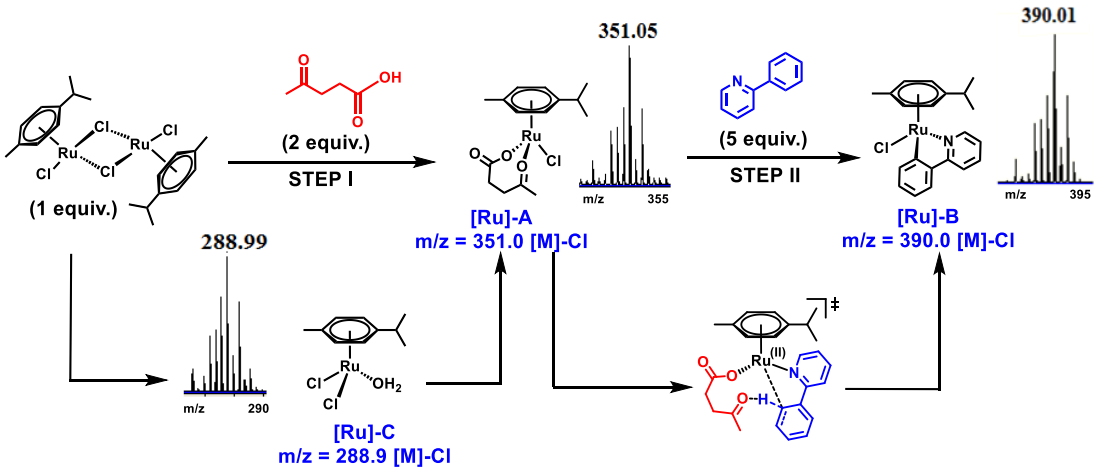


Figure 2. Mass spectral identification of several intermediate species formed during the *ortho* C-H bond activation/ arylation of **1a** over Ru catalyst under stoichiometric reaction conditions in the presence of levulinic acid (**L1**). Step I: water-ethanol (9:1 v/v), 80 °C, 1.5 h, N_2 atmosphere. Step II: K_2CO_3, water-ethanol (9:1 v/v), 80 °C, 1.5 h, N_2 atmosphere.

To further support our experimental findings, we performed DFT calculations (computational details given in supporting information)[21] for C-H bond activation/arylation of 2-phenylpyridine(**1a**) and calculated reaction free energies (ΔG) for the formation of the crucial cycloruthenated species [Ru(η^6-*p*-cymene)(κ^2-*C*,*N*-2-phenylpyridine)(H_2O)]$^+$ (**5**), in the presence and absence of ligand **L1**. As mass studies evidenced the presence of a water coordinated ruthenium species [(η^6-*p*-cymene)$RuCl_2(OH_2)$] (m/z 288, [M]-Cl) in the absence of ligand, we considered this as active catalytic species for DFT calculations under ligand-free condition. The reaction free energy profile, Figure 3, suggested that the formation of the crucial cycloruthenated species (**5**) is energetically favorable (ΔG = 14.0 kcal/mol) in the presence of the ligand **L1** compared to that for ligand-free condition (ΔG = 22.9 kcal/mol). These results further evidenced the crucial role of the ligand **L1** in the C-H activation of 2-phenylpyridine. Further, it was also evident from the DFT calculations that the species **2A-I** having acetyl group in the close proximity of *ortho* proton of 2-phenylpyridine was stable by 2.7 kcal/mol than the

species **2A-II** having carboxylate group in that place. These results are in concurrence with earlier reports,[14][15][20] suggesting that presumably the acetyl group was involved in the C-H bond activation of 2-phenylpyridine (Figure S5). Further, upon replacing the ligand **L1** with 2,5-hexanedione (**L8**), free energy calculations revealed that the C-H activation reaction was highly unfavorable in the presence of **L8** (ΔG = 30.7 kcal/mol) (Table S2). These results inferred that presumably the anionic carboxylate ensured the strong anchoring of ligand with the metal center, while the acetyl group facilitated C-H deprotonation via a facile coordination-decoordination inter-conversion pathway (Figure 3). Therefore, based on the above findings, we anticipated that the significantly enhanced catalytic activity of $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ in the presence of levulinic acid (**L1**) for C-H bond arylation of **1a** is presumably due to the involvement of acetyl group of **L1** in C-H bond deprotonation.

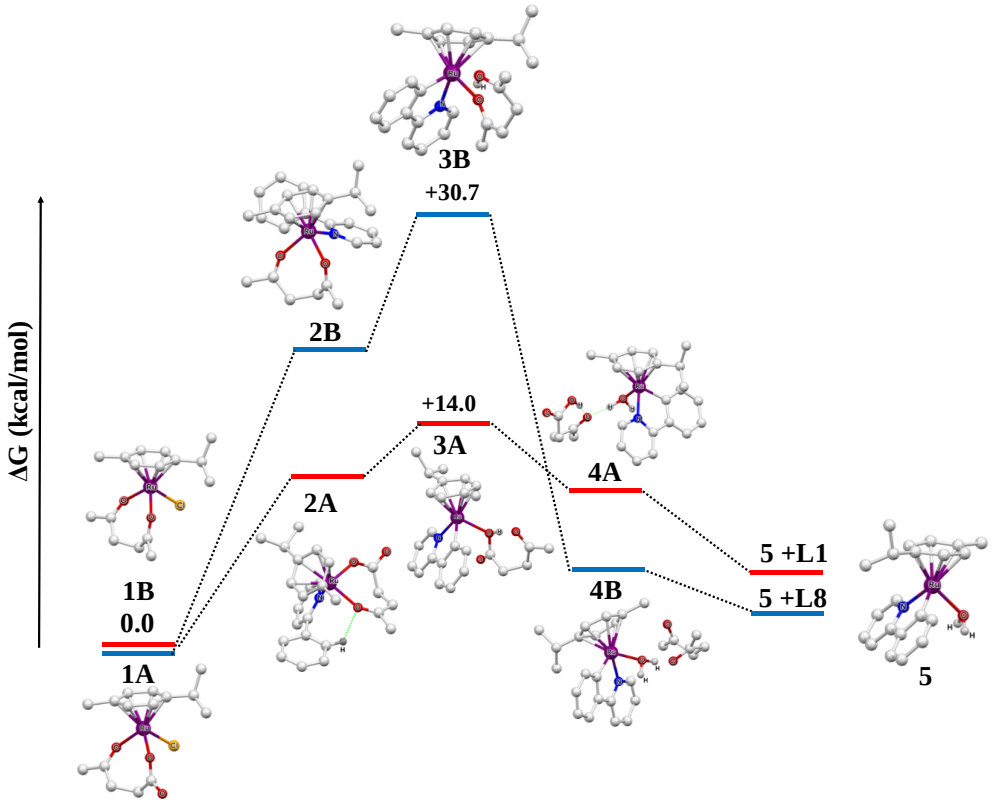


Figure 3. Reaction free energy profile, as calculated by DFT, to study the role of ligands, levulinic acid (**L1**) and 2,5-hexanedione (**L8**), in ruthenium catalyzed *ortho* C-H bond activation/arylation of 2-phenylpyridine (**1a**).

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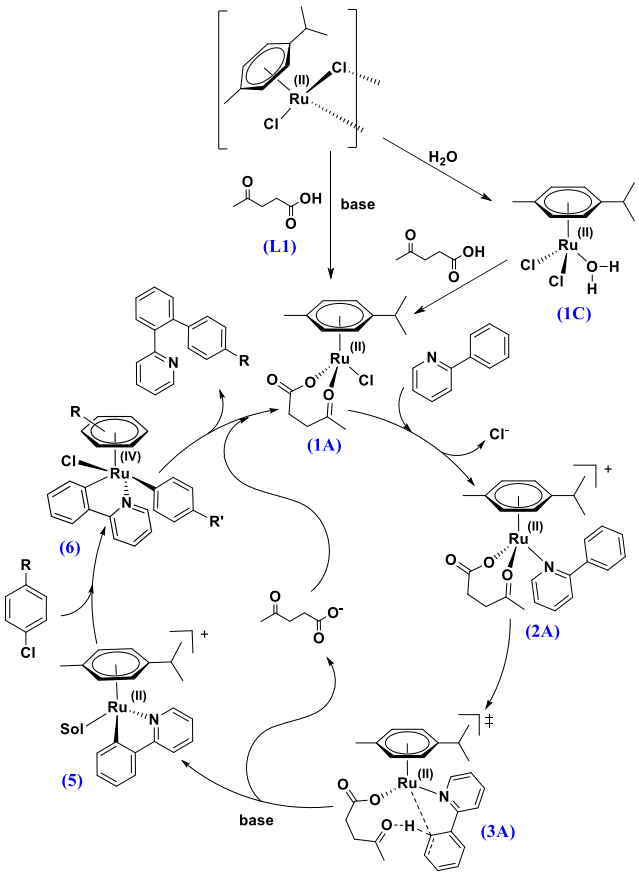
Based on our experimental findings and DFT calculations, a plausible reaction mechanism for biomass derived ligand accelerated *ortho* C-H bond activation/arylation of 2-phenylpyridine is depicted in Scheme 2. In the first step, the precatalyst $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ generates the active catalytic species **1A** by the direct coordination of ligand **L1** either to the precatalyst or via a water coordinated species **1C**. Subsequently, upon coordination of 2-phenylpyridine, species **2A** was generated. Further, the species **2A** was transformed to a cyclometalated species **5** *via* a ligand (**L1**)-accelerated concerted metalation deprotonation (CMD) step, and the ligand **L1** was released. Finally, the oxidative addition of arylhalide over the species **5**, and subsequently the release of the monoarylated product (**3a**) *via* reductive elimination step (**6→1A**) generated the active catalytic species **1A**.



Scheme 2. The plausible reaction pathway for the ruthenium catalyzed *ortho* C-H activation/arylation of 2-phenylpyridine in the presence of biomass-derived ligand **L1**.

After establishing that the ligand levulinic acid (**L1**) substantially accelerated the activity of ruthenium catalyzed C-H bond activation/arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**), C-H arylation of 2-phenylpyridine (**1a**) with other arylating agents was further explored under the optimized reaction conditions. As summarized in Table 2, a wide range of aryl chlorides (**2a-2h**) as coupling partners of 2-phenylpyridine (**1a**) delivered high yields for the monoarylated products (**3a-3h**), while biarylated products (**4a-4h**) were formed as minor products. C-H arylation of 2-phenypyridine (**1a**) with 4-chloroanisole (**2a**) afforded monoarylated product **3a** with 93% selectivity and 87% isolated yield (Table 2, entry, 1). The unsubstituted aryl halide, chlorobenzene (**2b**) showed >99% conversion with 85% yield for **3b** (Table 2, entry, 2)**.** Electron rich (**2a, 2c-2e**) and electron deficient (**2f**) aryl chlorides both exhibited high yield for the corresponding monoarylated products (**3a, 3c-3f**) of 2-phenylpyridine (**1a**). 4-chlorotoluene (**2c**) also afforded high conversion of 2-phenylpyridine (**1a**) to the corresponding monoarylated product (**3c**) with high selectivity (**3c:4c** = 96:4) and 89% yield (Table 2, entry 3). 4-Chlorostyrene (**2d**) and 4-chlorobenzhydrol (**2e**) also afforded appreciably very high selectivity (99:1) for the corresponding monoarylated products (**3d** and **3e,** Table 2, entries 4-5). Further, the electron deficient 4-chloromethylbenzoate (**2f**) also exhibited high selectivity (88%) and yield (65%) for **3f** (Table 2, entry, 6). Notably, the sulphur containing (hetero)aryl halides, 2-chlorothiophene (**2g**) and 5-methyl-2-chlorothiophene (**2h**) also resulted in remarkably high conversion with high yields for the corresponding monoarylated products **3g** (90%) and **3h** (83%) (Table 2, entries 7-8). In contrary to 2-chlorothiophene (**2g**), reaction with nitrogen containing heterocycle, 2-bromopyridine (**2i**) was found to be quite sluggish and only 20% conversion was observed in 4 h and 52% conversion, even after 24 h, with poor yield for the monoarylated product (**3i**) (Table 2, entry 9).

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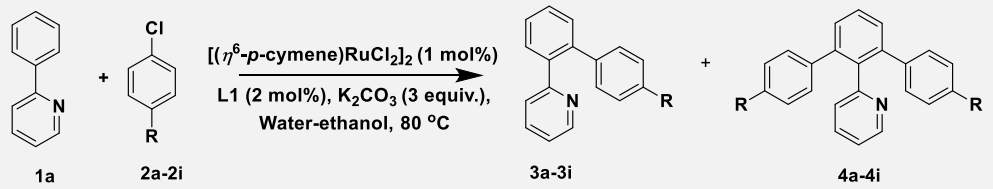
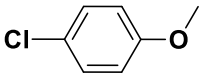
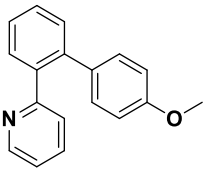
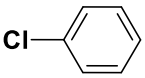
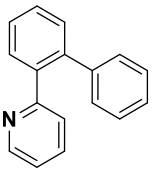
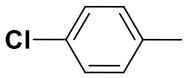
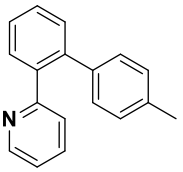
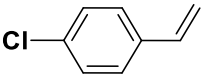
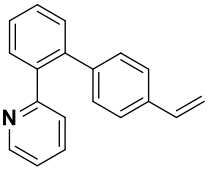
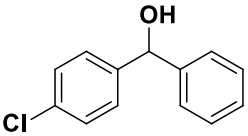
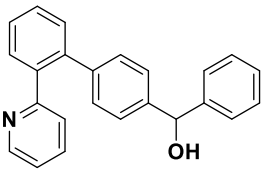
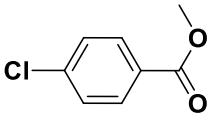
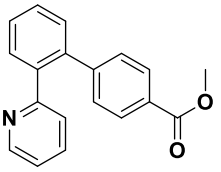
Table 2. Catalytic *ortho* C-H bond arylation of 2-phenylpyridine (**1a**) with various (hetero)arylhalides (**2a-2i**) over [(η^6-*p*-cymene)$RuCl_2$]$_2$ catalyst in the presence of levulinic acid (**L1**) ligand[a]



1a 2a-2i 3a-3i 4a-4i

Entry	Substrate	Conv. (%)	Sel. (%)	Yield (%)[d]
1	 **2a**	83% >99%[b] (8 h)	93/7 90/10[b] (**3a**:**4a**)	 **3a (87%)**[b]
2	 **2b**	>99%	93/7 (**3b**:**4b**)	 **3b (85%)**
3	 **2c**	>99%	96/4 (**3c**:**4c**)	 **3c (89%)**
4	 **2d**	90%	99/1 (**3d**:**4d**)	 **3d (83%)**
5	 **2e**	73%	99/1 (**3e**:**4e**)	 **3e (67%)**
6	 **2f**	80%	88/12 (**3f**:**4f**)	

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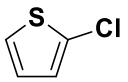
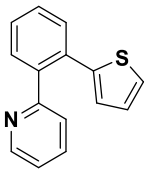
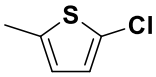
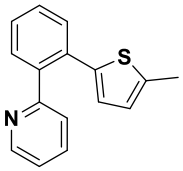
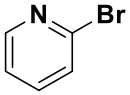
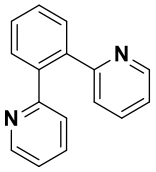
				3f (65%)
7	 **2g**	>99%	93/7 (**3g**:**4g**)	 **3g (90%)**
8	 **2h**	>99%	89/11 (**3h**:**4h**)	 **3h (83%)**
9	 **2i**	20% 52%[c] (24 h)	99/1 80/20 (**3i**:**4i**)	 3i (32%)[c]

[a] Reaction Conditions: [(η^6-*p*-cymene)$RuCl_2$]$_2$ (1 mol%), **L1** (2 mol %.), K_2CO_3 (3 equiv.), 2-phenylpyridine (**1a**) (0.6 mmol), aryl halide (**2a-2i**) (0.5 mmol), water-ethanol (9:1 v/v, 2 mL), 80 °C, 4 h, N_2 atmosphere, [b] time = 8 h, [c] time = 24 h, [d] isolated yield. Conversion and selectivity were determined by ^{1}H NMR.

Conclusion

In summary, we investigated in detail the role of several biomass-derived ligands as active additives for accelerated Ru(II) catalyzed C-H bond arylation reaction. Among the studied ligands, levulinic acid (**L1**) ligand afforded an excellent enhancement in the catalytic activity of [(η^6-*p*-cymene)$RuCl_2$]$_2$ for C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**1b**) in a water-based reaction condition. We achieved high compatibility of the studied Ru(II)-levulinate catalytic system for C-H bond arylation of 2-phenylpyridine (**1a**) with a wide range of electron rich and electron deficient aryl halides and heteroaryl halides. Kinetic studies and mass spectral identification of ligand coordinated Ru(II) species (**[Ru]-A**) and the crucial cyclometalated species (**[Ru]-B**) under the catalytic and controlled reaction condition evidenced the possible crucial role of the ligand **L1** in the observed accelerated catalytic

activity. In concurrence with the experimental findings, DFT calculations also revealed that the C-H bond activation of 2-phenylpyridine (**1a**) is energetically more favorable (by 8.9 kcal/mol) in the presence of ligand **L1** as compared to the ligand-free reaction. Our experimental findings and DFT calculations evidenced the involvement of acetyl group of the ligand **L1** in the deprotonation step, and suggesting that the anionic carboxylate group facilitated the strong anchoring of ligand to the metal center. Therefore, we believe that the present study utilizing biomass-derived ligands to achieve remarkably 7-fold enhanced catalytic activity for C-H bond activation/arylation over arene-Ru(II) catalyst is significant, and such systems will also help in the development of other ligand-tuned highly active catalytic system. Further investigations in this direction are underway in our laboratory.

Experimental section

Synthesis of 5-hydroxymethyl furfural (5-HMF) ***(L4)***. The biomass derived furan derivative 5-hydroxymethyl furfural (5-HMF) was prepared by slight modification in the previously reported method.[22] D-fructose (1 mmol, 0.180 g) was dissolved in 2 mL of 2-propanol followed by the addition of 0.5 mmol (0.027 g) of NH_4Cl. The reaction mixture was continued to stir at 120 ºC for 12 h and the progress of the reaction was monitored by thin-layered chromatography. After completion, 2-propanol was removed by evaporation under reduced vacuum. Then, 5 mL water was added in the remaining fraction and extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. All the volatiles were removed under vacuum to obtain the crude product. Product was purified by using column chromatography and confirmed by ^1H and ^{13}C NMR.

Synthesis of furan-2-carboxylic acid (2-furoic acid) ***(L7).*** The biomass derived furan derivative, furan-2-carboxylic acid (2-furoic acid) was prepared by following the reported procedure using $Ni_{0.90}Pd_{0.10}$ nanoparticles as a catalyst.[23] A two-neck round-bottom flask was charged with freshly prepared 5 mol % $Ni_{0.90}Pd_{0.10}$ nanoparticles followed by the addition of

furan 2-carboxyaldehyde (1 mmol, 82.8 µL). The reaction mixture was stirred at 80 ºC with a continuous flow of air for 1 h. The progress of the reaction was monitored by thin-layered chromatography. After the completion of the reaction, the catalyst was recovered from the reaction mixture by centrifugation and brine solution (5 mL) was added with the 1.2 M HCl (3 mL). The crude reaction mixture was extracted by using diethyl ether (5 × 10 mL) and combined organic layer was dried over anhydrous Na_2SO_4. Then all the volatiles were removed under vacuum to obtain the crude product. Then the product was purified by using column chromatography and confirmed by ^1H and ^{13}C NMR.

General procedure for the 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, $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (1 mol %, 0.005 mmol, 0.00306 g), ligand (2 equiv., 2 mol%) and K_2CO_3 (3 equiv., 1.5 mmol, 0.207 g) with water-ethanol (2 mL) in 9:1 v/v ratio. Water-ethanol solvent medium was chosen in order to avoid decomposition/polymerization of furan-based ligands. Solution was stirred for 15 minutes and then 2-phenylpyridine (0.6 mmol, 86 µL) and arylhalide (0.5 mmol) was added. The reaction was continued to stir at 80 ºC for 4 h under N_2 atmosphere and then cooled down to room temperature. Further, the reaction mixture was extracted with ethyl acetate (3×10 mL) and dried over anhydrous 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 ^1H 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.

Mass spectrometric analysis for the identification of reactive intermediate species. Mass studies were also carried out in a two necked reaction flask containing $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (1 mol%, 0.005 mmol, 0.00306 g) in 2 mL water-ethanol [(9:1) v/v] with or without base. Then

ligand (2 mol%) and 2-phenylpyridine (0.025 mmol, 3.6 µL) was added for maintaining the catalyst: ligand: substrate ratio i.e. C:L:S = 1:2:5. Reaction mixture was heated at 80 ºC under nitrogen atmosphere for 1.5 h. 100 µL of aliquot from the reaction mixture was withdrawn at different intervals of reaction time (0, 30, 60, 90 and 120 minutes) which was diluted with methanol and ESI-MS was recorded in positive mode. Mass spectra were analyzed, and active intermediates generated during the reaction have been identified.

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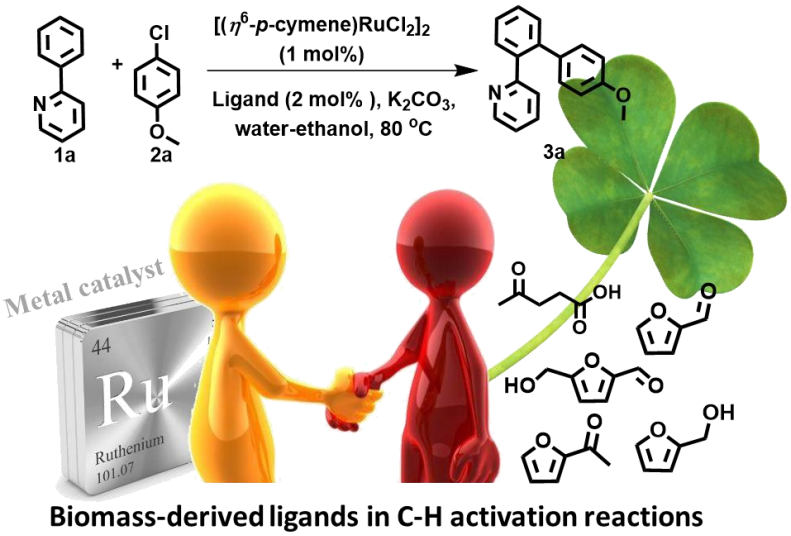
(Table of content)

Readily available biomass-derived ligands significantly accelerated catalytic activity of [(η^6-*p*-cymene)$RuCl_2$]$_2$ for *ortho* C-H bond activation/ arylation of 2-phenylpyridine with a variety of (hetero)aryl chlorides in a water-based reaction condition. Extensive mass studies, kinetic experiments and DFT studies evidenced the crucial role of the ligand levulinic acid to achieve 7-fold enhancement in catalytic activity of [(η^6-*p*-cymene)$RuCl_2$]$_2$, wherein the ligand assisted route is energetically more favorable presumably due to the involvement of acetyl group in facilitating the ruthenium catalyzed C-H deprotonation.



Biomass-derived ligands in C-H activation reactions