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Cooperative ruthenium complex catalyzed multicomponent synthesis of pyrimidines†

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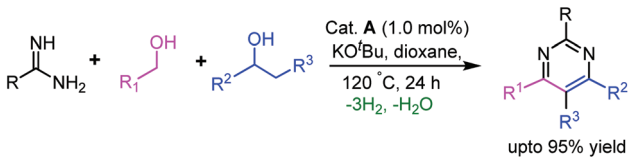
A new set of 2-(2-benzimidazolyl) pyridine ligand based air and moisture stable ruthenium complexes were synthesized and characterized. The catalytic behaviors of these complexes were evaluated towards the multicomponent synthesis of highly substituted pyrimidines directly from various amidines, primary alcohols, and secondary alcohols. Among all the metal complexes, 2-hydroxypyridine and benzimidazole fragments containing complex **A** showed the best reactivity in this reaction. In addition, it was observed that the N–H proton of benzimidazole and the hydroxyl group of pyridine played a critical role in enhancing catalytic activity. Several control experiments and mechanistic studies were carried out to understand this multicomponent synthesis of pyrimidines using complex **A**.

Introduction

Pyrimidines constitute an important class of N-heterocycles with diverse applications in pharmaceuticals, agrochemicals, dyes, molecular devices and functional materials.[1–10] Thus, the development of a sustainable and atom economical methodology is highly desirable for the synthesis of pyrimidine derivatives from easily available substrates. Alcohols are cheap precursors which can be easily accessed by various industrial processes and the catalytic conversion of lignocellulose biomass or fermentation processes.[11,12] Hence, efficient and sustainable methodologies for the catalytic transformation of alcohols to valuable N-heterocycles have become vital nowadays.[13–16] Acceptorless dehydrogenative coupling strategy has become a promising tool for eco-friendly C–C and C–N bond formation reactions using alcohols.[14,17–30] Multicomponent reactions are also a highly attractive strategy to construct structurally diverse and complex molecules starting from simple precursors.[31–34] The first multicomponent synthesis of pyrimidines from amidines and alcohols was reported by Kempe and co-workers using the (PNP)Ir catalyst.[35] Later, for a similar transformation, a few other reports emerged in the literature.[36–40] However, most of the homogeneous catalytic systems were based on either expensive air and moisture sensitive alkyl phosphine based ligand systems or required an excess amount of base as an additive. Hence, air and moisture stable alkyl phosphine free catalytic systems will be exciting to explore for the synthesis of pyrimidines from amidines and alcohols.

Based on the metal–ligand cooperation in homogeneous catalysis, various chemical transformations were extensively studied.[41–46] With these catalysts generally higher reaction rates were observed due to the simultaneous participation of both metals and ligands. Among the various cooperative ligands, 2-hydroxypyridine and benzimidazole fragment-based bifunctional ligands received considerable attention.[47–52] Apart from the –O–H fragment in 2-hydroxypyridine ligands, the benzimidazole –N–H unit also plays an important role in enhancing catalytic activity.[53–56]

We hypothesized that a combination of 2-hydroxypyridine and benzimidazole fragments in a same ligand platform would deliver more efficient catalysts where the unique characteristics of each fragment of this hybrid ligand will enhance the catalytic performance. Previously, we found that a similar hybrid ligand based iridium catalyst exhibited higher catalytic activity in the synthesis of various N-heterocycles in water.[28] Herein, we report the synthesis of various benzimidazole containing functionalized pyridine-based ruthenium complexes and compare their catalytic activity in the multicomponent synthesis of pyrimidines. To the best of our knowledge, a similar ruthenium catalyzed transformation has not been reported yet (Scheme 1).



Scheme 1 Multicomponent synthesis of pyrimidines.

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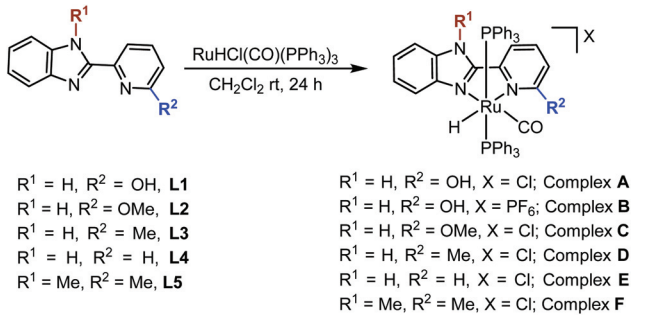
† Electronic supplementary information (ESI) available. CCDC 1937945, 1954543, 1953620 and 1953618 for complex **A**, **C**, **D** and **E** respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/C9DT04040D

Results and discussion

Various substituted 2-(2-benzimidazolyl) pyridine ligands were synthesized in good yields by following the reported literature, and their corresponding Ru(II) complexes were synthesized by the reaction with $RuHCl(CO)(PPh_3)_3$ in dichloromethane at room temperature (Scheme 2). All these new Ru(II) complexes were characterized by NMR spectroscopy, ESI-MS and elemental analysis. Complexes **A, C, D and E** were also characterized by X-ray diffraction study (Fig. 1 and 2).

In the ^{1}H-NMR spectrum, the hydride signal of the complexes **A, B, C, D, E** and **F** appeared as a triplet at δ = −12.15 ppm ($J_{H,P}$ = 20.0 Hz), −12.05 ppm ($J_{H,P}$ = 19.2 Hz), −12.05 ppm ($J_{H,P}$ = 20.4 Hz), −12.17 ppm ($J_{H,P}$ = 19.3 Hz), −11.63 ppm ($J_{H,P}$ = 19.3 Hz) and −12.14 ppm ($J_{H,P}$ = 18.4 Hz), respectively. $^{31}P\{^1H\}$-NMR resonances of the complexes **A, B, C, D, E** and **F** appeared as a singlet at δ = 46.54 ppm, 44.57 ppm, 45.77 ppm, 43.91 ppm, 44.58 ppm and 44.26 ppm respectively. The appearance of the singlet peak in ^{31}P-NMR indicated the presence of one type of phosphorus environment around the Ru(II) centre, which suggested that two PPh_3 molecules were *trans* to each other. The IR spectra of all these complexes were recorded and complex **F** displayed the lowest IR stretching frequency of carbonyl (ν_{CO}) which specified that **L5** was the most electron rich ligand compared to the other ligands (Table 1).



Scheme 2 Synthesis of Ru(II) metal complexes.

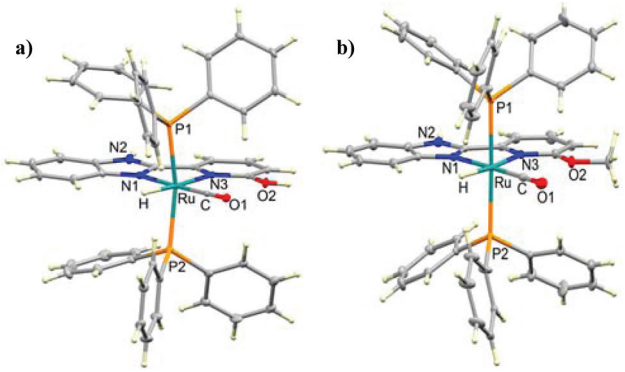


Fig. 1 (a) Solid state structure of complex **A** with 30% thermal ellipsoids. Selective bond distances (Å) and angles (°): Ru–N1 2.113(2), Ru–N3 2.253(2), Ru–P1 2.363(9), Ru–P2 2.367(9), C–O1 1.165(4), P1–Ru–P2 166.91(3), N1–Ru–N3 75.19(19), N1–Ru–P1 88.30(7), N3–Ru–P1 96.07(7), and N3–Ru–P2 96.09(7). (b) Solid state structure of complex **C** with 30% thermal ellipsoids. Selective bond distances (Å) and angles (°): Ru–N1 2.102(3), Ru–N3 2.216(3), Ru–P1 2.359(7), Ru–P2 2.359(7), C–O1 1.136(5), P1–Ru–P2 177.17(4), N1–Ru–N3 75.48(13), N1–Ru–P1 90.32(2), N3–Ru–P1 91.413(19), and N3–Ru–P2 91.412(19). The counter anion and solvent molecules were omitted for clarity.

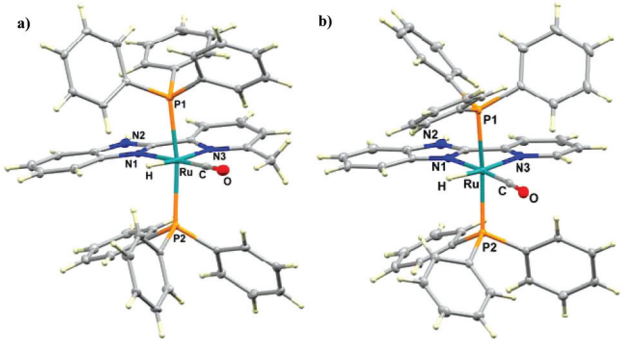


Fig. 2 (a) Solid state structure of complex **D** with 30% thermal ellipsoids. Selective bond distances (Å) and angles (°): Ru–N1 2.117(3), Ru–N3 2.304(3), Ru–P1 2.366(11), Ru–P2 2.358(11), C–O 1.154(4), P1–Ru–P2 170.53(4), N1–Ru–N3 75.43(12), N1–Ru–P1 86.49(8), N3–Ru–P1 91.66(8), and N3–Ru–P2 97.09(8). (b) Solid state structure of complex **E** with 30% thermal ellipsoids. Selective bond distances (Å) and angles (°): Ru–N1 2.112(3), Ru–N3 2.233(3), Ru–P1 2.361(11), Ru–P2 2.355(11), C–O 1.157(5), P1–Ru–P2 171.45(4), N1–Ru–N3 75.31(12), N1–Ru–P1 92.12(9), N3–Ru–P1 94.67(8), and N3–Ru–P2 93.57(8). The counter anion and solvent molecules were omitted for clarity.

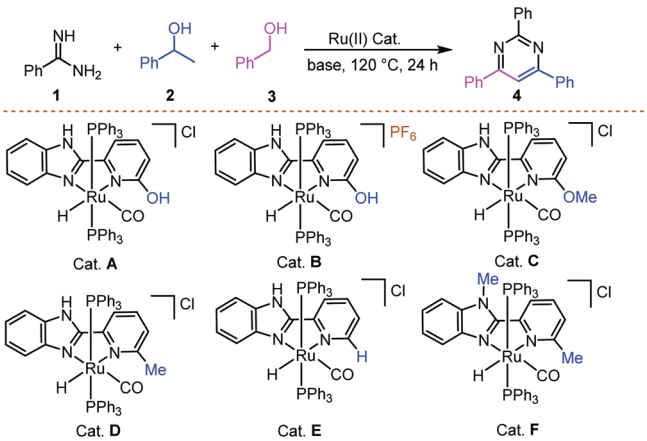
Table 1 Carbonyl IR stretching frequencies of Ru(II) complexes

Complex	A	B	C	D	E	F
IR [$\nu_{C=O}$ (cm^{-1})]	1957	1941	1937	1930	1934	1917

The solid state structure of the complexes **A, C, D,** and **E** showed a distorted octahedral coordination around the Ru(II) center. Each Ru(II) was coordinated to two *trans* PPh_3 molecules, one bidentate NN ligand, one hydride and one CO ligand which was *trans* to benzimidazole nitrogen (N1). The P1–Ru–P2 bond angles of complexes **A, C, D,** and **E** were 166.91°, 177.17°, 170.55°, and 171.45° respectively, indicating that two PPh_3 molecules were present in an axial arrangement. The Ru–PPh_3 bond length was slightly longer compared with the other adjacent Ru–N1, Ru–N3, Ru–CO and Ru–H bonds. The Ru–N1 bond length was relatively shorter (~0.1–0.2 Å) compared to Ru–N3 in all these complexes, which revealed that the binding of the benzimidazole nitrogen was stronger than that of the pyridine nitrogen with the Ru-center. A chloride ion was present outside the primary coordination sphere of all the complexes.

To obtain the most suitable reaction conditions, the coupling of benzamidine (**1**), 1-phenylethanol (**2**) and benzyl alcohol (**3**) was picked as the model reaction (Table 2). Initially, **1** (0.25 mmol), **2** (0.32 mmol) and **3** (0.32 mmol) were allowed to react in presence of 1 mol% of cat. **A** and KO^{t}Bu (0.13 mmol) in toluene for 24 h, which afforded 61% yield of

Table 2 Optimization of reaction conditions[a]



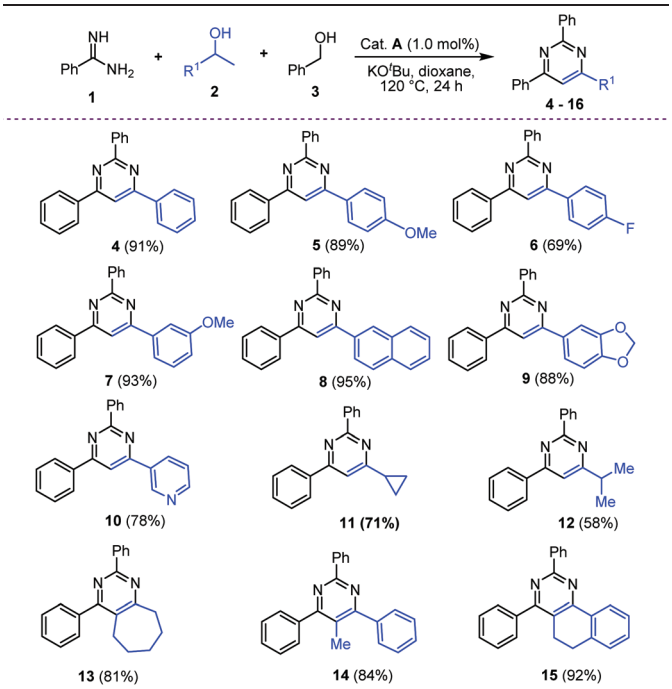
Entry	Amidine : 1° Alc : 2° Alc	Base (equiv.)	Ru(II) cat	Solvent	Yield[a] (%)
1	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **A**	Toluene	61
2	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **A**	*tert*-Amyl alcohol	42
3	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **A**	Diglyme	21
4	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **A**	Dioxane	79
5	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **B**	Dioxane	31
6	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **C**	Dioxane	43
7	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **D**	Dioxane	51
8	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **E**	Dioxane	28
9	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	Cat. **F**	Dioxane	37
10	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	$RuHClCO(PPh_3)_3$	Dioxane	39
11	1 : 1.3 : 1.3	KO^{t}Bu (0.5)	—	Dioxane	<10
12	1 : 1.3 : 1.3	KOH (0.5)	Cat. **A**	Dioxane	41
13	1 : 1.3 : 1.3	NaOH (0.5)	Cat. **A**	Dioxane	28
14	1 : 1.3 : 1.3	Cs_2CO_3 (0.5)	Cat. **A**	Dioxane	<10
15	1 : 1.3 : 1.3	K_2CO_3 (0.5)	Cat. **A**	Dioxane	<10
16	**1 : 1.3 : 1.3**	**KO^{t}Bu (1.0)**	**Cat. A**	**Dioxane**	**95**
17	1 : 1.3 : 1.3	KO^{t}Bu (1.0)	Cat. **A**	Dioxane	61[b]
18	1 : 1.3 : 1.3	KO^{t}Bu (1.0)	Cat. **A**	Dioxane	41[c]
19	1 : 1 : 1	KO^{t}Bu (1.0)	Cat. **A**	Dioxane	71

[a] Reaction conditions: Benzamidine (0.25 mmol), 1-phenylethanol (0.325 mmol), benzyl alcohol (0.325 mmol), and cat **A** (1.0 mol%). The amount (equiv.) of KO^{t}Bu was given with respect to the benzamidine substrate. Yields were determined by ^{1}H-NMR spectroscopy using 1,3,5-trimethoxy benzene as the internal standard. [b] Heated for 12 h. [c] Using 0.5 mol% cat. **A**.

the desired product **4** (Table 2, entry 1). To improve the yields, different solvents were screened and among them dioxane was found to be the most effective (Table 2, entries 2–4). Next, the effect of ligand substituents and the counter anion of the complex on the catalytic activity was screened (Table 2, entries 5–9). Upon changing the counter anion of catalyst **A** from chloride to hexafluorophosphate, the yield of **4** decreased considerably (Table 2, entry 5). Afterward, other Ru-complexes in which the substituents were varied from –OMe, –Me and –H to a ligand framework were tested (Table 2, entries 6–8). Notably, with these metal complexes, the yield of the desired product **4** was lower compared to that of cat. **A**. This suggested that the 2-hydroxypyridine moiety played a significant role in this catalytic process. Complex **F** bearing the ligand in which the N–H proton of benzimidazole was substituted with the methyl group showed considerably lower reactivity compared to complex **D** (Table 2, entry 9). This established the importance of the benzimidazole N–H proton in this catalytic reaction. Next, the effect of various bases was tested and KO^{t}Bu delivered the best result (Table 2, entries 12–15), while with only base, a lower yield of **4** was observed (entry 11). When the amount of base was increased to 1 equiv., the yield of **4** increased to 95% whereas, decreasing the amount of the catalyst as well as the reaction time led to a lower yield of the desired product (Table 1, entries 16–18). Moreover, decreasing the amount of both the alcohols to 1 equiv. afforded lower yields (Table 2, entry 19).

Inspired by the promising result (Table 2, entry 16), next, we investigated the scope of this protocol towards the synthesis of several pyrimidines as shown in Table 3. First, the compatibility of this methodology with respect to various secondary alcohols in reaction with benzamidine and benzyl alcohol was tested which produced several tri-substituted pyrimidine derivatives in good to excellent yields (69–95%). Apart from 1-phenylethanol, substituted secondary alcohols having both electron donating substituents like 4-methoxy and electron withdrawing groups like 4-fluoro afforded good to excellent yields of the desired products (Table 3, entries 4–6). *meta*-Substituted secondary alcohol also delivered excellent yield (Table 3, entry 7). Sterically bulky 1-(2-naphthyl)ethanol and heteroatom substituted alcohols *e.g.* 1-(3,4-methylenedioxyphenyl)ethanol and 1-(3-pyridyl)ethanol were also converted successfully (Table 3, entries 8–10). A slightly lower

Table 3 Synthesis of pyrimidines from various secondary alcohols and benzyl alcohol[a]

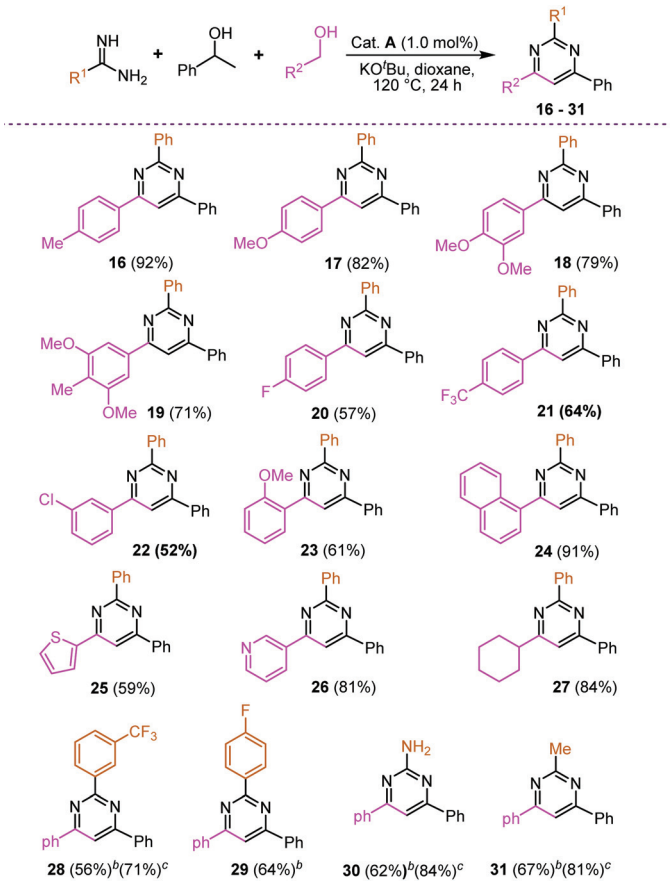


[a] Reaction conditions: benzamidine (0.5 mmol), secondary alcohol (0.65 mmol), benzyl alcohol (0.65 mmol), KO^{t}Bu (0.5 mmol), dioxane (2 mL), isolated yield.

yield was obtained with less reactive aliphatic alcohols like 1-cyclopropylethanol and 1,2-dimethylpropanol compared to the aromatic alcohols (Table 3, entries 11–12). Notably, several tetra-substituted pyrimidine derivatives were also synthesized in excellent yields following this protocol (Table 3, entries 13–15).

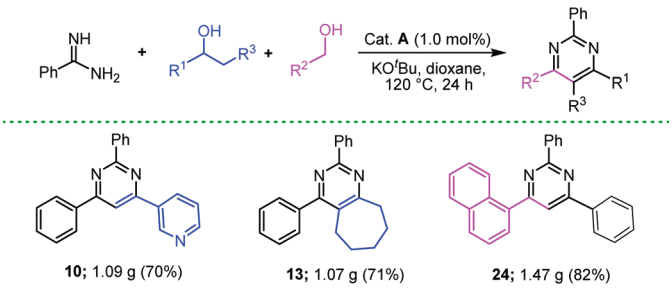
Next, the scope of primary alcohols was tested (Table 4). Mono, di- and tri-substituted primary alcohols with electron donating groups either in *para*- or *meta*- positions, afforded good to excellent yields of the desired products (Table 4, entries 16–19). A relatively lower yield was obtained for primary alcohols having electron withdrawing groups (Table 4, entries 20–22). With the halide substituted primary alcohols, lower yields of the desired products were observed due to the dehalogenation reaction. Along with the expected products, the dehalogenated final products were also isolated after the reaction. A comparatively lower yield was detected with *ortho*-substituted primary alcohol probably due to steric reasons (Table 4, entry 23). Moreover, the reaction with bulky

Table 4 Synthesis of pyrimidines from various primary alcohols and amidines in reaction with 1-phenylethanol[a]



[a] Reaction conditions: benzamidine (0.5 mmol), primary alcohol (0.65 mmol), 1-phenylethanol (0.65 mmol), KO^{t}Bu (0.5 mmol), dioxane (3 mL), isolated yield. [b] Amidine hydrochloride salts were used as the substrate and an additional 1.0 equiv. of KOH (0.5 mmol) was used to trap the HCl of amidine hydrochlorides. [c] Using 1.5 mol% Cat. **A**.

Table 5 Preparative scale synthesis of a few challenging substrates

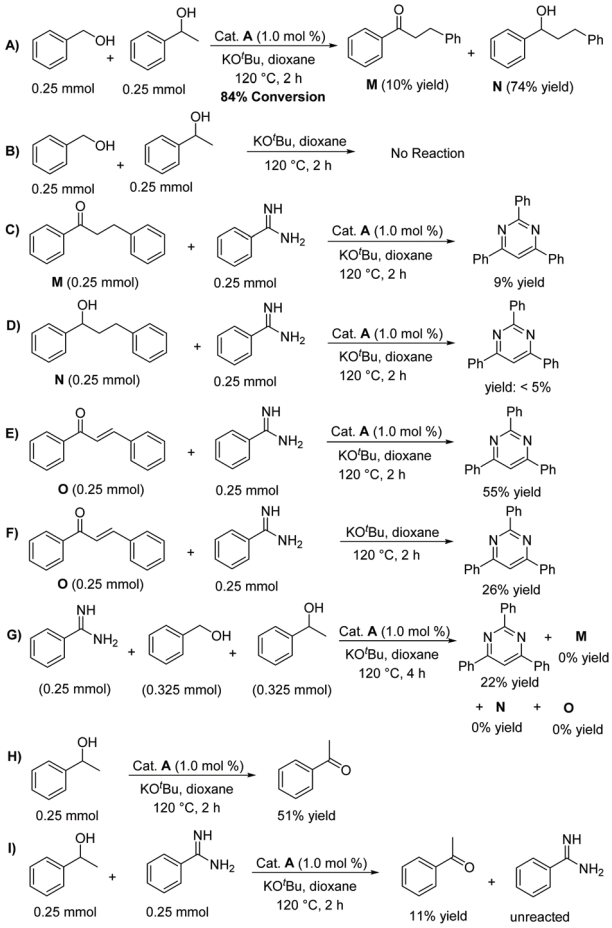


1-naphthalenemethanol, heteroatom containing 2-thiophenemethanol, 3-pyridinemethanol and cyclic aliphatic alcohols like cyclohexylmethanol delivered good to excellent yields (59–91%) (Table 4, entries 24–27). The scope of a few amidines was also investigated. Aryl amidines bearing electron withdrawing groups, and aliphatic amidines like acetamidine and guanidine could also be utilized under the optimized reaction conditions (Table 4, entries 28–31).

The synthetic competence of this methodology was further extrapolated by the gram scale synthesis of various substituted pyrimidines and 2-alkylaminopyrimidines (Table 5). These results demonstrated the practical applicability of this protocol.

Reaction mechanism

To gain insight into the reaction mechanism, several control experiments were performed. First, the cross coupling of benzyl alcohol and 1-phenylethanol was carried out under the standard reaction conditions (Scheme 3A). Within 2 h, 84% conversion of benzyl alcohol was achieved with the formation of β-alkylated alcohol as the major product, whereas in the absence of cat. **A**, both alcohols remained unreacted (Scheme 3B). This result suggested that the dehydrogenation of alcohols was catalyzed by cat. **A**. Notably, the coupling of benzamidine with either 1,3-diphenylpropan-1-one (**M**) or β-alkylated alcohol (**N**) produced a significantly lower amount of the desired pyrimidine product (Scheme 3C and D). However, when benzamidine was reacted with chalcone (**O**) in the presence and absence of cat. **A**, the pyrimidine product was obtained in 55% and 26% yields, respectively, within 2 h (Scheme 3E and F). Notably, when benzamidine, benzyl alcohol and 1-phenylethanol were reacted for 4 h, none of the potential intermediates (**M**, **N** and **O**) were observed and significant amounts of benzamidine and alcohols remained unreacted (Scheme 3G). The dehydrogenation of 1-phenylethaol under reaction conditions was much faster in the absence of benzamidine; 51% of acetophenone was produced after 2 h, whereas in the presence of benzamidine, only 11% of acetophenone was observed (Scheme 3H and I). These experiments revealed that for the synthesis of pyrimidine in this multicomponent reaction, chalcone was the plausible intermediate, and in the presence of benzamidine, the hydrogenation of chalcone and the dehydrogenation of alcohols

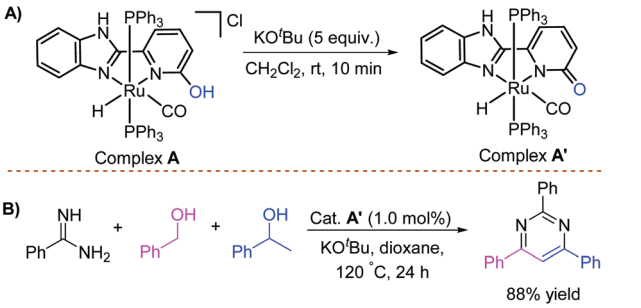


Scheme 3 Verifying experiments for the multicomponent synthesis of pyrimidines.

were inhibited. Also, it was evident that cat. **A** not only facilitated the dehydrogenation of alcohols but also played a significant role in the dehydrogenation of dihydropyrimidine derivative (**P**) for the production of pyrimidine (Scheme 3E and F).[36]

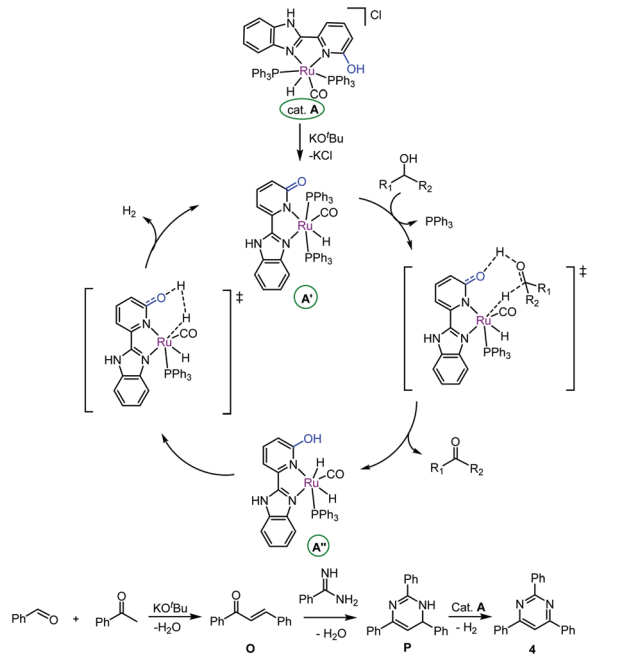
Based on the control experiments and the previous literature reports on 2-hydroxypyridine based bifunctional catalysts, a probable mechanism for the synthesis of pyrimidines was proposed (Scheme 5).[49,57–59] Initially, base mediated activation of pre-catalyst **A** would generate catalytically active species **A′**, having a pyridonate ligand fragment,[48,50,58,60] although the deprotonation of the N–H proton in the benzimidazole ring cannot be ruled out. To confirm the participation of ruthenium-pyridonate species (**A′**), they were synthesized independently by treating cat. **A** with 5 equiv. of KO^{t}Bu in dichloromethane (Scheme 4A).

Complex **A′** was characterized by NMR spectroscopy and elemental analysis. In the ^{1}H-NMR spectrum, it showed a sharp triplet at δ = −11.38 ppm (J_{H-P} = 22.0 Hz) which was different from the parent complex **A** (δ = −12.15 ppm, J_{H-P} = 20.0 Hz) and in the $^{13}C\{^1H\}$ NMR spectrum it presented a new peak at δ = 170.2 ppm (pyridonate C═O) which further confirmed the formation of complex **A′**.[61] In the ^{1}H-NMR spectrum of complex **A′**, the slight upfield shift of pyridine proton peaks



Scheme 4 A) Synthesis of intermediate **A′**; (B) reactivity of intermediate **A′**.

compared to that of **A** also confirmed that this complex contains a dearomatized pyridonate core. When, complex **A′** was used as the catalyst, under the standard reaction conditions, 88% yield of the desired product was obtained (Scheme 4B). This clearly indicated that complex **A′** was the active catalyst in this reaction. Next, a complex **A′** mediated dehydrogenation of alcohols through an *outer-sphere* pathway would give the corresponding aldehydes/ketones and Ru-hydride species (**A″**).[62,63] Our experimental findings (Table 2, entries 4 and 6) and previous reports suggested that for the dehydrogenation of alcohols with this system, the *outer-sphere* pathway was more favoured over the *inner-sphere* pathway.[62,64–66] However, all attempts to isolate the Ru-dihydride species (**A″**) were unsuccessful. Afterward, the ligand assisted hydrogen elimination from (**A″**) would regenerate the active catalyst **A′** (Scheme 5). Next, a base mediated aldol condensation between the aldehyde and ketone would produce the α,β-unsaturated ketone which subsequently would react with benzamidine to



Scheme 5 Proposed catalytic cycle for the multicomponent synthesis of pyrimidines.

give the dihydropyrimidine derivative (**P**). Finally, a complex **A′** mediated dehydrogenation of **P** would deliver the final pyrimidine product.[36]

Conclusions

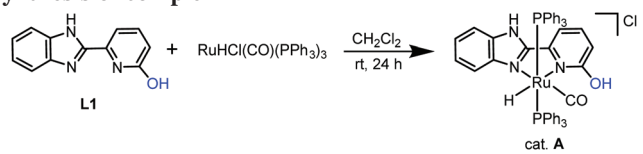
In summary, various 2-(2-benzimidazolyl) pyridine ligand based new ruthenium complexes were synthesized. Among them, cat. **A** exhibited the highest catalytic activity in the three component synthesis of substituted pyrimidines. A wide range of multi-substituted pyrimidine derivatives were synthesized in excellent yields from various alcohols and amidines. Several kinetic experiments were carried out to understand the mechanism of this reaction. Control experiments revealed that for the synthesis of pyrimidines, chalcone was the plausible intermediate. Notably, the Ru-pyridonate intermediate was successfully characterized and it was found to be the active catalyst in this multicomponent reaction. The synthetic competence of this methodology was also extended toward the gram scale synthesis of various pyrimidine derivatives. To the best of our knowledge, this is the first report of the ruthenium catalyzed multicomponent synthesis of pyrimidines from amidines and alcohols.

Experimental section

General procedure and materials

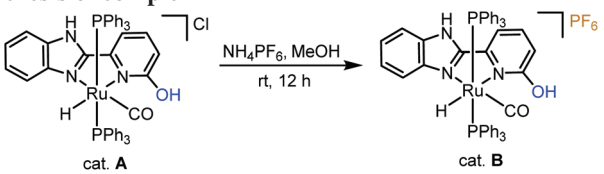
All reactions were performed under an inert atmosphere using standard Schlenk line techniques unless otherwise stated. Glassware was flame-dried under vacuum prior to use. Dry solvents were prepared according to literature methods, distilled under argon and deoxygenated prior to use. Chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Avra, SDFCL, and Spectrochem and used without further purification. The ligands were synthesized according to the reported procedures.[67–69] The synthesis of complexes **C** and **D** was previously reported by our group.[70] ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 400 and a 500 MHz spectrometer. ESI-MS were recorded on a Waters Micromass Quattro Micro triple-quadrupole mass spectrometer. GC analysis was done using an Agilent 7890 B gas chromatograph; GC-MS were recorded using an Agilent 7890 A gas chromatograph equipped with an Agilent 5890 triple-quadrupole mass system.

Synthesis of complex A



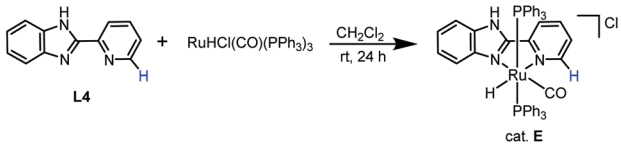
In a Schlenk flask, ligand **L1** (50 mg, 0.24 mmol) and [RuHCl(CO)(PPh$_3$)$_3$] (228 mg, 0.24 mmol) were taken. Then dry dichloromethane (15 mL) was added to it and stirred at room temperature for 24 h under an argon atmosphere. The resulting solution was filtered and the precipitate was washed with diethyl ether to afford pure complex **A** (156 mg, yield: 72%) as a yellow solid. Single crystals suitable for X-ray diffraction were grown in CH_2Cl_2/diethyl ether by a slow evaporation process at ambient temperature. **^{1}H NMR** (500 MHz, DMSO-d$_6$): δ = 13.81 (s, 1H), 7.54 (t, $J_{H,H}$ = 7.8 Hz, 1H), 7.25 (d, $J_{H,H}$ = 7.3 Hz, 1H), 7.15 (d, $J_{H,H}$ = 8.2 Hz, 1H), 7.12–7.0 (m, 30H), 6.95 (t, $J_{H,H}$ = 7.7 Hz, 1H), 6.79 (d, $J_{H,H}$ = 8.3 Hz, 1H), 6.72 (d, $J_{H,H}$ = 8.3 Hz, 1H), 6.62 (d, $J_{H,H}$ = 7.6 Hz, 1H), −12.15 (t, $J_{H,H}$ = 20 Hz, 1H). Due to the poor solubility of this complex in common NMR solvents, we were unable to record the ^{13}C-NMR spectrum of this complex. **^{31}P{^{1}H} NMR** (160 MHz, DMSO-d$_6$): δ = 46.54 ppm. **IR** ($\nu_{C=O}$, KBr, cm^{-1}): 1957; **HRMS (ESI)**: calcd for $C_{49}H_{40}N_3O_2P_2Ru$, [M − Cl]$^+$: 866.1639; found: 866.1621. Anal. calculated ($C_{49}H_{40}N_3O_2P_2RuCl$): C, 65.30; H, 4.47; N, 4.66; found: C, 65.46; H, 4.32; N, 4.55.

Synthesis of complex B



In a Schlenk flask, complex **A** (50 mg, 0.055 mmol) and NH_4PF_6 (0.825 mmol) were taken and dry methanol (15 mL) was added to it and stirred at room temperature for 12 h under an argon atmosphere. The resulting solution was filtered and the insoluble part was removed. The filtrate was evaporated to dryness under reduced pressure and washed with diethyl ether to afford complex **B** (45 mg, yield: 81%) as a light yellow solid. **^{1}H NMR** (500 MHz, DMSO-d$_6$): δ = 7.98–7.91 (m, 2H), 7.37 (d, $J_{H,H}$ = 7.5 Hz, 2H), 7.24–7.12 (m, 31H), 6.94 (t, $J_{H,H}$ = 7.5 Hz, 2H), −12.05 (t, $J_{H,H}$ = 19.2 Hz, 1H). **^{13}C{^{1}H} NMR** (125 MHz, DMSO-d$_6$): δ = 151.15, 144.45, 139.43, 134.07, 133.29, 132.68, 132.52, 132.35, 130.38, 128.49, 125.35, 123.16, 119.12, 112.96, 112.75. **^{31}P{1H} NMR** (160 MHz, $CDCl_3$): δ = 44.57 ppm. **IR** ($\nu_{C=O}$, KBr, cm^{-1}): 1941; **HRMS (ESI)**: calcd for $C_{49}H_{40}N_3O_2P_2Ru$, [M − PF$_6$]$^+$: 866.1639; found: 866.1639. Anal. calculated ($C_{49}H_{40}F_6N_3O_2P_2RuPF_6$): C, 58.22; H, 3.99; N, 4.16; found: C, 58.09; H, 3.81; N, 3.98.

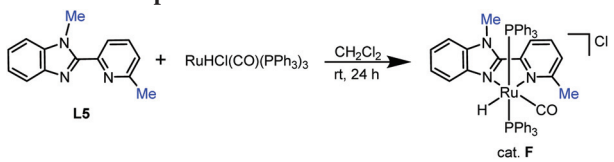
Synthesis of complex E



In a Schlenk flask, ligand **L4** (50 mg, 0.26 mmol) and [RuHCl(CO)(PPh$_3$)$_3$] (248 mg, 0.26 mmol) were taken. Then dry dichloromethane (15 mL) was added to it and stirred at room temperature for 24 h under an argon atmosphere. The resulting solution was filtered and the insoluble part was removed. The filtrate was evaporated to dryness under reduced pressure and washed with diethyl ether to afford complex **E** (180 mg, yield: 78%) as a yellow solid. Single crystals suitable for X-ray

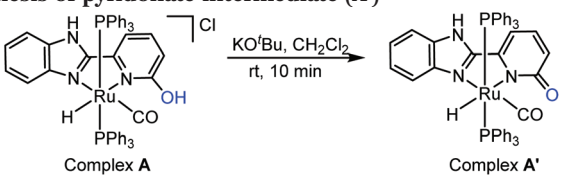
diffraction were grown in CH_2Cl_2/benzene by the slow evaporation process at ambient temperature. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 9.20 (d, $J_{H,H}$ = 5.1 Hz, 1H), 8.03 (d, $J_{H,H}$ = 7.1 Hz, 1H), 7.90 (t, $J_{H,H}$ = 7.7 Hz, 1H), 7.59–7.50 (m, 1H), 7.36–7.27 (m, 3H), 7.24–7.11 (m, 30H), 6.88 (d, $J_{H,H}$ = 8.6 Hz, 1H), 6.81 (t, $J_{H,H}$ = 7.4 Hz, 1H), −11.63 (t, $J_{H,H}$ = 19.3 Hz, 1H). **^{13}C{^{1}H} NMR** (125 MHz, DMSO-d_6): δ = 210.95, 155.81, 150.09, 146.14, 139.16, 138.59, 133.14, 132.17, 131.95, 130.56, 128.77, 126.77, 125.48, 123.42, 122.93, 118.83, 113.32. **^{31}P{^{1}H} NMR** (160 MHz, $CDCl_3$): δ = 44.58 ppm. **IR** ($\nu_{C=O}$, KBr, cm^{-1}): 1934; **HRMS (ESI)**: calcd for $C_{49}H_{40}N_3OP_2Ru$, $[M - Cl]^+$: 851.1768; found: 867.1741. Anal. calculated ($C_{49}H_{40}N_3OP_2RuCl$): C, 66.48; H, 4.55; N, 4.75; found: C, 66.32; H, 4.39; N, 4.61.

Synthesis of complex F



In a Schlenk flask, ligand **L5** (50 mg, 0.22 mmol) and [RuHCl(CO)(PPh_3)$_3$] (213 mg, 0.22 mmol) were taken. Then dry dichloromethane (15 mL) was added to it and stirred at room temperature for 24 h under an argon atmosphere. The resulting solution was filtered and the insoluble part was removed. The filtrate was evaporated to dryness under reduced pressure and washed with diethyl ether to afford complex **F** (139 mg, yield: 69%) as a yellow solid. **^{1}H NMR** (500 MHz, DMSO-d_6): δ = 8.13 (d, $J_{H,H}$ = 7.7 Hz, 1H), 8.0 (t, $J_{H,H}$ = 8.1 Hz, 1H), 7.46 (d, $J_{H,H}$ = 7.5 Hz, 1H), 7.33 (d, $J_{H,H}$ = 7.8 Hz, 1H), 7.25–7.22 (m, 7H), 7.17–7.10 (m, 25H), 6.94 (t, $J_{H,H}$ = 7.7 Hz, 1H), 3.93 (s, 3H), 2.12 (s, 3H), −12.14 (t, $J_{H,H}$ = 18.4 Hz, 1H). **^{13}C{^{1}H} NMR** (125 MHz, DMSO-d_6): δ = 207.16, 149.88, 146.42, 138.88, 137.65, 135.95, 134.16, 133.01, 132.75, 132.58, 130.57, 128.69, 125.64, 123.87, 122.81, 119.42, 112.03, 33.85, 28.79. **^{31}P{^{1}H} NMR** (160 MHz, $CDCl_3$): δ = 44.26 ppm. **IR** ($\nu_{C=O}$, KBr, cm^{-1}): 1917; **HRMS (ESI)**: calcd for $C_{51}H_{44}N_3OP_2Ru$, $[M - Cl]^+$: 879.2081; found: 879.2076. Anal. calculated ($C_{51}H_{44}N_3OP_2RuCl$): C, 67.06; H, 4.86; N, 4.60; found: C, 66.89; H, 4.78; N, 4.49.

Synthesis of pyridonate intermediate (A′)



In a J-Young NMR tube, complex **A** (20 mg, 0.022 mmol) and KO^{t}Bu (12.5 mg, 0.11 mmol) were taken and dry dichloromethane (1 mL) was added to it and stirred at room temperature for 10 min under an argon atmosphere. The resulting solution was filtered and the insoluble part was removed. The filtrate was evaporated to dryness under reduced pressure and washed with diethyl ether to afford complex **A′** (45 mg, yield: 81%) as a yellow solid. **^{1}H NMR** (500 MHz, DMSO-d_6): δ = 7.01 (brs, 12H), 6.94–6.88 (m, 7H), 6.82 (t, $J_{H,H}$ = 7.5 Hz, 12H), 6.48 (t, $J_{H,H}$ = 7.8 Hz, 1H), 6.27–6.26 (m, 2H), 6.14 (d, $J_{H,H}$ = 6.6 Hz, 1H), 5.93 (t, $J_{H,H}$ = 7.6 Hz, 1H), 5.65 (d, $J_{H,H}$ = 8.4 Hz, 1H), −11.38 (d, $J_{H,P}$ = 20.0 Hz, 1H). **^{13}C{^{1}H} NMR** (125 MHz, DMSO-d_6): δ = 206.90, 170.29, 163.54, 150.89, 147.11, 134.51, 134.36, 134.20, 133.67, 128.60, 127.08, 117.23, 116.94, 116.13, 115.65, 113.07, 102.02. **^{31}P{^{1}H} NMR** (160 MHz, $CDCl_3$): δ = 48.84 ppm. Anal. calculated ($C_{49}H_{39}N_3O_2P_2Ru$): C, 68.05; H, 4.55; N, 4.86; found: C, 67.89; H, 4.47; N, 4.76.

General procedure for the synthesis of pyrimidines

In a Schlenk tube, amidine (0.5 mmol), primary alcohol (0.65 mmol), secondary alcohol (0.65 mmol), cat. **A** (1.0 mol%), KO^{t}Bu (0.5 mmol) and dioxane (3.0 mL) were taken. The tube was sealed and the reaction mixture was heated to 120 °C in a preheated oil bath for 24 h. After the reaction, it was cooled to room temperature and then 1,3,5-trimethoxy benzene was added as the internal standard. Then the reaction mixture was filtered through a small plug of neutral alumina and a small portion was taken for the determination of yield. The yield was determined by the analysis of the ^{1}H-NMR spectra of the crude reaction mixture using $CDCl_3$ as the NMR solvent. The final products were purified by silica-gel column chromatography using hexane/ethyl acetate as the eluent. (**Caution:** *All the catalytic reactions were carried out inside the fume hood and after the reactions Schlenk tubes were carefully opened under proper ventilation to release the hydrogen gas produced in the reactions.*)

Procedure for gram scale reaction

In a Schlenk tube, amidine (5.0 mmol), primary alcohol (6.5 mmol), secondary alcohol (6.5 mmol), cat. **A** (1.0 mol%), KO^{t}Bu (5.0 mmol) and dioxane (3.0 mL) were taken. The tube was sealed and the reaction mixture was heated at 120 °C in a preheated oil bath for 24 h. After the reaction, it was cooled to room temperature and the final products were purified by silica-gel column chromatography using hexane/ethyl acetate as the eluent.

Conflicts of interest

There are no conflicts to declare.

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