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## Phosphine–Free Pincer–Ruthenium Catalyzed Biofuel Production: High Rate, Yields and Turnovers of Solventless Alcohol Alkylation

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Phosphine-free pincer-ruthenium carbonyl complexes based on bis(imino)pyridine and 2,6-bis(benzimidazole-2-yl) pyridine ligands have been synthesized. For the  $\beta$ -alkylation of 1-phenyl ethanol with benzyl alcohol at 140 °C under solvent-free conditions, (Cy2NNN)RuCl<sub>2</sub>(CO) (0.00025 mol %) in combination with NaOH (2.5 mol %) was highly efficient (ca. 93% yield, 372000 TONs at 12000 TOh $^{-1}$ ). These are the highest reported values hitherto for a ruthenium based catalyst. The  $\beta$ -alkylation of various alcohol combinations were accomplished with ease which culminated to give 380000 TONs at 19000 TOh<sup>-1</sup> for the  $\beta$ -alkylation of 1-phenyl ethanol with 3-methoxy benzyl alcohol. DFT studies were complementary to mechanistic studies and indicate the  $\beta$ -hydride elimination step involving the extrusion of acetophenone to be the overall RDS. While the hydrogenation step is favored for the formation of  $\alpha$ -alkylated ketone, the alcoholysis step is preferred for the formation of  $\beta$ -alkylated alcohol. The studies were extended for the upgradation of ethanol to biofuels. Among the pincer-ruthenium complex based on bis(imino)pyridine, (Cv2NNN)RuCl2(CO) provided high productivity (335 TONs at 170 TOh<sup>-1</sup>). Sterically more open pincer–ruthenium complexes such as (<sup>Bim2</sup>NNN)RuCl<sub>2</sub>(CO) based on 2,6-bis(benzimidazole-2-yl) pyridine ligand, demonstrated better reactivity and gave not only good ethanol conversion (ca. 58%) but also high turnovers (ca. 2100) with a good rate (ca. 710 TOh<sup>-1</sup>). Kinetic studies indicate first order dependence on concentration of both catalyst and ethanol. Phosphine-free catalytic systems operating with unprecedented activity at a very low base loading to couple lower alcohols to higher alcohols of fuel and pharmaceutical importance are the salient features of this report.

## Introduction

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Carbon–carbon bond forming reactions are pivotal to the synthesis of several valuable precursors to fuel, fine chemicals, agrochemicals, pharmaceutical and natural products.<sup>1</sup> Well explored approaches towards greener and sustainable C–C bond forming reactions involve catalytic C–X (X = H, Cl, Br, I) activation and subsequent cross coupling either involving radical mechanisms<sup>2</sup> or purely organometallic mechanisms.<sup>3</sup> Recently, emphasis has shifted to the use of alcohols as alkylating agents with water as the sole byproduct. The reactivity is based on the concept of hydrogen–borrowing that involves tandem catalytic dehydrogenation, aldol condensation and catalytic hydrogenation that leads to a net  $\beta$ –alkylation of alcohol.

The  $\beta$ -alkylation of alcohols under metal–free conditions,<sup>4</sup> are limited by stoichiometric amounts of base that generates

equivalent amount of waste.<sup>4b, c</sup> On the other hand, transition metal catalyzed  $\beta$ -alkylation has enjoyed great success. The reports include several homogeneous catalysts derived not only from precious metals such as palladium,<sup>5</sup> iridium,<sup>6</sup> rhodium<sup>7</sup> and ruthenium<sup>6b, d, j, 8</sup> but also from cheap transition metals such as copper,<sup>9</sup> cobalt,<sup>10</sup> manganese<sup>11</sup> and nickel.<sup>12</sup>

Ruthenium complexes have performed exceedingly well in catalyzing the  $\beta$ -alkylation of alcohols. Cho reported the RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> catalyzed  $\beta$ -alkylation of secondary alcohols.<sup>8f</sup> The Lau group have accomplished alcohol  $\beta$ -alkylation using ruthenium complexes based on cyclopentadienyl (Cp), hydrotris(pyrazolyl)borato (Tp), and bipyridine (Bipy) ligands.<sup>6b</sup> They have attributed the catalytic activity to the formation of a Ru-hydrido species.<sup>6b</sup> Crabtree has demonstrated the excellent catalytic activity of Cp-ruthenium complexes with chelating *N*-heterocyclic carbene (NHC) ligands towards  $\beta$ -alkylation of alcohols.<sup>6d</sup> Musa, Ackermann and Gelman have



Figure 1. Efficient ruthenium catalysts for  $\beta$ -alkylation of alcohols.

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Electronic Supplementary Information (ESI) available: X-ray crystallographic parameters, NMR spectra and computational data (PDF) and X-ray crystallo-graphic data (CIF). CCDC 1986710 and 1986711. For ESI and crystallographic data in CIF or other electronic format see DOI:

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investigated the activity of pincer-ruthenium complexes based on triptycene framework in catalyzing the  $\beta$ -alkylation of alcohols.6j

The Kundu group designed bifunctional Ru(II) catalysts based on 2-(2-pyridyl-2-ol)-1,10-phenanthroline<sup>8e</sup> and 6,6'-dihydroxy-2,2'-bipyridine<sup>8d</sup> ligands for efficient catalytic  $\beta$ -alkylation of alcohols. Apurba *et.al.* have utilized a phosphine-pyridone pincer-ruthenium(II) complex for the catalytic synthesis of  $\alpha$ -alkylated ketones via the cross coupling of alcohols.<sup>8b</sup> Yu has studied the use of Ru(III) pincer catalysts containing unsymmetrical pyridyl based N-heterocyclic ligands for the alcohol  $\beta$ -alkylation.<sup>8c</sup> The Chen group have obtained good TONs of  $\alpha$ -alkylated ketones and  $\beta$ -alkylated alcohols by the use of a Ru(II) bifunctional catalyst that consists of 6-hydroxy-2,2'-bipyridine ligands with a uncoordinated pyridyl group.<sup>13</sup> Chen subsequently improved the catalytic efficiency by employing a ruthenium pyridonate complex that contains a thiazolyl pendant group.8a

Figure 1 depicts the reported ruthenium catalysts that demonstrate exceptional activity towards  $\beta$ -alkylation of alcohols. Notably, the successful catalysts are based on bidentate ligands and most of them have PPh<sub>3</sub> ancillary ligands. Following up on our recent success in the synthesis<sup>14a,c</sup> of pincer-ruthenium complexes of the type (1a-e) and their application in efficiently catalyzing the N-alkylation<sup>15</sup> and glycerol dehydrogenation,<sup>14c</sup> we envisaged their utility in accomplishing related involving tandem reactions dehydrogenation.

synthesis In the current study, we report the of pincer-ruthenium carbonyl complexes based on based bis(imino)pyridine (2a-d) and on 2,6-bis(benzimidazole-2-yl) pyridine ligands (2e-f) (Figure 2). The activities of these phosphine-free complexes have been compared with our previous reported catalysts (1a-e)14a,c towards catalytic  $\beta$ -alkylation of secondary alcohols. Among the considered catalysts, (Cy2NNN)RuCl<sub>2</sub>(CO) (2b) provides 380000 TONs at 19000 TOh<sup>-1</sup> at 140 °C that is unprecedented when compared with the best of the reported ruthenium catalysts (Figure 1). The complexes have been fulther of the upgrade ethanol to butanol with good efficiency leading to conditions that give high conversions (ca. 58%) and rate (ca. 710 TOh<sup>-1</sup>).

## **Results and Discussions**

### Synthesis and Characterization of Pincer-Ruthenium Complexes Based on Bis(imino)pyridine and Based on 2,6-Bis(benzimidazole-2-yl) Pyridine Ligands.

The ligands (3a-f) were synthesized using a protocol that was recently reported by us<sup>14a,c</sup> and others.<sup>14b</sup> Treatment of 3a-f (Scheme 1) with dichloro(*p*-cymene)ruthenium(II) dimer in refluxing THF followed by introduction of an atmosphere of CO provided the corresponding pincer-ruthenium(II) carbonyl complexes (2a-f).

The newly synthesized pincer-ruthenium complexes (2a-d) were fully characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR and HRMS(ESI) analysis. While the carbonyl carbon of 2a appeared at 207.2 ppm, the corresponding carbonyl signals for **2b** and **2c** were found around 205 ppm. The complexes 2d, 2e and 2f were highly insoluble and NMR analysis was not possible. The IR studies of 2a, 2b, 2c, 2d, 2e and 2f also revealed the presence of carbonyl group and the prominent C–O stretching frequency was observed at 1934 cm<sup>-1</sup>, 1944 cm<sup>-1</sup>, 1952 cm<sup>-1</sup>, 1954 cm<sup>-1</sup>, 1965 cm<sup>-1</sup> and 1939 cm<sup>-1</sup> respectively. The HRMS(ESI) analysis of the carbonyl complexes 2a-f revealed m/z values that correspond to ions formed by loss of chloride ions [(R2NNN)RuCl(CO)]+.

Attempts made to grow single crystals by slow diffusion of hexane into the dichloromethane solution of these complexes gave good quality crystals with 2b and 2c which were characterized by X–ray diffraction studies (Figure 3).<sup>‡</sup> Both complexes were found to adopt a slightly distorted octahedral



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omitted for the sake of clarity.

# (2b) CCDC 1986710 (2b) CCDC 1986710 (2b) CCDC 1986710 (2c) CCDC 1986710 (2c) CCDC 1986710 (2c) CCDC 1986711 (2c) CCDC 1986711

geometry with the pincer ligand occupying *meridional* configuration. In stark contrast to the structures of their phosphine analogues (**1b** and **1c**) which had the PPh<sub>3</sub> molecule *trans* to one of the chlorides,<sup>14</sup> the carbonyl ligand in both **2b** and **2c** are *trans* to pyridyl N and *cis* to both the chlorides. The crystallographic data and the selected bond parameters around the metal centre for both the complexes are provided in Table S1a and Table S1b respectively.

# Catalytic Activity of 2a–d Towards $\beta$ –Alkylation of Secondary Alcohols.

The initial optimization of the catalytic conditions was performed with **2b** (0.05 mol %) for the  $\beta$ -alkylation of 1-phenyl ethanol **5** with benzyl alcohol **4** in the presence of various base (Table 1, S2a) at 140 °C under solvent-free conditions. In the **2b** (0.05 mol %) catalyzed  $\beta$ -alkylation of **5** with **4**, bases (5 mol %) such as NaO<sup>t</sup>Bu, KO<sup>t</sup>Bu, NaOH and KOH

provided good yields with good selectivity towards the  $\beta$ -alkylated alcohol **7** (entries 1–4, Table S2a). Meteresting  $\beta$ ,  $\beta$  as a of sodium (5 mol %) to generate the base in-situ<sup>15a</sup> (prior to addition of 2b) also resulted in good yields of 7 (entry 5, Table S2a). Relatively poor reactivity was observed upon use of K<sub>2</sub>CO<sub>3</sub> and Na<sub>2</sub>CO<sub>3</sub> (entries 6 and 7, Table S2a). The total yield of products obtained with 2.5 mol % base loading was better than the yield obtained with a base loading of either 5 mol % or 10 mol % (Entry 8 vs. entries 2 & 9, Table S2a; entry 2 vs. entries 1 & 3, Table 1). The total yield of products increased upon lowering the loading of 2b to 0.025 mol % (entry 4, Table 1, entry 13, Table S2a). Notably, the  $\beta$ -alkylation did not proceed either in the absence of catalyst or in the absence of base (entries 14 and 15, Table S2a). The rest of the catalytic reactions were performed with 2.5 mol % NaOH as the total yield of products was better with selectivity towards 7 comparable to that obtained with KO<sup>t</sup>Bu. Upon further lowering the **2b** loading, the total yields were comparable (entries 5 and 6, Table 1). The apparent decrease in selectivity towards 7 at lower catalyst loadings (Entries 3-6, Table 1) is attributable to secondary dehydrogenation of 7 to 6 (vide infra). Gratifyingly, the turnovers (ca. 372000) observed with 0.00025 mol % of 2b is the highest reported yet with any ruthenium based catalytic systems. Among the other variants of the carbonyl complexes, while 2a (entry 11, Table 1) and 2c (entry 12, Table 1) gave slightly lower yields in comparison to 2b (entry 6, Table 1), the activity of 2d (entry 13, Table 1) was considerably lower. Similarly, among the corresponding PPh<sub>3</sub> analogues (1a–d), the complex 1d (entry 10, Table 1) performed poorly in comparison with (1a-c) (entries 7-9, Table 1).

| Table 1. Catal | ytic $\beta$ –Alkylation of        | 5 with 4 Under Varying Conditions. <sup>a</sup>                                   |                       |      |                    |           |                                       |
|----------------|------------------------------------|---|-----------------------|------|--------------------|-----------|---------------------------------------|
| (4)            | OH + (5)                           | Base (X Mol %), Catalyst (Y Mol %)<br>Open vessel, Ar atmosphere,<br>20 h, 140 °C | → (4 <sup>4</sup> ) + | (5') | (6)                |           | (7)                                   |
| Entry          | Catalyst<br>(Y Mol %) <sup>b</sup> | Base<br>(X Mol %) <sup>b</sup>  | % Yield <sup>c</sup>  |      | Total Yield<br>(%) | Total TON | <b>7</b> Selectivity <sup>d</sup> (%) |

| Entry | Catalyst            | Base      | % Yield <sup>c</sup> |    |    | Total Yield | Total TON | 7 Selectivity <sup>a</sup> (%) |    |
|-------|---------------------|-----------|----------------------|----|----|-------------|-----------|--------------------------------|----|
|       | (1 1007 %)*         |           | 4′                   | 5′ | 6  | 7           | _ (/0)    |                                |    |
| 1     | <b>2b</b> (0.05)    | NaOH, 5   | 0                    | 10 | 12 | 63          | 85        | 1700                           | 84 |
| 2     | <b>2b</b> (0.05)    | NaOH, 2.5 | 0                    | 7  | 7  | 79          | 93        | 1860                           | 91 |
| 3     | <b>2b</b> (0.05)    | NaOH, 10  | 0                    | 10 | 10 | 65          | 85        | 1700                           | 88 |
| 4     | <b>2b</b> (0.025)   | NaOH, 2.5 | 0                    | 14 | 13 | 70          | 97        | 3880                           | 84 |
| 5     | <b>2b</b> (0.0025)  | NaOH, 2.5 | 0                    | 16 | 16 | 63          | 99        | 39600                          | 79 |
| 6     | <b>2b</b> (0.00025) | NaOH, 2.5 | 0                    | 1  | 19 | 73          | 93        | 372000                         | 79 |
| 7     | <b>1a</b> (0.00025) | NaOH, 2.5 | 0                    | 2  | 7  | 78          | 87        | 348000                         | 92 |
| 8     | <b>1b</b> (0.00025) | NaOH, 2.5 | 0                    | 1  | 7  | 81          | 89        | 356000                         | 92 |
| 9     | <b>1c</b> (0.00025) | NaOH, 2.5 | 0                    | 2  | 9  | 75          | 86        | 344000                         | 89 |
| 10    | 1d (0.00025)        | NaOH, 2.5 | 0                    | 2  | 15 | 65          | 80        | 320000                         | 81 |
| 11    | <b>2a</b> (0.00025) | NaOH, 2.5 | 0                    | 1  | 10 | 78          | 89        | 356000                         | 88 |
| 12    | <b>2c</b> (0.00025) | NaOH, 2.5 | 0                    | 1  | 10 | 78          | 89        | 356000                         | 88 |
| 13    | <b>2d</b> (0.00025) | NaOH, 2.5 | 0                    | 2  | 3  | 57          | 62        | 248000                         | 95 |

<sup>a</sup>Reaction conditions: 4.14 mmol of **4**, 4.14 mmol of **5**, X mol % of base and Y mol % of pincer-ruthenium. <sup>b</sup>Mol % of base and catalyst is with respect to total alcohol content (**4+5**). <sup>c</sup>Yield is determined from <sup>1</sup>H NMR using toluene as external standard. <sup>d</sup>Selectivity = Yield of **7**/Total Yield.

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Figure 4 depicts the time course of the  $\beta$ -alkylation of **5** with **4** at different loadings of 2b. At a higher loading (0.025 mol %) of 2b, the absence of an initial build-up of 6 (Figure 4a) indicates that, the formation of 7 via 6 is very rapid (Scheme 3 and mechanistic studies vide infra). The observed growth of 6 in minor amounts actually occurs through a secondary dehydrogenation of 7 catalyzed by 2b at a stage when its activity eventually levels off (Figure 4a). Evidence to this understanding could be obtained by slowing down the  $\beta$ -alkylation (Figure 4b and S1c). Accordingly, in the reaction carried out with 0.0025 mol % 2b and 0.00025 mol % 2b, the formation of 6 was observed only after 3 h (Figure 4b) and 6 h (Figure S1c) of reaction respectively. Similar results were observed by Guelcemal in Ir(I) catalyzed reactions.<sup>6h</sup> This points to the fact that in the **2b** catalyzed  $\beta$ -alkylation of **5** with **4**, the hydrogenation and/or alcoholysis step leading to both 6 and 7 are very fast compared to dehydrogenation of 4 and 5 (Scheme 3 and mechanistic studies vide infra). This implies that the overall rate-determining step (RDS) is in the dehydrogenation segment (Scheme 3, Figure 5 and mechanistic studies vide infra).6h Nevertheless, the initial rate of catalysis was very high (10972 TOh $^{-1}$  and 12000 TOh $^{-1}$ ) at 0.0025 mol % and 0.00025 mol % loading of **2b** respectively (Figure 4b and S1c). Interestingly, according to the initial rate method, the plot of initial rate vs. [2b] was found to be linear indicative of the first order dependence of the rate of the reaction on the catalyst concentration (Figure S1d).

The most efficient catalyst **2b** was selected for  $\beta$ -alkylation of substituted 1-phenyl ethanols with various benzyl alcohols using 2.5 mol % NaOH at 140 °C (Table 2). Electron-donating groups such as methyl and methoxy either on benzyl alcohol or on 1-phenyl ethanol provided better yields of 7 (7b, 7c, 7i, 7k and 7q; Table 2). On the other hand, substrates with electron-withdrawing groups gave poor results (7a, 7g, 7j and 7r; Table 2). These observations indicate that the C-H bond breaking step ( $\beta$ -hydride elimination) is hampered by electron-withdrawing groups while being accelerated by electron-donating groups. This fortifies the fact that the overall RDS is present in the dehydrogenation segment (Scheme 3 and mechanistic studies vide infra). The  $\beta$ -alkylation of 1-phenyl ethanol with aliphatic alcohols (7n, 7o, 7p and 7s; Table 2) and primary alcohols containing heterocyclic groups (7d, 7e, 7f, 7l and 7m; Table 2) proceeded with lower efficiency.

Mechanism of  $\beta$ -Alkylation of Alcohols Catalyzed by 1 and 2. Recently, we have shown that benzaldehyde (4') is formed in the 1a catalyzed dehydrogenation of benzyl alcohol (4) along with the liberation of hydrogen (eq. 1, Scheme 2). $^{15a}$  The catalytic intermediates were also identified (Scheme 3a).15a Similarly, we could expect the formation of acetophenone (5') starting from 1-phenyl ethanol (5). Several studies including those of Kundu<sup>8d, e</sup> and Ding<sup>10a</sup> have shown that benzaldehyde reacts with acetophenone in the presence of base to give the  $\alpha,\beta$ -unsaturated ketone (6') (eq. 2, Scheme 2). The fact that we do not observe 6' indicates its fast transformation to product 7 via 6 which is catalyzed by the NNN pincer ruthenium catalysts (1a-f and 2a-f). These observations form the basis of our proposed mechanism (Scheme 3) using 2c as a model catalyst. The first step of the  $\beta$ -alkylation involves dissociation of either PPh<sub>3</sub><sup>15a</sup> from **1c** or CO<sup>15b-f</sup> from **2c** to generate the 16–electron five-coordinate dichloride species. In the presence of benzyl alcohol (4) and 1-phenyl ethanol (5), salt-metathesis of 16-electron five-coordinate dichloride species with KO<sup>t</sup>Bu results in the formation of **8** and **9** respectively.<sup>15a</sup> A  $\beta$ -hydride elimination to give either benzaldehyde (4') from 8 or acetophenone (5') from 9 results in formation of Ru-H species 12 via TSs 10 or 11. This is followed by a  $\sigma$ -bond metathesis between Ru–H of 12 and O–H of 4/5 as in TS 13/14 that results in liberation of  $\mathrm{H}_2$  along with the regeneration of the active species 8/9 (Scheme 3a). The formation of 4' and  $H_2$  in these reactions have been recently reported by us.15a

The benzaldehyde (4') and acetophenone (5') formed in the dehydrogenation segment react with each other in the presence of base to form the  $\alpha,\beta$ -unsaturated ketone (6') (eq. 2, Scheme 2). The C-C double bond in molecule 6' undergoes

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aReaction conditions: 4.14 mmol of 4, 4.14 mmol of 5, 0.207 mmol of NaOH and 20 µmol of 2b. bYield is determined from <sup>1</sup>H NMR using toluene as external standard <sup>c</sup>Selectivity = Yield of 7/Total Yield. <sup>d</sup>Reaction performed with 0.025 mol % of 2b

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an insertion into the Ru–H bond in **12** to generate the species **16** via TS **15** (Scheme 3b). Only the H<sup>-</sup> transfer to the  $\alpha$  carbon is considered owing to steric reasons. The product 6 formation step along with the generation of catalytically active species 12/8/9 could occur either by a  $\sigma$ -bond metathesis between Ru-C of 16 and O-H of 4/5 via TS 18/19 (alcoholysis) or by  $\sigma$ -bond metathesis between Ru–C of **16** and H–H while going through TS 17 (hydrogenation) (Scheme 3b). A similar hydrogenation and/or alcoholysis path can account for the transformation of 6 to 7 (Scheme 3c). Kinetic studies (Figure 4, vide supra) is indicative of a facile transformation of 6 to 7. Furthermore, kinetic studies performed on the transformation of pincer-ruthenium catalyzed upgradation of ethanol to butanol provide evidence for the proposed mechanism (Figure 6).



#### Quantum Mechanical Calculations on the NNN Pincer-Ruthenium (1,2) Catalyzed $\beta$ -Alkylation of Alcohols.

Additional mechanistic information was obtained from DFT studies by modelling the various transition states (TSs) and intermediates involved in the pincer-ruthenium (1, 2) catalyzed  $\beta$ -alkylation of **5** with **4** (Figure 5). The formation of benzaldehyde (4') and the Ru–H species 12 via a  $\beta$ -hydride elimination from 8 through TS 10 ( $\Delta G^{*}_{140}$  = 14.94 kcal/mol) is a thermodynamically downhill process ( $\Delta G_{140} = -4.56$  kcal/mol) (Blue lines, Figure 5a). Interestingly the corresponding formation of acetophenone (5') is also downhill ( $\Delta G_{140} = -6.59$ kcal/mol) but with a higher barrier (TS:11,  $\Delta G_{140}^* = 21.71$ kcal/mol) (Magenta lines, Figure 5a). The steps involving the  $\sigma$ -bond metathesis of Ru–H in **12** with the O–H of **4** (Blue lines, Figure 5a) and with the O-H of 5 (Magenta lines, Figure 5a) are uphill ( $\Delta G_{140}$  = 3.03 and 2.08 kcal/mol respectively) with almost similar barriers (TS:13,  $\Delta G^{*}_{140}$  = 21.55 kcal/mol and TS:14,  $\Delta G^{*}_{140}$ = 20.97 kcal/mol). For the dehydrogenation segment, the  $\beta$ -hydride elimination step involving the extrusion of acetophenone (5') is the rate determining step (RDS).

The insertion of the double bond in the  $\alpha,\beta$ -unsaturated ketone (6') into the Ru-H in 12 to give species 16 via TS 15 is slightly uphill ( $\Delta G_{140}$  = 1.60 kcal/mol) with a barrier of 12.23 kcal/mol. In comparison to the alcoholysis step (brown lines, Figure 5b), the hydrogenation step (purple lines, Figure 5b) is more favorable as it is not only more downhill by 3.5 kcal/mol but also has lower barrier (TS:17,  $\Delta G^{+}_{140}$  = 16.54 kcal/mol). Thus, in the



Scheme 3. Plausible mechanism involved in the 2 catalyzed  $\beta$ -Alkylation of 1-phenyl ethanol with benzyl alcohols.

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Figure 5. Relative free energies (140 °C) of intermediates involved in pincer-ruthenium catalyzed (a) dehydrogenation of 4/5 (b) transformation of 6' to 6 and (c) conversion of 6 to 7.

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transformation of **6'** to **6**, the hydrogenation\_vistep.ic.is\_the preferred pathway and it is the RDS. DOI: 10.1039/DOCY01679A The first step in the conversion of **6** to **7** that involves the insertion of the carbonyl group of **6** into Ru–H in **12'** (Figure 5c) is a thermodynamically downhill process ( $\Delta G_{140} = -21.12$ kcal/mol) and proceeds with a low barrier (TS:**20**,  $\Delta G^{+}_{140} = 5.15$ kcal/mol). The alcoholysis step (brown lines, Figure 5c) is more favored than the hydrogenation step (purple lines, Figure 5c) owing to its lower barrier (TS:**23**,  $\Delta G^{+}_{140} = 4.70$  kcal/mol). The insertion of **6** into the Ru–H bond in **12'** is the RDS for the conversion of **6** to **7**. For the **1** and **2** catalyzed  $\beta$ -alkylation, the  $\beta$ -hydride elimination step involving the extrusion of **5'** is the overall RDS. This satisfactorily explains the absence of **6** during the initial time in the  $\beta$ -alkylation (Figure 4b and S1c).

# Application of NNN–Pincer Catalyzed $\beta$ –Alkylation of Alcohols towards Upgradation of Ethanol.

The fast depleting fossil fuels in combination with the ever-increasing energy demand has triggered an intense pursuit for alternative energy sources.<sup>16</sup> In comparison to conventional gasoline, ethanol is widely accepted to be a sustainable fuel.<sup>17</sup> However, use of ethanol has several drawbacks, as it has poor energy density (70% with respect to gasoline),<sup>16b, 17a, 18</sup> it is corrosive in nature towards engines<sup>19</sup> and has higher water absorptivity.<sup>18a, 20</sup> These limitations can be circumvented by the use of butanol, which not only has a higher energy density (86%), but also is non-corrosive while being immiscible in water.<sup>19, 21</sup> Not surprisingly, the Guerbet reaction<sup>22</sup> that involves the transformation of bio-ethanol to butanol has been widely explored.<sup>23</sup> Heterogeneous catalysts often require harsh conditions and suffer from selectivity issues.<sup>24</sup> However, these methods that upgrade ethanol to either butanol or higher analogues with higher energy density<sup>18b</sup> are a subject of great interest.

The last decade has witnessed development of several homogenous catalysts for Guerbet reaction. In 2009, Ishii reported that [Ir(COD)(acac)]/dppp complex catalyzes the ethanol to butanol transformation in presence of 1,5-cyclooctadiene.<sup>25</sup> Notably, the higher butanol selectivity (up to 67%) could be obtained by use of [Ir(COD)(acac)]/dppb in the presence of sodium ethoxide. In 2015, Jones group have reported a bifunctional catalytic system comprising of iridium and a base comprising of a nickel/copper complex for the upgradation of ethanol.<sup>26b</sup> Wass and co-workers have reported that the use of trans-[RuCl2(dppm)2] in presence sodium ethoxide (5 mol %), resulted in 1300 TONs with 91% selectivity towards the *n*-butanol formation.<sup>23b</sup> The same group has demonstrated ruthenium  $\eta^6$ -complex with varying bidentate ligands to obtain high selectivity (99%) at 98 TONs. At the highest productivity (314 TON) of *n*-butanol, the selectivity drops to 93%.<sup>23c</sup>

Szymczak reported a NNN–Ru pincer catalyst for butanol formation at an ethanol conversion of 53% with 78% selectivity towards *n*–butanol (TON 530).<sup>23a</sup> Milstein and co–workers investigated PNP-Ru complexes for the Guerbet reaction, which converted 73.4% ethanol (ca. 18000 TONs) to the product.<sup>26</sup> Recently, Liu developed a highly efficient (114120 TONs) PNP–



Table 3. The Upgradation of Ethanol (4v) to n-Butanol (4p) Catalyzed by Phosphine-Free

manganese pincer to upgrade ethanol to higher alcohol in the presence of NaOEt.<sup>27</sup> Using the same complex but an arrivation of NaOEt loading, the Jones group demonstrated a drop in catalytic activity (145 TONs).<sup>27</sup> In this context, we wished to investigate the catalysts (**1a–f** and **2a–f**) towards upgradation of ethanol to *n*–butanol.

The lower reactivity (Table 2) of aliphatic alcohols towards catalytic  $\beta$ -alkylation prompted us to revisit optimization conditions for the upgradation of ethanol using **2b** (Table S2c) at 140 °C. In the **2b** (0.05 mol %) catalyzed reactions, very high turnovers (ca. 335, entry 14, Table S2c) were obtained with 90% selectivity towards *n*-butanol after 24 h using a protocol following our recent approach<sup>15a</sup> of generating the base *in-situ*, where 10 mol % Na was used to generate 10 mol % NaOEt (prior to **2b** addition). Upon continuing the reaction to 48 h, the productivity was further enhanced with no loss of selectivity (entry 15, Table S2c). This condition was used for further optimization with various catalysts (Table 3, Figure S57–S68).

Table 4. The Upgradation of Ethanol (4v) to  $\mathit{n}-\text{Butanol}$  (4p) Catalyzed by Varying Amounts of  $2e.^{\,\text{a}}$ 

| OH         NaOEt (10 Mol %),<br>2e (Y Mol %),<br>Closed vessel,<br>(4v)         (4o)         (4o)           (4v)         Ar atmosphere,<br>th, 140 °C,         (4p)         (4o') | + (4n)<br>+ (4n')<br>(4n')              |
|---|---|
| Entry Catalyst Time (h) Butar   | nol Total                               |
| Selectiv  | vity <sup>[b]</sup> TONs <sup>[b]</sup> |
| 1 0.025 0.5 989   | % 336                                   |
| 72 709  | % 2100                                  |
| 2 0.035 0.5 909   | % 165                                   |
| 72 659  | % 1670                                  |
| 3 0.05 0.5 859  | % 355                                   |
| 72 809  | % 975                                   |
| 4 0.075 0.5 959   | % 255                                   |
| 72 709  | % 737                                   |
| 5 0.1 0.5 989   | % 223                                   |
| 72 759  | % 582                                   |

<sup>a</sup>Reaction conditions: 8.56 mmol of ethanol, 0.86 mmol of base and 0.05 mol % of **2e**. <sup>b</sup>Selectivity and TON were calculated by GC analysis using toluene as an internal standard.

The ethanol upgradation was first tested for a series of NNN pincer–ruthenium complexes containing PPh<sub>3</sub> ancillary ligands (entry 1–6, Table 3, Figure S57–S62). Among **(1a–1f)**, while the catalyst **1e** exhibited the highest (3.1 folds) productivity (1115 TONs after 72 h, entry 5, Table 3), the *N*–methyl analogue **1f** demonstrated the highest rate (ca. 840 TOh<sup>-1</sup>). The phosphine–free complexes **(2a–f)** were also tested as catalysts for the Guerbet reaction (entry 7–12, Table 3, Figure S63–S68). In comparison to **1a** and **1b**, their phosphine–free counterparts **2a** and **2b** exhibited a better rate towards the ethanol upgradation reaction (entries 7 and 8, Table 3). The rate of ethanol upgradation catalyzed by **2c** and **2d** were comparable (entries 9 and 10, Table 3) and about 1.3–1.5 times slower that **2a** and **2b**. The rate of **2f** catalyzed (entry 12, Table 3) Guerbet

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Pincer-Ruthenium Complexes.<sup>a</sup>

<sup>&</sup>lt;sup>a</sup> Reaction conditions: 8.56 mmol of ethanol, 0.86 mmol of base and 0.05 mol % of **2**. <sup>b</sup>Calculated by GC analysis using toluene as an internal standard.

reaction was two folds faster than that catalyzed by **2c** and **2d**. Among all the catalysts screened, the catalyst **2e** demonstrated not only very good rate (ca. 710 TOh<sup>-1</sup>) but also high productivity (975 TONs at 49% ethanol conversion) (entry 11, Table 3). Hence, further exploration involving the variation of catalyst loading for Guerbet reaction was carried out using the phosphine–free catalyst **2e** (Table 4).



Figure 6. Plot depicting the (a) initial rate vs. [2e] and (b) initial rate vs. [Ethanol].

The highest rate (ca. 710 TOh<sup>-1</sup>) was obtained in 0.05 mol % **2e** catalyzed reaction (entry 3, Table 4). While the highest turnovers (ca. 2100) were obtained at 0.025 mol % loading of **2e** (entry 1, Table 4), the highest conversion (ca. 58%) of ethanol to products was obtained upon use of either 0.035 mol % (entry 2, Table 4) or 0.1 mol % (entry 5, Table 4) of **2e**. Kinetic experiments were carried out on the Guerbet reaction catalyzed by **2e** at 140 °C at varying catalyst loading (Figure S69–S73) and varying ethanol concentration (Figure S74–S77). With the aid of initial rate method, it was observed that the plot of initial rate vs. [**2e**] (Figure 6a) and initial rate vs. [ethanol]

(Figure 6b) was linear. This points to the first order dependence of rate on concentration of both **2e** and ethalion **3** (Sinital first order dependence on [**2b**] was observed for the  $\beta$ -alkylation of **5** (Figure S1d). Not surprisingly these observations indicate the involvement of a mechanistic path as depicted in Scheme 3 with a rate = ( $k_2$ )[( $i^{pr2}$ NNN)RuCIH][EtOH] (equation (1), Scheme S1).

### Conclusions

We report here the synthesis and characterization of a series of phosphine-free NNN pincer-ruthenium carbonyl complexes based on bis(imino)pyridine and 2,6-bis(benzimidazole-2-yl) pyridine ligands. These complexes have been utilized with great success to execute the catalytic alkylation of alcohols under solvent–free conditions. For the  $\beta$ –alkylation of 1–phenyl ethanol with benzyl alcohol at 140 °C, (<sup>Cy2</sup>NNN)RuCl<sub>2</sub>(CO) (0.00025 mol %) in combination with NaOH (2.5 mol %) was found to be the most efficient among the considered catalysts. Gratifyingly, at such a low loading of the catalyst and the base, the  $\beta$ -alkylated product was obtained in high yield (ca. 93%, 372000 TONs at 12000 TOh<sup>-1</sup>) after 20 h. A variety of alcohol combinations could be  $\beta$ -alkylated by employing this catalytic system. Unprecedented activities (380000 TONs at 19000 TOh<sup>-1</sup>) were observed for the  $\beta$ -alkylation of 1–phenyl ethanol with 3-methoxy benzyl alcohol. Hitherto, this is the highest reported rate and turnovers for a ruthenium based catalyst.

Mechanistic studies provide key information about the presence of the overall rate determining step (RDS) in the dehydrogenation segment. Complementary evidence was obtained from DFT studies that indicate the  $\beta$ -hydride elimination step involving the extrusion of acetophenone is the overall RDS. While the hydrogenation step is favored for the formation of  $\alpha$ -alkylated ketone, the alcoholysis step is preferred for the formation of  $\beta$ -alkylated product.

The catalytic  $\beta$ -alkylation protocol was applied to investigate the upgradation of ethanol to biofuels such as butanol and higher alcohols. Use of (Cy2NNN)RuCl<sub>2</sub>(CO) resulted in high productivity (335 TONs at 170 TOh<sup>-1</sup>) among the pincer-ruthenium carbonyl complexes based on bis(imino)pyridine ligands. By employing sterically more open pincer-ruthenium carbonyl complexes such as and (MeBim2NNN)RuCl<sub>2</sub>(CO) (<sup>Bim2</sup>NNN)RuCl<sub>2</sub>(CO) based on 2,6-bis(benzimidazole-2-yl) pyridine ligands, the catalytic activity was greatly enhanced. It is gratifying to note that we have arrived at conditions that give not only good ethanol conversion (ca. 58%) but also high turnovers (ca. 2100) with a good rate (ca. 710 TOh<sup>-1</sup>) in the (Bim2NNN)RuCl<sub>2</sub>(CO) catalyzed upgradation of ethanol. Kinetic studies on the ethanol upgradation catalyzed by (Bim2NNN)RuCl2(CO) exhibit linear dependence of rate on the concentration of both catalyst and ethanol which is in strong agreement with the DFT studies.

### Conflicts of interest

There are no conflicts to declare.

### ARTICLE

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## Notes and references

**‡** CCDC 1986710 and 1986711 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <a href="http://www.ccdc..cam.ac.uk/structures">http://www.ccdc..cam.ac.uk/structures</a>.

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phosphine-free pincer-ruthenium catalysts at a very low base loading. Kinetic 'studies and DFT calculations were found to be complementary and provide a clear understanding on the mechanism.

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