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Bifunctional Ru (II) Complex Catalysed Carbon–Carbon Bond Formation: An Eco- friendly Hydrogen Borrowing Strategy

Kaushik Chakrabarti, Bhaskar Paul, Milan Maji, Bivas Chandra Roy, Sujan Shee and Sabuj Kundu*

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India

Abstract: Atom economical borrowing hydrogen methodology enables the use of alcohols as alkylating agents for selective C-C bond formation. Bifunctional 2-(2-pyridyl-2-ol)-1,10-phenanthroline (phenpy-OH) based Ru(II) complex (2) was found to be a highly efficient catalyst for the one-pot β -alkylation of secondary alcohols with primary alcohols and double alkylation of cyclopentanol with different primary alcohols. Exploiting the metal-ligand cooperativity in complex 2, several aromatic, aliphatic and heteroatom substituted alcohols were selectively cross-coupled in high yields using significantly low catalyst loading (0.1 mol%). An *outer-sphere* mechanism is proposed for this system as exogenous PPh₃ has no significant effect in rate of the reaction. Notably, this is a rare one-pot strategy for β -alkylation of secondary alcohols using a bifunctional Ru(II)-complex. Moreover, this atom-economical methodology displayed the highest cumulative turn over frequency (TOF) among all the reported transition metal complexes in cross coupling of alcohols.

Keywords: C-C bond formation, Bifunctional, Ruthenium, Hydrogen Borrowing Strategy, Outer-sphere mechanism.

Introduction

C-C bond forming reactions are one of the most crucial and fundamental reactions in organic chemistry to synthesize functionalized molecules with increasing complexity, rationally and predictability.¹⁻³ To construct a new C-C bond following the conventional synthetic approach requires toxic, expensive alkyl halides and strong bases which generate stoichiometric amounts of salts as waste.^{4, 5} This led chemists to develop cleaner and greener methodologies for this chemical transformation. In this regard, substituting alkyl halides with cheap and easy to handle alcohols as electrophiles has a great advantage.⁶⁻⁸



Scheme 1 Proposed strategy for β -alkylation of secondary alcohol by using bifunctional Ru complex

Self-coupling of alcohols using strong bases and heterogeneous transition metal catalysts at very high temperature is known for more than a century as the Guerbet reaction.⁹ In the last decade, significant effort has been invested in this field to make this reaction

practically viable.¹⁰⁻¹⁵ Several transition metals such as Ir,¹⁶⁻²⁵ Rh,²⁶ Pd,²⁷ Ru,^{21, 23, 24, 28-37} Ni,³⁸ Fe,³⁹ and Cu^{40, 41} based complexes were tested for the C-C bond formation via alcohol activation following the "borrowing hydrogen" strategy. This methodology consist mainly of three steps; starting with dehydrogenation of alcohols to generate the corresponding carbonyl compounds followed by base catalyzed aldol condensation to afford α , β -unsaturated ketones which are subsequently hydrogen approach is highly attractive as it provides a wide range of valuable organic molecules with loss of only environment friendly water.⁴²⁻⁴⁶



Fig. 1 Cumulative TOF of the reported Ru and Ir catalysts in β-alkylation of alcohols

Catalytic activities of recently reported various complexes in alcohol cross-coupling are listed in Fig. 1. Although, noteworthy progress have been made in this field, still the cumulative TOF of these catalysts are significantly low and far from any real-world applicability. From industrial and sustainable chemistry perspectives, it is essential to develop a new catalytic system for the efficient synthesis of β -alkylated alcohols with greater selectivity and yield under more environment friendly conditions. Carefully designed bifunctional ligand has the potential to craft better performing catalysts to enable the advancement of this reaction.

2-Hydroxypyridine (2-HP) emerged as an exciting fragment in bifunctional ligand design in both tautomeric forms depending on the reaction conditions (Scheme 2).^{47, 48} The presence of the pendent -OH group in these metal complexes enhances their catalytic ability. Yamaguchi et al. demonstrated dehydrogenation of various alcohols and diols bearing a bifuncitional iridium complexes containing 6,6'-dihydroxy-2,2'-bipyridine ligand.^{3, 49-51} Recently, Li and co-workers reported bipyridonate iridium catalyzed α -alkylation of ketones using primary alcohols.¹⁸ They also showed β -alkylation of secondary alcohols with primary alcohols in two steps using the same catalysts (TOF= 7.5 h⁻¹).¹⁶ Dehydrogenative cross-coupling of alcohols were also reported by Gelman et al. by using bifunctional PC(sp³)P pincer Ir (TOF= 7.8 h⁻¹) and Ru (TOF= 1.9 h⁻¹) complexes.²⁴



Scheme 2 Metal-ligand cooperativity in phenpy-OH based Ru complex (2)

We have recently demonstrated that bifunctional RuCl(phenpy-OH)(PPh₃)₂PF₆ (2) catalyst was highly effective in transfer hydrogenation of ketones and nitriles.⁵² Two 2-HP containing similar Ru(II)-6,6'-dihydroxy terpyridine complex showed very poor activity in transfer hydrogenation with bulkier ketones as the extra pendent *ortho*-OH may hinder the approach of the substrate to the active site.^{53, 54} To exhibit the metal-ligand cooperativity only one 2-HP unit is theoretically sufficient. However, all the reported 2-HP-derived catalysts in dehydrogenation of alcohols^{2, 3, 49-51} as well as α -alkylation^{16, 18} contain at least two 2-HP units.

These observations encouraged us to investigate the catalytic properties of this bifunctional ruthenium complex 2 in direct β -alkylation of secondary alcohols with primary alcohols. Fascinated by the high catalytic activity of 2-HP based Ir-complexes in "ligand-promoted dehydrogenation" of alcohols,² we envisioned that Ru-complexes bearing bifunctional tridentate ligand containing one 2-HP unit may facilitate the β -alkylation of secondary alcohols (Scheme 1). However, to the best of our knowledge no such cooperative complex has been reported for the one-pot synthesis of β -alkylated secondary alcohols. Herein, we report a new, highly efficient bifunctional Ru(II) complex catalyzed tandem β -alkylation of secondary alcohols with primary alcohols without any sacrificial hydrogen acceptors.

Result and Discussion

In the initial experiment, reaction of 1-phenylethanol with benzyl alcohol was selected as the benchmark reaction to evaluate the catalytic activities of a series of NNN-pincer Ru(II) complexes for the β -alkylation of secondary alcohols with primary alcohols. The progress of the reaction was monitored by ¹H-NMR spectroscopy and the results are shown in Table 1. Complexes 1, 3 and 4 were found to be moderately active, whereas, complex 2 bearing (phenpy-OH) bifunctional 2-(2-pyridyl-2-ol)-1,10-phenanthroline ligand exhibited significantly higher activity among all the complexes (Table 1). By using 0.1 mol% of catalyst 2, 73% conversion of 1-phenylethanol was detected after 1 hour of heating with highest 1,3-diphenylpropan-1-ol to 1,3-dipheynlpropan-1-one ratio (A:B = 97:3) and within 90 minutes it presented 99% conversion. To the best of our knowledge, the highest reported cumulative TOF value in similar reaction was 198 h⁻¹, which was reported by Crabtree et al. using terpyridine based Ir complex (Fig. 1).³² To our delight, in comparison to this Ir complex, catalyst 2/NaOH exhibited much higher activity (TOF= 640 h⁻¹). Notably, using very low catalyst loading (0.002 mol%) this system displayed remarkably high 31500 TON after 16 h.

Table 1 β -alkylation of 1-phenylethanol with benzyl alcohol catalysed by different Ru(II) NNN pincer complexes^{*a*}





Reaction Condition: catalyst (0.1 mol%), 1-phenylethanol (0.654 mmol), benzyl alcohol (0.654 mmol) and NaOH (0.327 mmol) at 125 °C for 60 min (*90 min heating). Conversion and selectivity were determined by ¹H NMR based on secondary alcohol.

In order to optimize the reaction conditions and to investigate the influence of base and solvent, β -alkylation of 1-phenylethanol with benzyl alcohol was carried out with 0.1 mol% of complex **2** and the results are summarized in Table 2. Conversion of 1phenylethanol was much higher in toluene than dioxane probably due to higher boiling point of toluene (Table 2 entry 6). Although complex **2** was not fully soluble in toluene at room temperature; under the reaction conditions in the presence of base it produced a homogenous solution which was confirmed by Hg⁰ poisoning test. Among the various bases tested in this reaction, NaOH exhibited the highest efficiency. To determine whether the amount of base influenced the generation of the active catalyst via deprotonation of the *ortho*-OH group of the pyridine moiety which affects the reaction rate; we inspected the dependence of the base in the β -alkylation of 1-phenylethanol with benzyl alcohol using complex **2**.⁵⁴ Conversion of 1-phenylethanol increased steadily with increasing amounts of NaOH up to 0.5 eq., as can be seen in Fig. 2. However, higher than 0.5 eq. of base did not significantly increase the conversion and saturation behaviour was observed. As expected, no conversion was accomplished without the base or the ruthenium complex (Table 2, entries 12 and 13).



Fig. 2 Dependence of NaOH (with respect to 1-phenylethanol) in β -alkylation of 1-phenylethanol with benzyl alcohol catalysed by complex 2

Table 2 Effect of the base and solvent in the β -alkylation of 1-phenylethanol with benzyl alcohol catalysed by complex 2^a

OH .	OH cat. 2 (0.1 base, tolue	mol%) ene, reflux	 	
Entry	Base (eq.)	Solvent	$\begin{array}{c} \text{Conv.} \\ (\%)^b \end{array}$	A/B ratio ^c
1	$\mathrm{KO}^{t}\mathrm{Bu}\left(0.5\right)$	Toluene	51	92:8
2	KOH (0.5)	Toluene	50	87:13
3	NaOH (0.5)	Toluene	73	97:3
4	NaOH (0.3)	Toluene	52	93:7
5	NaOH (1.0)	Toluene	77	97:3
6	NaOH (0.5)	Dioxane	13	94:6
7	$NaO^{i}Pr(0.5)$	Toluene	65	90:10
8	$NaO^{t}Bu$ (0.5)	Toluene	66	91:9
9	$Na_2CO_3(0.5)$	Toluene	<1	ND
10	$K_2CO_3(0.5)$	Toluene	<1	ND
11	$Cs_2CO_3(0.5)$	Toluene	<2	ND
12	No base	Toluene	0	ND
13 ^d	NaOH (0.5)	Toluene	0	ND

^{*a*}Reaction Condition: catalyst (0.1 mol%), 1-phenylethanol (0.654 mmol), benzyl alcohol (0.654 mmol) and base (0.327 mmol) at 125 \degree C for 60 min. ^{*b*}Determined by GC analysis based on secondary alcohol. ^{*c*}Determined by ¹H NMR analysis. ^{*d*}No catalyst. ND = Not Determined.

To evaluate the scope of the present catalytic system, β -alkylation of 1-phenylethanol with a variety of primary alcohols was conducted (Table 3). Benzylic alcohols bearing both electron-donating and electron-withdrawing groups at *para*- position, such as methoxy, methyl, chloro, bromo, and fluoro groups afforded corresponding long chain β -alkylated secondary alcohols selectively in high yields (Table 3, entries 1, 4-7). Substrates with electron-donating and electron-withdrawing groups at *ortho*- and *meta*- positions also gave moderate to good yields with high selectivity (Table 3, entries 2, 3, and 8). Furthermore, 1-naphthylmethanol, heteroaromatic substrate 2-thiophenemethanol and cyclohexylmethanol also successfully acted as a β -alkylating agents and generating the desire products selectively in moderate to good yields (Table 3, entries 9-11). Catalyst **2** showed excellent reactivity in β -alkylation of 1-phenylethanol with more challenging straight chain alcohols, such as 1-butanol, 1-hexanol and 1-octanol (Table 3, entries 12, 13 and 14). Although the reaction rate was slightly slower compared with benzylic alcohols, interestingly no self-coupling products were detected.⁵⁵

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OF	H ` + R^OH <u>NaO</u> tolue	2 (0.1 mol%) H (0.5 eq.) ene, reflux, 90 min.	^R ₊	O B
Entr y	Primary alcohol	Product	Yield ^b	A/B ratio ^b
1	СІ	CI CI	89	94:6
2	CI	ÖH CO	96	93:7
3	ССС	OH CI	55	99:1
4	Br	OH Br	88	93:7
5	F	OH F	90	94:6
6	H ₃ C OH	OH CH ₃	92	92:8
7	H3CO OH	OH OCH3	87	97:3
8	ОН ОСН3	H ₃ CO	65	99:1
9	OH	OH C	82	93:7
10	S OH	OH S	70	99:1

Table 3 Variation of primary alcohols in β -alkylation with 1-phenylethanol^{*a*}



^aReaction Condition: catalyst (0.1 mol%), secondary alcohol (0.654 mmol), benzyl alcohol (0.654 mmol) and NaOH (0.327 mmol) at 125 °C for 90 min. ^bDetermined by ¹H NMR with respect to secondary alcohol. ^cHeating for 4 hours.

The generality of this catalytic reaction was further expanded by reacting benzyl alcohol with different secondary alcohols (Table 4). 1-phenylethanol bearing both electrondonating and electron-withdrawing groups at different positions, such as methoxy, methyl, chloro, bromo, and fluoro groups afforded the corresponding β -alkylated alcohols in excellent yields with high selectivity (Table 4, entries 1-8). 1-(naphthalen-2-yl)ethanol and 1-tetralinol were successfully converted to the coupled alcohol products with high yields (Table 4, entries 9 and 10). The β -alkylation of 1-phenyl-1-propanol with benzyl alcohol gave moderate yield but selectivity was high (Table 4, entry 11). Aliphatic secondary alcohols, such as 1-cyclopropylethanol, 3-methylbutan-2-ol and 2-heptanol were also converted to the desired products in good yields, although 2 equiv. of secondary alcohol was required (Table 4, entries 12-14). In addition, heteroaromatic 1-(pyridin-3-yl)ethanol also gave moderate conversion with high selectivity in this catalytic condition (Table 4, entry 15).

Table 4 Variation of secondary alcohols in β -alkylation with benzyl alcohol^{*a*}

OH R∕∕ +	OH Cat. 2 (0.1 m NaOH (0.5 c toluene, refl	$\begin{array}{c} \text{OH} \\ \stackrel{\text{eq.}}{} \\ \text{ux, 90 min.} \end{array} \qquad \begin{array}{c} \text{OH} \\ \text{R} \\ \\ \text{A} \end{array}$	→ R	O B
Entry	Secondary alcohol	Product	Yield ^b	A/B ratio ^b
1	OH CH ₃	OH	99	99:1
2	CI CH3	CI CI	93	94:6
3	OH CH₃ CI	OH	51	93:7

4	OH Br	Br OH	92	95:5
5	CH ₃	P P P P P P P P P P P P P P P P P P P	93	93:7
6	OH CH ₃	H ₃ C	96	88:12
7	OH CH ₃	H _S CO	91	87:13
8	OH OCH ₃	OH OCH3	93	92:8
9	OH CH ₃	OH CCC CC	96	85:15
10	OH	OH C	95	84:16
11	OH	OH C	52	99:1
12 ^c	OH	OH /	70	93:7
13 ^c	HO	HO	72	97:3
14 ^c	ОН	ОН	88	93:7
15 ^d	OH N	OH N	69	99:1

^{*a*}Reaction Condition: catalyst (0.1 mol%), secondary alcohol (0.654 mmol), benzyl alcohol (0.654 mmol) and NaOH (0.327 mmol) at 125 °C for 90 min. ^{*b*}Determined by ¹H NMR with respect to secondary alcohol. ^{*c*}2 mmol secondary alcohol and 1 mmol benzyl alcohol were used. ^{*d*} 0.3 mol% catalyst was used and heated for 5 hr.

To exploit the versatility of this catalytic system, the one-pot double alkylation reaction was tested by treatment of cyclopentanol with various primary alcohols in the presence of complex **2**. To our delight, this catalytic system afforded the desired double alkylated secondary alcohol products in moderate to good yields (Table 5). Electronic withdrawing group at *para* position increased the yield of this reaction (Table 5, 5b) where reverse was true for electron donating group (Table 5, 5d and 5e). Heteroaromatic 2-thiophenemethanol was also successfully utilized as double alkylating agent which showed moderate yield (Table 5, 5f).





^{*a*}Reaction Condition: catalyst (0.5 mol%), cyclopentanol (0.696 mmol), benzyl alcohol (1.46 mmol) and NaOH (0.696 mmol) at 125 °C for 10 h. Yield determined by ¹H NMR with respect to primary alcohol (isolated yields are given in parenthesis).

Reaction Mechanism

Based on the bifunctional nature of the catalyst 2 and related literature reports,^{2, 3, 16, 18,} 54 we proposed a probable mechanism for the β -alkylation of secondary alcohols with primary alcohols as shown in Scheme 3. In the initial step, in presence of base complex 2 is converted to Ru(II)-bipyridonate complex (P) and addition of alcohol following concerted *outer-sphere* pathway would generate the ruthenium hydride species (\mathbf{R}) and the corresponding carbonyl compound. This outer-sphere pathway is more favoured over the inner-sphere mechanism as indicated by many recent reports.⁵⁶⁻⁵⁹ However, addition of alcohol to **P** followed by β -hydrogen elimination to afford **R** cannot be completely ruled out. Next, base-mediated cross-aldol condensation between the resulting aldehydes and ketones produces the α,β -unsaturated ketones. Finally, metal-ligand cooperativity enables the hydrogenation of the double bond of the α,β -unsaturated ketone by simultaneous transfer of hydroxyl proton from the ligand and the hydride on the ruthenium centre to produce the which then further reduces to alcohol (A) following similar outer-sphere ketone (**B**), mechanism.

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Scheme 3 Proposed mechanism for β -alkylation of secondary alcohol with primary alcohol catalysed by complex 2

To confirm the possible steps in this proposed mechanism several control experiments were carried out. The reaction of 1-phenylethanol with benzaldehyde in presence of complex **2** under optimum catalytic conditions provided a mixture of products comprising 72% of 1,3-diphenylpropan-1-one (**B**), 11% of 1,3-diphenylpropan-1-ol (**A**), and 17% of 1,3-diphenylpropen-1-one (chalcone) (91% conversion of 1-phenylethanol based on ¹H NMR analysis) (Scheme 4, Eq. 1). Similar results were observed when the reverse reaction i.e. reaction of acetophenone with benzyl alcohol was performed (Scheme 4, Eq. 2). In this case, the product distribution was 75% of **B**, 9% of **A** and 16% of chalcone (93% conversion of 1-phenylethanol based on ¹H NMR analysis). In both of these control experiments among the product mixtures, saturated ketone 1, 3-diphenylpropan-1-one (**B**) was identified as the major and 1,3-diphenylpropen-1-one (**C**, chalcone) as a minor product which clearly indicates that the transfer of hydrogen from starting alcohols to the unsaturated aldol condensation product (**C**) happened smoothly. The absence of 1,3-diphenylprop-2-en-1-ol (only ketone hydrogenated product) indicates that the reduction of C=C bond of the α , β -unsaturated ketone was much faster than the reduction of C=O bond under the catalytic conditions.³⁹



Scheme 4 Control experiments for mechanistic studies of β-alkylation of alcohols

To obtain more information regarding the hydrogenation mechanism of the α , β unsaturated ketones, two control experiments with chalcone were executed. The transfer hydrogenation of chalcone in the presence of 1-phenylethanol afforded exclusively **B** in 87% yield (Scheme 5, Eq. 3). Under similar conditions, reaction of benzyl alcohol with chalcone produced 76% of **B** and 3 % of **A** (Scheme 5, Eq. 4). These results further suggest that complex **2** can effectively catalyze the transfer of hydrogen from the starting alcohols to the C=C bond of chalcone and the reduction of the C=C bond is preferred over the C=O bond.^{24, 60, 61}



Scheme 5 Transfer hydrogenation of chalcone using 1 equiv. alcohol

To inspect if the Ru metal center was involved in the cross-aldol condensation step, reaction of acetophenone and benzaldehyde was performed in presence and absence of complex 2 using the optimum catalytic conditions. In the presence of complex 2, 1-phenylethanol was quantitatively converted to chalcone (C) within 90 minutes (Scheme 6, Eq. 5). However, in the absence of 2, only 74% conversion of 1-phenylethanol was observed (Scheme 6, Eq. 6). In this reaction small amount of benzoic acid and benzyl alcohol were generated from base induced Cannizzaro reaction of benzaldehyde and trace amounts of 1,3-diphenylbut-2-en-1-one were also produced from self-condensation of acetophenone. Results from these experiments may indicate the involvement of the ruthenium catalyst in the cross-aldol condensation reaction. With the NHC-Ir complex a similar result was also reported by Oro et al.⁶²



Scheme 6 Cross aldol condensation in presence and absence of cat. 2

In order to probe the selectivity in β -alkylation of secondary alcohols with primary alcohols, we studied time dependent product distribution of this catalytic reaction. As reported in Fig. 3, the concentrations of 1-phenylethanol and benzyl alcohol gradually decreased and concurrently, the concentration of 1,3-diphenylpropan-1-ol (**A**) increased. During the whole course of reaction, the concentration of 1,3-diphenylpropan-1-one (**B**) was minimal and also did not change significantly. On the other hand, we never detected a trace amount of cross-aldol product. This result advocated that with increasing reaction time the selectivity of alcohol (**A**) increases; whereas throughout the process the concentration of keto (**B**) remain the same.⁶²



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Fig. 3 Time dependent product distribution in β -alkylation of 1-phenylethanol with benzyl alcohol catalysed by complex 2

In the hydrogenation reaction excess of PPh₃ significantly reduces the reaction rate for a catalytic system following *inner-sphere* mechanism as ligand dissociation is considered as an initiation step.⁶³⁻⁶⁸ In contrast, an excess of PPh₃ has no significant effect on the catalytic activity of a system following *outer-sphere* mechanism.⁶⁹ In order to inspect which mechanism our system was following, β -alkylation of 1-phenylethanol with benzyl alcohol was carried out using both the complexes **1** and **2** in presence of excess of PPh₃ (2-8 eq.). The rate of β -alkylation of secondary alcohol was significantly affected when excess of PPh₃ was added to the reaction mixture containing complex **1** (Fig. 4). After 3 h, in absence of additional PPh₃ conversion of 1-phenylethanol was 77% with complex **1**. But, under similar reaction conditions with 8 eq. of PPh₃ conversion of 1-phenylethanol was decreased drastically to 28%. However, with catalyst **2** exogenous PPh₃ had no significant effect (Fig. 4). This result clearly validates that in the rate determined step dissociation of PPh₃ did not occur with the **2**/NaOH system and probably it was following an *outer-sphere* mechanism.

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Fig. 4 Effect of externally added PPh₃ (with respect to cat.) on cat. **1** and cat. **2** in β -alkylation of 1-phenylethanol with benzyl alcohol. Conditions: 0.1 mmol% cat., 1-phenylethanol (0.654 mmol), benzyl alcohol (0.654 mmol), NaOH (0.327 mmol), toluene, 125 °C. Time for Cat. **1** (180 mins.) and Cat **2** (90 mins.).

Conclusion

A ruthenium(II) complex bearing a bifunctional phenpy-OH ligand was found to be a highly efficient catalyst for the atom economical β -alkylation of secondary alcohols with primary alcohols. This work demonstrates a new, practical and greener methodology to construct C-C bonds using readily available, less toxic alcohols and produces only H₂O as byproduct. The metal-ligand cooperativity in complex 2 accounts for the remarkably high catalytic activity in coupling of a variety of secondary alcohols with numerous primary alcohols to yield the corresponding β -alkylated alcohols with high selectivity. Notably, double alkylation of cyclopentanol with various primary alcohols also proceeded smoothly. Control experiments indicated involvement of the ruthenium catalyst in cross-aldol condensation and that hydrogenation of the C=C bond of the α , β -unsaturated ketone was much faster than the hydrogenation of the ketone with this system. Mechanistic studies with excess of PPh₃ in β -alkylation of 1-phenylethanol with benzyl alcohol revealed that the 2/NaOH system was following an *outer-sphere* mechanism. To the best of our knowledge, this present protocol is a rare one-pot atom economical synthetic strategy for β -alkylation of secondary alcohols with primary alcohols using a bifunctional Ru(II)-complex which exhibited highest reactivity among all the reported catalysts.

Experimental Section

General Procedures and Materials: All reactions were carried out under an inert atmosphere using standard Schlenk-line techniques. Glasswares were flame-dried under vacuum prior to use. Solvents were dried according to literature methods, distilled under argon and deoxygenated prior to use. RuCl₃.nH₂O (39% Ru) and PdCl₂ (60% Pd) were purchased from Arora Matthey, India. 2-bromo phenanthroline, 5-methoxy-2-(tributylstannyl)pyridine, 5-methyl-2-(tributylstannyl)pyridine, 2-(tributylstannyl)pyridine were synthesized following the literature procedures.⁷⁰⁻⁷⁴ Synthesis of complexes 1 and 2 were already reported from our group.⁵² All the chemicals were purchased from Sigma-Aldrich, Alfa Aesar, SDFCL and Spectrochem. ¹H, ¹³C, ³¹P NMR spectra were recorded on JEOL 400 and 500 MHz spectrometers. Elemental analyses was performed on a Thermoquest EA1110 CHNS/O analyser. The crystallized compounds were powdered, washed several times with dry diethyl ether and dried under vacuum for at least 48 h prior to elemental analyses. ESI-MS were recorded on a Waters Micromass Quattro Micro triple-quadrupole mass spectrometer. All the GC analysis were done using Perkein Elmer Clarus 600 Gas

Chromatograph and GC-MS were taken using Agilent 7890 A Gas Chromatograph equipped with Agilent 5890 triple-quadrupole mass system.

Synthesis of 2-(6-methylpyridin-2-yl)-1, 10-phenanthroline: A mixture of 2-bromo phenanthroline (0.772 mmol, 0.20 g), 5-methyl-2-tributhylstannylpyridine (1.544 mmol, 0.589 g) and Pd(PPh₃)₄ (0.077 mmol, 0.089 g) in 30 mL of toluene was heated at the reflux temperature for 4 days. The mixture was allowed to cool to room temperature and the solvent was removed in vacuum. The final product was purified by column chromatography (using neutral alumina) with hexane-ethyl acetate as eluent. A light yellow product was obtained (0.170 g, 81%). ¹H NMR (400 MHz, CDCl₃): δ = 9.21 (dd, *J*_{H,H} = 4.12 Hz, *J*_{H,H} = 2.28 Hz, 1H), 8.79 (d, *J*_{H,H} = 8.24 Hz, 1H), 8.72 (d, *J*_{H,H} = 7.76 Hz, 1H), 8.33 (d, *J*_{H,H} = 8.24 Hz, 1H), 8.24 (dd, *J*_{H,H} = 8.02 Hz, *J*_{H,H} = 6.40 Hz, 1H), 7.82-7.75 (m, 3H), 7.63 (dd, *J*_{H,H} = 8.24 Hz, 1H), 7.21 (d, *J*_{H,H} = 7.32 Hz, 1H), 2.67 (s, 3H) . ¹³C {¹H} NMR (500 MHz, CDCl₃) : 157.9, 156.6, 155.5, 150.4, 146.4, 145.4, 137.2, 136.9, 136.2, 129.1, 128.7, 126.6, 123.8, 122.9, 121.0, 119.8, 24.7. ESI-MS: m/z = 273.1182 (100%, MH⁺).

Synthesis of 2-(pyridin-2-yl)-1,10-phenanthroline : A mixture of 2-bromo phenanthroline (0.772 mmol, 0.2 g), 2-tributhylstannylpyridine (1.543 mmol, 0.568 g) and Pd(PPh₃)₄ (0.077 mmol, 0.089 g) in 30 mL of toluene was heated at the reflux temperature for 3 days. The mixture was allowed to cool to room temperature and the solvent was removed in vacuum. The final product was purified by column chromatography (using neutral alumina) with hexane-ethyl acetate as eluent. A cream white product was obtained (0.163 g, 82%). ¹H NMR (400 MHz, CDCl₃): δ = 9.22 (dd, *J*_{H,H} = 4.58 Hz, *J*_{H,H} = 3.08 Hz, 1H), 8.98 (d, *J*_{H,H} = 7.96 Hz, 1H), 8.79 (d, *J*_{H,H} = 8.56 Hz, 1H), 8.72 (d, *J*_{H,H} = 4.92 Hz, 1H), 8.36 (d, *J*_{H,H} = 8.56 Hz, 1H), 8.26 (dd, *J*_{H,H} = 8.56 Hz, 1H), 7.64 (dd, *J*_{H,H} = 7.94 Hz, *J*_{H,H} = 3.68 Hz, 1H), 7.36 (dt, *J*_{H,H} = 5.04 Hz, *J*_{H,H} = 1.24 Hz, 1H). ¹³C{¹H} NMR (500 MHz, CDCl₃), δ = 156.2, 156.1, 150.4, 149.1, 146.3, 145.7, 137.1, 137.0, 136.3, 129.1, 128.8, 126.8, 126.6, 124.2, 123.0, 122.8, 120.9. ESI-MS: m/z = 258.1030 (100%, MH⁺).

Synthesis of trans-RuCl(phenpyMe)(PPh₃)₂PF₆(3) : In a Schlenk flask 2-(6-methylpyridin-2-yl)-1, 10-phenanthroline (0.020 g; 0.074 mmol) and RuCl₂(PPh₃)₃ (0.071 g; 0.074 mmol) was taken and 40 mL dry methanol was added. The mixture was refluxed for 24 hours under argon atmosphere. It was allowed to cool to room temperature and solid ammonium hexafluorophosphate (0.240 g; 1.474 mmol) was added to the solution. The solution was stirred at room temperature overnight, during which a red precipitate emerged. The precipitate was filtered, washed with dry diethyl ether and hexane and dried under vacuum to provide the title compound as a brick red powder. (0.041 g; 70 %). ¹H NMR (500 MHz, CD_2Cl_2), $\delta = 9.23$ (d, $J_{H,H} = 5.2$ Hz, 1H), 8.35 (d, $J_{H,H} = 8.19$ Hz, 1H), 8.26 (d, $J_{H,H} = 8.75$ Hz, 1H), 8.15 (d, J_{HH} = 8.75 Hz, 1H), 7.98 (d, J_{HH} = 7.55 Hz, 1H), 7.94 (bs, 2H), 7.86-7.77 (m, 2H), 7.45 (d, $J_{H,H}$ = 7.6 Hz, 1H), 7.35 (t, $J_{H,H}$ = 4.3 Hz, 6H), 7.28-7.15 (m, 12H), 6.92-6.65 (m, 12H), 2.68 (s, 3H). ${}^{13}C{}^{1}H$ NMR (125 MHz, CD_2Cl_2) : $\delta = 157.72$, 137.10, 135.36, 134.54, 134.15, 132.89, 132.72, 130.46, 130.42, 130.11, 129.11, 129.64, 128.82, 128.69, 128.21, 127.91, 127.86, 126.91, 125.26, 121.46, 120.84, 116.33, 28.21. ³¹P{¹H} NMR, (202 MHz, CD₂Cl₂), $\delta = 17.90$ (s, PPh₃), -145.06 (sep., J = 703.6, PF₆⁻). ESI-MS: m/z = 932.1780 $([M-PF_6]^+)$. Anal. Calculated $(C_{54}H_{43}ClF_6N_3P_3Ru)$ (Found): C, 60.20 (59.85); H, 4.02 (3.81); N, 3.90 (3.62).

Synthesis of *trans*-RuCl(phenpy)(PPh₃)₂PF₆ (4) : In a Schlenk flask 2-(pyridin-2-yl)-1,10phenanthroline (0.020 g; 0.077 mmol) and RuCl₂(PPh₃)₃ (0.075 g; 0.077 mmol) was taken

and 40 mL dry methanol was added. The mixture was refluxed for 24 hours under argon atmosphere. It was allowed to cool to room temperature and solid ammonium hexafluorophosphate (0.253 g; 1.554 mmol) was added to the solution. The solution was stirred at room temperature overnight, during which a red precipitate emerged. The precipitate was filtered, washed with dry diethyl ether and hexane and dried under vacuum to provide the title compound as a crimson red powder. Yield: (0.037 g; 74 %). ¹H NMR (500 MHz, CD₂Cl₂): δ = 9.46 (d, *J*_{H,H} = 4.60 Hz, 1H), 9.12 (d, *J*_{H,H} = 5.00 Hz, 1H), 8.17 (d, *J*_{H,H} = 8.05 Hz, 1H), 7.90 (d, *J*_{H,H} = 7.30 Hz, 6H), 7.79-7.69 (m, 4H), 7.56-7.50 (m, 2H), 7.19 (t, *J*_{H,H} = 5.9 Hz, 1H), 7.13 (t, *J*_{H,H} = 7.30 Hz, 6H), 7.07-7.04 (m, 12H), 6.96 (t, *J*_{H,H} = 7.2 Hz, 6H), 6.93 (t, *J*_{H,H} = 7.6 Hz 12H), 6.82-6.86 (m, 12H), 7.07-7.04 (m, 12H), 6.96 (t, *J*_{H,H} = 7.55 Hz, 12H). ¹³C {¹H} NMR (100 MHz, CD₂Cl₂) : δ = 157.75, 156.99, 156.70, 156.10, 147.76, 136.72, 135.01, 132.58, 129.90, 129.52, 129.36, 129.20, 129.07, 128.35, 128.05, 127.98, 126.99, 126.93, 125.40, 122.68, 120.93. ³¹P {¹H} NMR, 202 MHz (CD₂Cl₂), δ (ppm): 19.45 (s, PPh₃), -145.08 (sep., *J* = 704.4, PF₆⁻). ESI-MS: m/z = 918.1582 ([M-PF₆]⁺). Anal. Calculated (C₅₃H₄₁CIF₆N₃P₃Ru) (Found): C, 59.86 (59.57); H, 3.89 (3.73); N, 3.95 (3.57).

General Procedure for the Catalytic β-Alkylation of Alcohols: The catalyst solution was prepared by dissolving complex **2** in CH₃CN (1 mL) in an argon filled glovebox. Then red catalyst solution (0.1 mol%) was taken into a Schlenk tube and solvent was removed under vacuum. After that secondary alcohol (0.654 mmol), primary alcohol (0.654 mmol), NaOH (0.327 mmol) and 3.0 ml toluene were added under an argon atmosphere. Then, the tube was dipped at oil bath (the red color immediately changed to purple) and heated for 90 minutes at 125 °C (oil bath temperature). It was cooled to room temperature and 10 µL solution was syringed out for GC analysis (faint purple color). The reaction mixture was concentrated under reduced pressure and submitted crude for NMR to calculate the conversion and product selectivity. The final desired alcohol (**A**, major) and ketone (**B**, minor) products were isolated and purified by column chromatography (silica) using hexane-ethyl acetate as eluent.

General Procedure for the Catalytic Double β-Alkylation of Cyclopentanol: The catalyst solution was prepared by dissolving complex 2 in CH₃CN (1 mL) in an argon filled glovebox. Then red catalyst solution (0.5 mol %) was taken into a Schlenk tube and solvent was removed under vacuum. After that cyclopentanol (0.696 mmol), primary alcohol (1.46 mmol), NaOH (0.696 mmol) and 3.0 mL toluene were added under argon atmosphere. Then, the tube was dipped at oil bath (the red color immediately changed to purple) and heated for 10 hours at 125 °C (oil bath temperature). It was cooled to room temperature (faint purple color), concentrated under reduced pressure and submitted crude for NMR to calculate the conversion. The final desired products were isolated and purified by column chromatography (silica) using hexane-ethyl acetate as eluent.

Associated Content

Supporting Information. General procedures for PPh₃ dependence studies, control experiments procedure, Hg^0 poising experiment, characterization data and NMR spectra of the products are available. This material is available free of charge via the Internet at <u>http://pubs.rsc.org</u>.

Author Information

Corresponding Author

*Email: sabuj@iitk.ac.in;_Tel.: +91-512-2597425.

Notes

The authors declare no competing financial interests.

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References

- 1. G. Casiraghi, L. Battistini, C. Curti, G. Rassu and F. Zanardi, *Chem. Rev.*, 2011, **111**, 3076-3154.
- 2. R. Kawahara, K.-i. Fujita and R. Yamaguchi, J. Am. Chem. Soc., 2012, 134, 3643-3646.
- 3. R. Kawahara, K.-i. Fujita and R. Yamaguchi, Angew. Chem. Int. Ed., 2012, 51, 12790-12794.
- 4. C. S. Yeung and V. M. Dong, Chem. Rev., 2011, 111, 1215-1292.
- 5. F. Huang, Z. Liu and Z. Yu, Angew. Chem. Int. Ed., 2016, 55, 862-875.
- 6. O. Junzo, *Modern Carbonyl Chemistry*, Wiley-VCH: Weinheim, Germany, 2000.
- 7. E. Skucas, M.-Y. Ngai, V. Komanduri and M. J. Krische, *Acc. Chem. Res.*, 2007, **40**, 1394-1401.
- 8. G. Guillena, D. J. Ramón and M. Yus, Angew. Chem. Int. Ed., 2007, 46, 2358-2364.
- 9. M. Guerbet, C.R. Acad. Sci., 1909, 49, 129.
- 10. R. L. Wingad, E. J. E. Bergstrom, M. Everett, K. J. Pellow and D. F. Wass, *Chem. Commun.*, 2016, **52**, 5202-5204.
- 11. K.-N. T. Tseng, S. Lin, J. W. Kampf and N. K. Szymczak, *Chem. Commun.*, 2016, **52**, 2901-2904.
- R. L. Wingad, P. J. Gates, S. T. G. Street and D. F. Wass, ACS Catal., 2015, 5, 5822-5826.
- 13. D. Gabriels, W. Y. Hernandez, B. Sels, P. Van Der Voort and A. Verberckmoes, *Catal. Sci. Technol.*, 2015, **5**, 3876-3902.
- 14. S. Chakraborty, P. E. Piszel, C. E. Hayes, R. T. Baker and W. D. Jones, J. Am. Chem. Soc., 2015, **137**, 14264-14267.
- 15. G. R. M. Dowson, M. F. Haddow, J. Lee, R. L. Wingad and D. F. Wass, *Angew. Chem. Int. Ed.*, 2013, **52**, 9005-9008.
- 16. R. Wang, J. Ma and F. Li, J. Org. Chem., 2015, 80, 10769-10776.
- 17. D. Wang, K. Zhao, C. Xu, H. Miao and Y. Ding, ACS Catal., 2014, 4, 3910-3918.
- 18. F. Li, J. Ma and N. Wang, J. Org. Chem., 2014, 79, 10447-10455.
- 19. C. Xu, L. Y. Goh and S. A. Pullarkat, Organometallics, 2011, 30, 6499-6502.
- 20. C. Segarra, E. Mas-Marzá, J. A. Mata and E. Peris, Adv. Synth. Catal., 2011, 353, 2078-2084.
- A. Pontes da Costa, M. Viciano, M. Sanaú, S. Merino, J. Tejeda, E. Peris and B. Royo, *Organometallics*, 2008, 27, 1305-1309.
- 22. K.-i. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett.*, 2005, 7, 4017-4019.
- 23. D. Gnanamgari, E. L. O. Sauer, N. D. Schley, C. Butler, C. D. Incarvito and R. H. Crabtree, *Organometallics*, 2009, **28**, 321-325.
- 24. S. Musa, L. Ackermann and D. Gelman, Adv. Synth. Catal., 2013, 355, 3077-3080.
- 25. D. Wang, K. Zhao, X. Yu, H. Miao and Y. Ding, RSC Adv., 2014, 4, 42924-42929.

Organic & Biomolecular Chemistry Accepted Manuscript

- 26. P. Satyanarayana, G. M. Reddy, H. Maheswaran and M. L. Kantam, *Adv. Synth. Catal.*, 2013, **355**, 1859-1867.
- 27. O. Kose and S. Saito, Org. Biomol. Chem., 2010, 8, 896-900.
- 28. C. S. Cho, B. T. Kim, T.-J. Kim and S. C. Shim, J. Org. Chem., 2001, 66, 9020-9022.
- C. S. Cho, B. T. Kim, H.-S. Kim, T.-J. Kim and S. C. Shim, *Organometallics*, 2003, 22, 3608-3610.
- 30. G. R. A. Adair and J. M. J. Williams, *Tetrahedron Lett.*, 2005, 46, 8233-8235.
- 31. H. W. Cheung, T. Y. Lee, H. Y. Lui, C. H. Yeung and C. P. Lau, *Adv. Synth. Catal.*, 2008, **350**, 2975-2983.
- 32. D. Gnanamgari, C. H. Leung, N. D. Schley, S. T. Hilton and R. H. Crabtree, *Org. Biomol. Chem.*, 2008, **6**, 4442-4445.
- 33. X. Chang, L. W. Chuan, L. Yongxin and S. A. Pullarkat, *Tetrahedron Lett.*, 2012, **53**, 1450-1455.
- 34. W. Bai and G. Jia, Inorg. Chim. Acta, 2015, 431, 234-241.
- 35. A. Prades, M. Viciano, M. Sanaú and E. Peris, *Organometallics*, 2008, 27, 4254-4259.
- 36. Q. Wang, K. Wu and Z. Yu, Organometallics, 2016, 35, 1251-1256.
- 37. C. Schlepphorst, B. Maji and F. Glorius, ACS Catal., 2016, 6, 4184-4188.
- 38. G. Tang and C.-H. Cheng, Adv. Synth. Catal., 2011, 353, 1918-1922.
- 39. J. Yang, X. Liu, D.-L. Meng, H.-Y. Chen, Z.-H. Zong, T.-T. Feng and K. Sun, *Adv. Synth. Catal.*, 2012, **354**, 328-334.
- 40. S. Liao, K. Yu, Q. Li, H. Tian, Z. Zhang, X. Yu and Q. Xu, Org. Biomol. Chem., 2012, 10, 2973-2978.
- 41. T. Miura, O. Kose, F. Li, S. Kai and S. Saito, Chem. Eur. J., 2011, 17, 11146-11151.
- 42. M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555-1575.
- 43. G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681-703.
- 44. J. T. Kozlowski and R. J. Davis, *ACS Catal.*, 2013, **3**, 1588-1600.
- 45. S. Pan and T. Shibata, ACS Catal., 2013, 3, 704-712.
- 46. Y. Obora, ACS Catal., 2014, 4, 3972-3981.
- 47. J. R. Khusnutdinova and D. Milstein, Angew. Chem. Int. Ed., 2015, 54, 12236-12273.
- 48. J. Frank and A. R. Katritzky, J. Chem. Soc., Perkin Trans. 2, 1976, 1428-1431.
- 49. K.-i. Fujita, Y. Tanaka, M. Kobayashi and R. Yamaguchi, J. Am. Chem. Soc., 2014, 136, 4829-4832.
- 50. K.-i. Fujita, W. Ito and R. Yamaguchi, *ChemCatChem*, 2014, 6, 109-112.
- 51. K.-i. Fujita, N. Tanino and R. Yamaguchi, Org. Lett., 2007, 9, 109-111.
- 52. B. Paul, K. Chakrabarti and S. Kundu, *Dalton Trans.*, 2016, 45, 11162-11171.
- 53. C. M. Moore and N. K. Szymczak, Chem. Commun., 2013, 49, 400-402.
- 54. C. M. Moore, B. Bark and N. K. Szymczak, ACS Catal., 2016, 6, 1981-1990.
- 55. T. Matsu-ura, S. Sakaguchi, Y. Obora and Y. Ishii, J. Org. Chem., 2006, 71, 8306-8308.
- 56. G. Zeng, S. Sakaki, K.-i. Fujita, H. Sano and R. Yamaguchi, *ACS Catal.*, 2014, 4, 1010-1020.
- 57. S. Qu, Y. Dang, C. Song, M. Wen, K.-W. Huang and Z.-X. Wang, *J. Am. Chem. Soc.*, 2014, **136**, 4974-4991.
- H. Li, X. Wang, F. Huang, G. Lu, J. Jiang and Z.-X. Wang, *Organometallics*, 2011, 30, 5233-5247.
- 59. H. Li, G. Lu, J. Jiang, F. Huang and Z.-X. Wang, *Organometallics*, 2011, **30**, 2349-2363.
- 60. R. Ouyang and D.-e. Jiang, ACS Catal., 2015, 5, 6624-6629.

Organic & Biomolecular Chemistry Accepted Manuscript

- 61. D. Loffreda, F. Delbecq, F. Vigné and P. Sautet, Angew. Chem. Int. Ed., 2005, 44, 5279-5282.
- 62. M. V. Jiménez, J. Fernández-Tornos, F. J. Modrego, J. J. Pérez-Torrente and L. A. Oro, *Chem. Eur. J.*, 2015, **21**, 17877-17889.
- 63. S. E. Clapham, A. Hadzovic and R. H. Morris, *Coord. Chem. Rev.*, 2004, **248**, 2201-2237.
- 64. C. P. Casey, T. B. Clark and I. A. Guzei, J. Am. Chem. Soc., 2007, 129, 11821-11827.
- S. Enthaler, B. Hagemann, S. Bhor, G. Anilkumar, M. K. Tse, B. Bitterlich, K. Junge, G. Erre and M. Beller, *Adv. Synth. Catal.*, 2007, 349, 853-860.
- 66. J. Bosson, A. Poater, L. Cavallo and S. P. Nolan, J. Am. Chem. Soc., 2010, 132, 13146-13149.
- 67. Ó. Pablo, D. Guijarro, G. Kovács, A. Lledós, G. Ujaque and M. Yus, *Chem. Eur. J.*, 2012, **18**, 1969-1983.
- 68. K. Li, J.-L. Niu, M.-Z. Yang, Z. Li, L.-Y. Wu, X.-Q. Hao and M.-P. Song, Organometallics, 2015, 34, 1170-1176.
- 69. A. Comas-Vives, G. Ujaque and A. Lledós, Organometallics, 2007, 26, 4135-4144.
- 70. M. Böttger, B. Wiegmann, S. Schaumburg, P. G. Jones, W. Kowalsky and H.-H. Johannes, *Beilstein J. Org. Chem.*, 2012, **8**, 1037-1047.
- 71. T. Honda, R. Takahashi and H. Namiki, J. Org. Chem., 2005, 70, 499-504.
- 72. C. Hirschhäuser, C. A. Haseler and T. Gallagher, *Angew. Chem. Int. Ed.*, 2011, **50**, 5162-5165.
- 73. T. N. Y. Hoang, M. Humbert-Droz, T. Dutronc, L. Guénée, C. Besnard and C. Piguet, *Inorg. Chem.*, 2013, **52**, 5570-5580.
- K. Kamata, A. Suzuki, Y. Nakai and H. Nakazawa, Organometallics, 2012, 31, 3825-3828.



Bifunctional Ru(II) complex (0.1 mol%) catalysed one-pot β-alkylation of secondary alcohols with primary alcohols and double alkylation of cyclopentanol were carried out successfully following the atom economical borrowing hydrogen methodology. Notably, this greener methodology displayed significantly higher reactivity among all the reported complexes which exhibited remarkably high 31500 TON.

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