

Communication

Highly Efficient *N*-Heterocyclic Carbene/Ruthenium Catalytic Systems for the Acceptorless Dehydrogenation of Alcohols to Carboxylic Acids: Effects of Ancillary and Additional Ligands

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Abstract: The transition-metal-catalyzed alcohol dehydrogenation to carboxylic acids has been identified as an atom-economical and attractive process. Among various catalytic systems, Ru-based systems have been the most accessed and investigated ones. With our growing interest in the discovery of new Ru catalysts comprising *N*-heterocyclic carbene (NHC) ligands for the dehydrogenative reactions of alcohols, we designed and prepared five NHC/Ru complexes ([Ru]-1–[Ru]-5) bearing different ancillary NHC ligands. Moreover, the effects of ancillary and additional ligands on the alcohol dehydrogenation with KOH were thoroughly explored, followed by the screening of other parameters. Accordingly, a highly active catalytic system, which is composed of [Ru]-5 combined with an additional NHC precursor L5, was discovered, affording a variety of acid products in a highly efficient manner. Gratifyingly, an extremely low Ru loading (125 ppm) and the maximum TOF value until now (4800) were obtained.

Keywords: ruthenium (Ru); *N*-heterocyclic carbenes (NHCs); carboxylic acids; ancillary ligands; additional ligands

1. Introduction

Direct conversion of primary alcohols into carboxylic acids is a representative organic transformation [1,2]. The traditional way to access carboxylic acids is the direct oxidation of primary alcohols [3]. However, this method usually requires toxic or strong oxidants and produces large amounts of by-products [4–6]. Even though oxygen is occasionally utilized as an oxidant [7–17], explosive mixtures may be formed and oxygen-sensitive substrates are not compatible. Therefore, green and sustainable alternatives for the production of various carboxylic acids are still in high demand. In recent years, a catalytic process in which various carboxylic acids could be afforded via alcohol dehydrogenation has been developed. Notably, this is a sustainable and atom-economical

reaction, which releases dihydrogen gas as the sole byproduct. Originally, Grützmacher et al. pioneered this catalytic process by utilizing a hydrogen acceptor [18]. Later, they reported several other hydrogen acceptors for this transformation [19,20]. A major breakthrough in this area was accomplished by Milstein et al. who achieved this catalysis in an acceptorless manner [21]. With 0.2 mol % of a pincer-type Ru complex, several carboxylic acids were synthesized from the respective primary alcohols in an aqueous NaOH solution. Afterward, other research groups also reported efficient catalytic systems, including Ru- [22–34], Rh- [35], Pd- [36], Ir- [37–39], Ag- [40], Fe- [41], Mn- [41,42], and Zn-based [43] catalytic systems, for this dehydrogenation. In particular, Ru systems with catalyst loadings ranging from 250 ppm to 5.0 mol % have been most accessed.

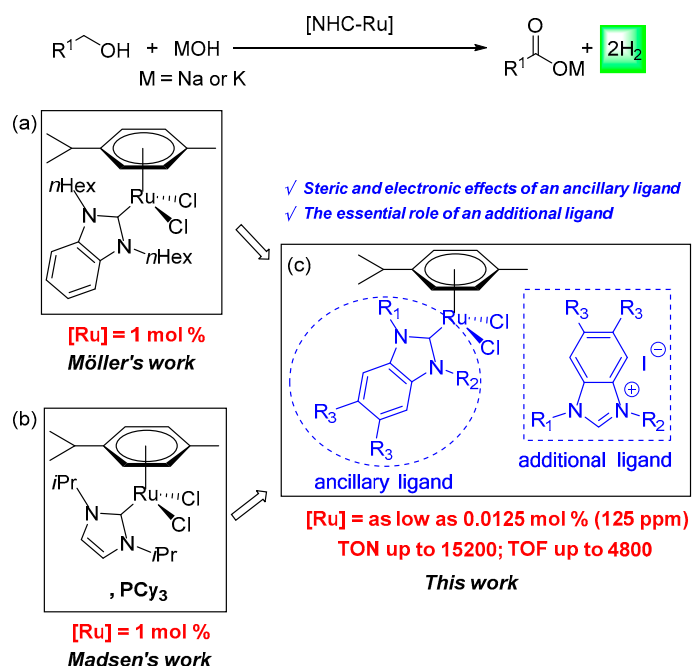


Figure 1. The design strategy (a) Möller's work; (b) Madsen's work; (c) this work. Note: NHC = N-heterocyclic carbene, TON = turnover number, TOF = turnover frequency.

In practice, ancillary ligands are pivotal for the catalytic activity and stability of organometallic complexes. The steric and electronic profiles also play a central role in tweaking their properties, as well as their catalytic performance [44]. N-Heterocyclic carbenes (NHCs) have evolved as ideal ligands for numerous metal catalysts, as their steric and electronic parameters could be easily modified to achieve the optimized properties required for efficient catalysis [45–50]. Hence, two monodentate NHC/Ru complexes were developed for this reaction. In 2014, Möller et al. reported a benzimidazole-based arene/Ru/NHC complex (as shown in Figure 1a), affording plenty of carboxylic acids applying 1 mol % of this Ru complex [23]. Later, an imidazole-derived NHC/Ru complex was also prepared, leading to satisfactory results with 1 mol % of the NHC/Ru complex combined with PCy₃ as an additional ligand (Figure 1b) [26]. Despite these examples, the discovery of new and highly efficient NHC/Ru catalytic systems for this catalytic process is still of vital significance. Therefore, elucidating the steric and electronic effects of the ancillary NHC ligands is invaluable for the design and discovery of new efficient catalysts. Herein, we aimed to prepare several NHC/Ru complexes incorporating varied NHC ligands to explore the influence of steric/electronic changes to the ligands on the acceptorless conversion of alcohols into carboxylic acids (as shown in Figure 1c). On the other hand, inspired by our previous work in which the involvement of an additional NHC ligand considerably enhanced the catalytic potency for the dehydrogenative alcohol amidation to amides [51], we therefore evaluated the effects of an additional ligand on the catalytic performance (Figure 1c). Gratifyingly, an optimized catalytic

system that demonstrated outstanding efficiency was discovered through extensive optimization. Notably, a catalyst loading of 125 ppm was applied for most substrates. Moreover, the maximum turnover number (TON) of 15,200 and the highest turnover frequency (TOF) of 4800 were attained. It is noteworthy that the catalyst loading (125 ppm) and maximum TOF value (4800) are superior over all reported catalytic systems (Tables S1 and S2, Supplementary Materials).

2. Results and Discussion

[Ru]-1, an NHC/Ru complex from our previous work [51], was synthesized first, and four other NHC/Ru complexes ([Ru]-2–[Ru]-5) bearing distinct backbone and wingtip substituents on the NHC ligands were prepared for comparative studies (Figure 2). The structures of [Ru]-3–[Ru]-5 (three new NHC/Ru complexes) were further identified with X-ray crystallography (Figure 3). The catalytic activity of the above five complexes was then assessed at different temperatures. A typical catalytic reaction using benzyl alcohol (**1a**) and KOH as reactants was selected, while 0.1 mol % of an NHC/Ru complex and a reaction time of 12 h were fixed (as shown in Figure 2). It appeared that all the complexes showed relatively high activity at 120 and 145 °C, but significantly lower activity at 100 and 165 °C. Presumably, the relatively low temperature of 100 °C was insufficient to efficiently promote this catalysis, and these complexes and the generated key catalytic intermediates may not be very stable at the high temperature of 165 °C. To probe the steric effects of the NHC ligands, we compared the activity of [Ru]-1–[Ru]-3 at various temperatures. It was observed that [Ru]-1 and [Ru]-2 displayed analogous activity, whereas a drop in activity was observed for [Ru]-3 at almost all temperatures. The results implied that a sterically encumbering *i*Pr group in the N-terminus of [Ru]-3 was probably detrimental to the catalytic dehydrogenation. Furthermore, [Ru]-1, [Ru]-4, and [Ru]-5 were presented to explore the electronic effects of NHC ligands. In comparison with [Ru]-1, [Ru]-4 (with two methyl groups on the backbone of the benzimidazole framework) exhibited comparable or marginally reduced activity. Interestingly, [Ru]-5, which bears an electron-deficient NHC ligand, triggered remarkably improved activity compared to [Ru]-1 and [Ru]-4. It is also worth mentioning that [Ru]-5 could generate acid **2a** in 85% yield at 120 °C, which was substantially higher than the other two complexes at the same temperature. All these facts allowed us to assume that the electron-deficient nature of [Ru]-5 could probably facilitate the catalytic cycle in a faster manner, and thus [Ru]-5 was selected as the optimal NHC/Ru complex, and toluene at 120 °C was retained for the following experiments.

After selecting the optimal NHC/Ru complex for this reaction, we explored the impact of an additional ligand (**L5**) on this catalysis (as illustrated in Figure 4). It was worth noting that a suspension of [Ru]-5, **L5**, KOH, and dry toluene were heated at 120 °C for 0.5 h. After **1a** was added to the reaction mixture, heating was then continued for another 12 h. When the Ru loading was changed from 500 to 250, 125, and 100 ppm, the yield of **2a** dramatically deteriorated from 52% to 15%. To our delight, introducing **L5** into the catalytic system resulted in enhanced catalytic performance at all catalyst loadings, consistent with our previous observation for the NHC/Ru-catalyzed dehydrogenative alcohol amidation to amides [51]. As the ratio of **L5**/[Ru]-5 gradually increased, the yield of **2a** increased up to a 4:1 ratio. Therefore, the optimized ratio of **L5**/[Ru]-5 was identified as 4:1. At relatively high Ru loadings (500 and 250 ppm), more than 90% of **2a** could be achieved in the end. With regard to 125 and 100 ppm of [Ru]-5, maximum yield of 75% and 68% was obtained, respectively. From the perspectives of both catalytic loadings and the yield of **2a**, 125 ppm (equal to 0.0125 mol %) of [Ru]-5 was finally chosen for further investigations.

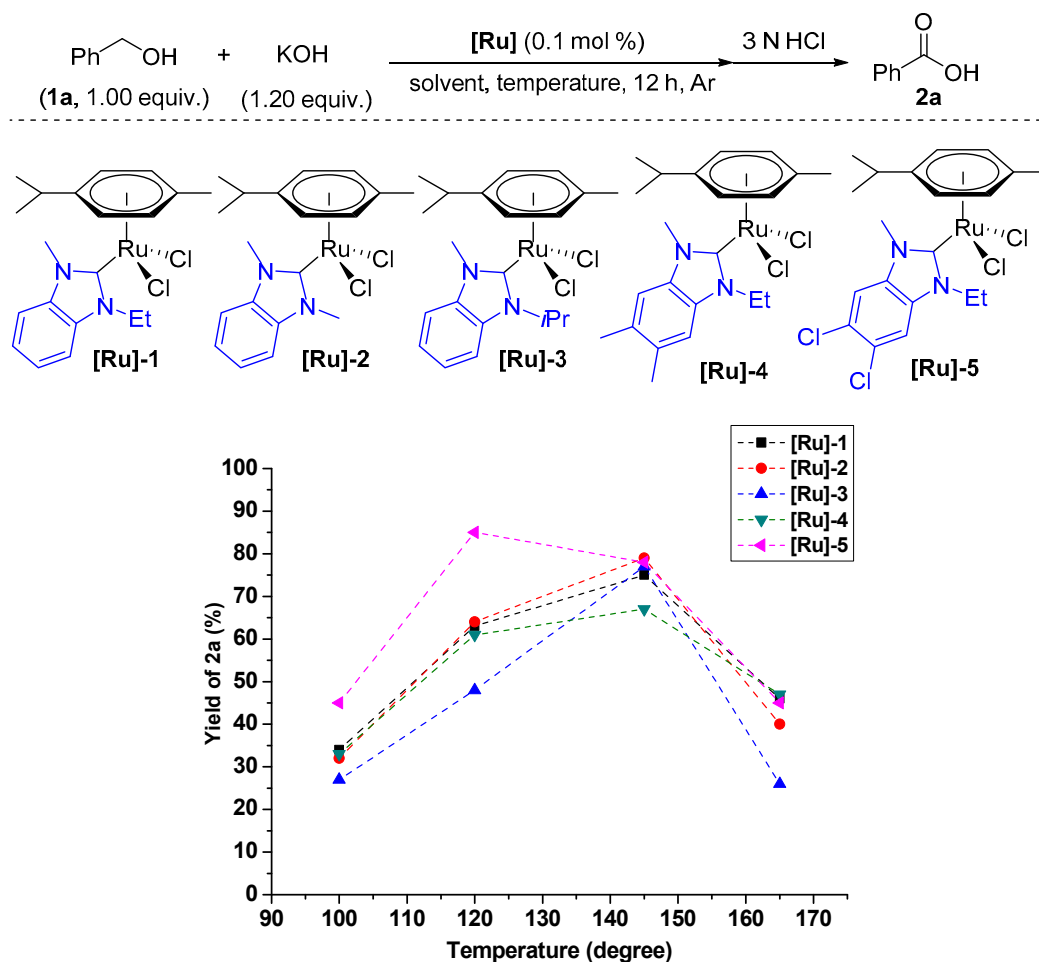


Figure 2. Effects of ancillary ligands on the catalytic activity of **[Ru]-1**–**[Ru]-5** under different temperatures. Note: The solvents used for the experiments were toluene (for 100 °C), toluene (for 120 °C), *m*-xylene (for 145 °C), and mesitylene (for 165 °C).

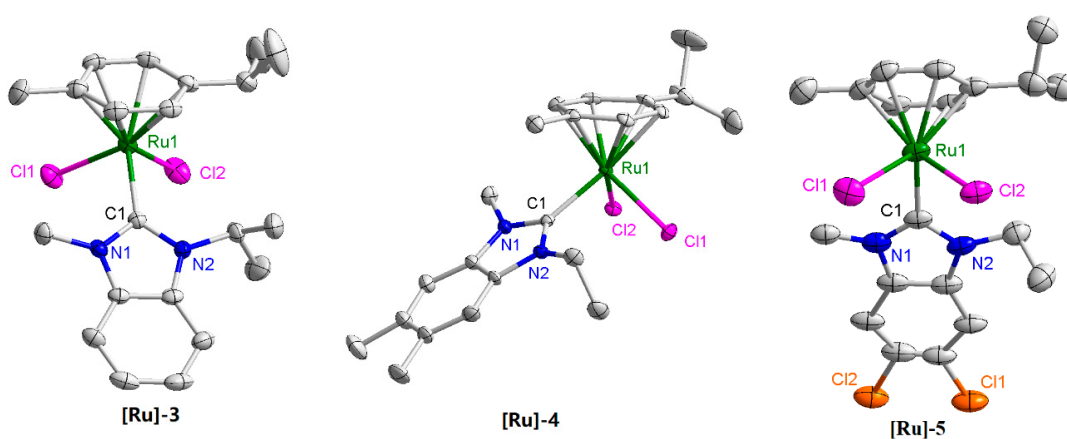


Figure 3. The molecular structures of complexes **[Ru]-3**–**[Ru]-5**, showing the atom labeling scheme of carbon atoms C1 and the heteroatoms. The hydrogen atoms and solvent molecules were omitted for clarity, and the ellipsoids of atoms were shown at probability levels of 30% for **[Ru]-3**–**[Ru]-4** and 20% for **[Ru]-5**.

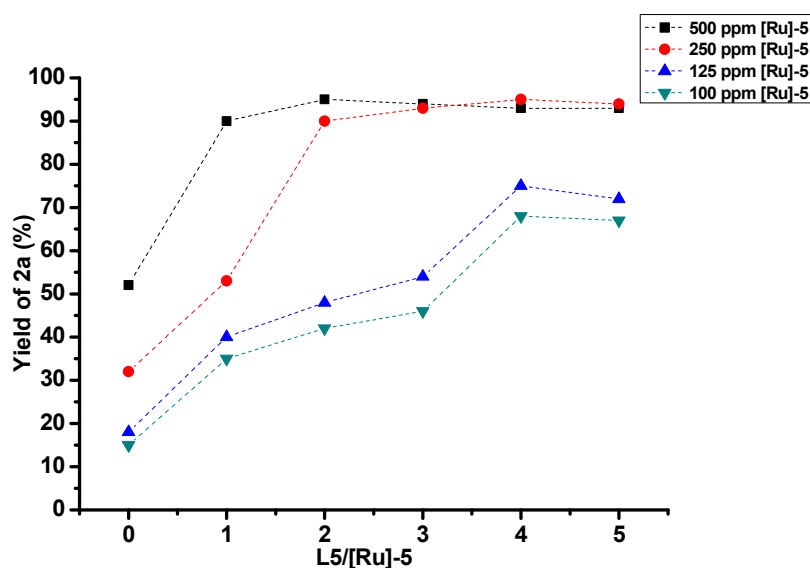


Figure 4. Effects of an additional ligand (L5) on the catalytic activity at different catalyst loadings.

Intending to further increase the yield of **2a**, we continued to optimize other parameters (Table 1). As already discussed above, [Ru]-5 alone gave 18% of **2a**, with the majority of **1a** remaining (entry 1). Nevertheless, introducing an additional amount of L5 (the ratio of L5/[Ru]-5 was optimized as 4:1) imparted a markedly improved yield of **2a** (entry 2). Afterwards, it was expected that pre-heating [Ru]-5, L5, and KOH in toluene at 120 °C for different periods could affect the efficiency of this catalysis. If everything was added simultaneously, only 18% of product **2a** and 78% of unreacted **1a** were detected (entry 3). However, the catalytic performance varied, with the pre-heating time spanning from 0.5 to 2.5 h (entries 2, 4–7), with 1.5 h as the optimum time (entry 5). Moreover, the volume of toluene was noticed to influence the reaction (entries 5, 8, 9). Either a larger or smaller amount of toluene prompted slightly lower yield of **2a** and conversion (entries 8–9). It was found that a catalytic amount of L5 alone, or no catalyst, gave rise to only trace amounts of **2a**, which demonstrated the essential role of Ru in this catalysis (entry 10–11). Finally, the Ru loading was decreased to 0.0025 mol % to obtain the maximum TON and TOF values, leading to a TOF of 4800 after 1 h and a TON of 15,200 after 36 h (entries 12–13). Therefore, the optimized conditions, recognized as 0.0125 mol % (equal to 125 ppm) of [Ru]-5, 0.05 mol % (equal to 500 ppm) of L5, 1.00 equiv. of **1a**, and 1.20 equiv. of KOH in dry toluene at 120 °C (as listed in entry 5 of Table 1), were finalized.

Furthermore, we decided to thoroughly explore the substrate tolerance of our catalytic system (Figure 5). At the outset, several substituted benzyl alcohols were attempted. Under the optimized conditions, substrates containing electron-donating groups reacted smoothly with KOH to yield the respective acids (**2b–2d**) in excellent yield. In contrast, electron-deficient alcohols **1e–1g** produced acids **2e–2g** in moderate yield at a higher Ru loading (250 ppm of [Ru]-5 combined with 1000 ppm of L5). Similar to our previous observation [33], the desired product **2e** and the reduced by-product **2a** were detected for the reaction of 4-chlorobenzyl alcohol (**1e**) and KOH. Moreover, it seemed that the positions of the substituents on the phenyl group had a considerable impact on the product yield. 3-Methylbenzoic acid (**2h**) was assembled from 3-methylbenzyl alcohol (**1h**) in 80% yield, whereas 2-methylbenzyl alcohol (**1i**) generated product **2i** in moderate yield even if a higher catalyst loading and longer reaction time were used. Additionally, substrates bearing a naphthyl group or a sulfur atom (**1j** and **1k**) were also tolerated. With the exception of aromatic carboxylic acids, a handful of aliphatic carboxylic acids were prepared utilizing this NHC/Ru-catalyzed protocol, although a longer period was generally required to secure full conversion. Sterically non-hindered alcohols such as 1-hexanol (**1l**), cyclohexylmethanol (**1m**), and 3-phenylpropan-1-ol (**1n**) were efficiently converted to carboxylic acids **2l–2n** in 88%–95% yield after 24 h. In addition, heterocycle-containing substrate **1o**

afforded acid **2o** in 56% yield. In terms of hex-5-en-1-ol (**1p**) which comprises a terminal C=C bond, 74% of product **2p**, 6% of isomerized by-product **2q**, as well as 16% of reduced by-product **2l** were obtained. Nevertheless, the alcohol containing an internal C=C bond was exclusively transformed into the desired acid (**2q**), without the observation of the isomerized and reduced byproducts. Finally, amino alcohols **1r–1s** reacted well with KOH to furnish amino acids **2r–2s** in a 65%–78% yield.

Table 1. Optimization of other reaction parameters ^a.

$ \begin{array}{c} \text{Ph-CH}_2\text{-OH} \\ \text{(1a, 1.00 equiv.)} \xrightarrow[\text{toluene, 120 } ^\circ\text{C, n h, Ar}]{\text{toluene, 120 } ^\circ\text{C, m h, Ar}} \xrightarrow{3 \text{ N HCl}} \text{Ph-COOH} \\ \text{2a} \end{array} $								
$ \begin{array}{c} \text{[Ru]-5 (x mol \%)} \\ \text{L5 (y mol \%)} \\ \text{KOH (1.20 equiv.)} \end{array} $								
Entry	x	y	m	n	Yield (%) ^b		TONs for 2a	TOFs for 2a
					2a	Unreacted 1a		
1	0.0125	0	0.5	12	18	80	1440	120
2	0.0125	0.05	0.5	12	75	23	6000	500
3	0.0125	0.05	0	12	18	78	1440	120
4	0.0125	0.05	1.0	12	86	11	6880	573
5	0.0125	0.05	1.5	12	94	3	7520	627
6	0.0125	0.05	2.0	12	92	5	7360	613
7	0.0125	0.05	2.5	12	89	8	7120	593
8 ^c	0.0125	0.05	1.5	12	85	13	6800	567
9 ^d	0.0125	0.05	1.5	12	91	8	7280	607
10	0	0.05	1.5	12	trace	91	-	-
11	0	0	1.5	12	trace	92	-	-
12	0.0025	0.01	1.5	1	12	87	4800	4800
13	0.0025	0.01	1.5	36	38	59	15,200	422

^a (1) A suspension of [Ru]-5 (x mol %), L5 (y mol %), KOH (1.20 equiv.), and dry toluene (2.0 mL) was stirred at 120 °C for m hours; (2) **1a** (1.00 equiv.) was added and the mixture was stirred at 120 °C for n hours; (3) 3N HCl aqueous solution was added. ^b NMR yield (average of two consistent runs) using 1,3,5-trimethoxybenzene as an internal standard. ^c Dry toluene (1.0 mL). ^d Dry toluene (4.0 mL). Note: TONs = turnover numbers, TOFs = turnover frequencies.

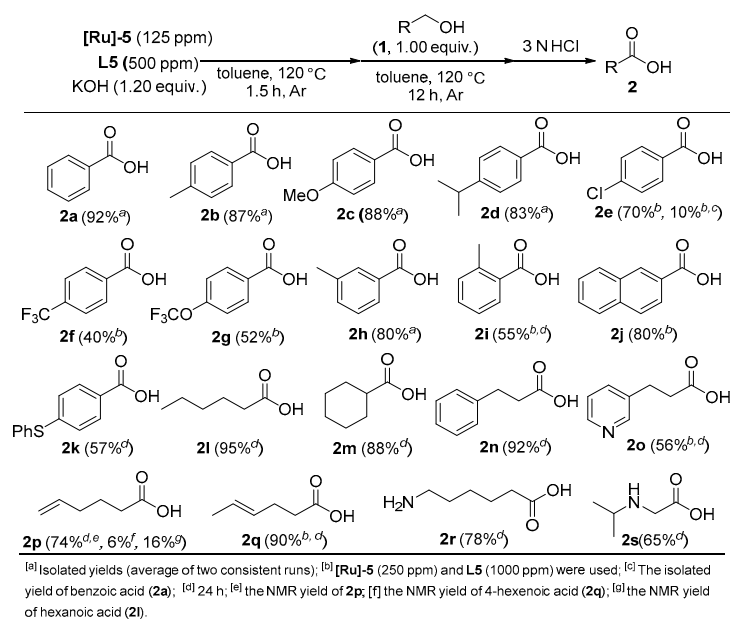


Figure 5. Synthesis of carboxylic acids from various alcohols and KOH catalyzed by [Ru]-5 combined with L5.

To probe the nature of the active species in this study, further investigations were carried out. Catalyst poisoning experiments were first conducted by the mercury test (as listed in Table S3, Supplementary Materials). It appeared that metallic mercury had almost no impact on the activity of our optimized catalytic system (entries 2–4 vs. entry 1), demonstrating the homogeneous nature of the real catalyst. Since the generation of Ru hydride species was reported to be crucial for the NHC/Ru-catalyzed dehydrogenative coupling of alcohols with amines or hydroxides [33,51–56], Ru hydride formation was monitored by two NMR reactions utilizing **[Ru]-5** with and without **L5**, respectively (Figures S1 and S2, Supplementary Materials). These results implied that Ru-hydride species were involved in the reactions and probably paramount in the catalytic cycle. From the above contents and the previous reports about NHC/Ru-catalyzed alcohol dehydrogenation to acids [26,33], a plausible mechanism including various NHC/Ru species was presented (Figure 6). A refluxing mixture of **[Ru]-5**, **L5**, KOH, and toluene resulted in NHC/Ru species **I**, which could undergo ligand exchange to provide intermediate **II**. It is expected that the electron-deficient NHC ligand in **[Ru]-5** promotes this step faster than other NHC ligands [54], consistent with our experimental results. After the formation of intermediate **II**, an analogous pathway was proposed with our previous publication [33].

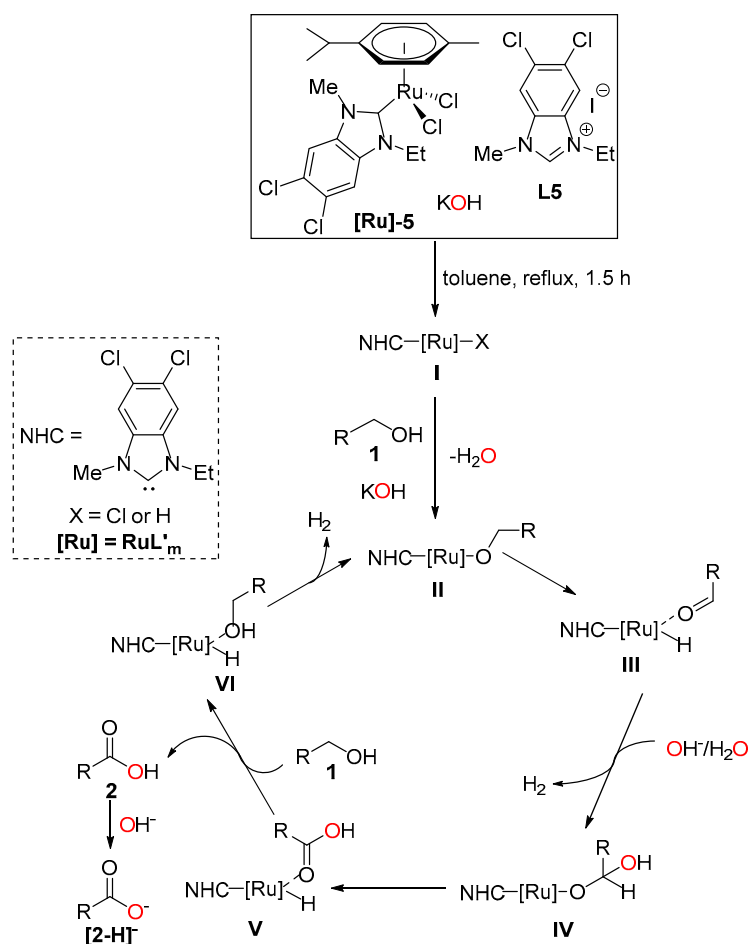


Figure 6. The plausible mechanism for this **[Ru]-5/L5**-catalyzed acid synthesis from alcohols and KOH.

3. Experimental Section

3.1. General Considerations

Most operations were done inside a glovebox, while most catalytic reactions were performed utilizing the standard Schlenk techniques. ^1H NMR spectra were recorded on a Bruker Avance 500 spectrometer (Billerica, MA, USA) in CDCl_3 , $\text{DMSO}-d_6$, or D_2O with/without TMS as the internal

reference, and ^{13}C NMR spectra were recorded in CDCl_3 , $\text{DMSO}-d_6$, or D_2O on a Bruker Avance 500 (126 MHz) spectrometer (Billerica, MA, USA). Single-crystal samples were analyzed by a Bruker APEX-II CCD diffractometer (Billerica, MA, USA). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd = doublet of doublets, tt = triplet of triplets, qq = quartet of quartets, and ddd = doublet of doublets of doublets. Melting points were taken on a Buchi M-560 melting point apparatus (Flawil, Switzerland) and were uncorrected. HRMS analysis was done with a Bruker Daltonics microTOF-QII instrument (Billerica, MA, USA). Generally, the chemicals were purchased from commercial suppliers including Aladdin (Shanghai, China), Energy Chemical (Shanghai, China) and Innochem (Beijing, China), and used directly for our experiments. NHC precursors **L1** [57], **L2** [54], **L3** [57], **L4** [58], and NHC/Ru complexes **[Ru]-1** [51] and **[Ru]-2** [59] were prepared according to literature procedures.

3.2. General Procedure for the Synthesis of **L5**

To a solution of 5,6-dichloro-1H-benzo[d]imidazole (1.12 g, 6.00 mmol) in dry DMF (5.0 mL) at 0 °C was added NaH (60% dispersion in mineral oil) (0.26 g, 6.60 mmol), and the suspension was warmed to room temperature and stirred for 2 h. Afterward, methyl iodide (0.41 mL, 6.60 mmol) was added, allowing the mixture to react for another 4 h. After the reaction was complete, ice-cold water was added dropwise to quench the reaction. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with water (3 × 50 mL), brine (50 mL), and dried over Na_2SO_4 , followed by the evaporation of the solvent to afford a pale yellow solid. Afterwards, a mixture of the above pale yellow solid, ethyl iodide (1.91 mL, 24.00 mmol), and acetone (20 mL) was refluxed for 16 h. The reaction mixture was cooled to room temperature and concentrated to give crude **L5**, which was washed with diethyl ether to provide 1.61 g of pure **L5** in 75% yield (in two steps).

3.3. General Procedure for the Synthesis of **[Ru]-3–[Ru]-5**

To a 25 mL sealed tube were added **L5** (357.0 mg, 1.00 mmol), Ag_2O (115.9 mg, 0.50 mmol), and dry dichloromethane (5.0 mL), and the mixture was refluxed in the dark for 12 h. Then $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (306.1 mg, 0.50 mmol) was added, allowing the resulting suspension to reflux for 6 h. Afterward, the mixture was filtered and the filtrate was then concentrated. A small amount of methanol was added to dissolve the residue, and an excess amount of diethyl ether was added to give a brown precipitate, which was then washed with diethyl ether a few times to obtain the analytically pure product **[Ru]-5** as a brownish red powder. Yield: 62% (331.9 mg, 0.62 mmol).

Synthesis of **[Ru]-3–[Ru]-4** was similar to that of **[Ru]-5** mentioned above.

3.4. General Procedure for the NHC/Ru-Catalyzed Acceptorless Dehydrogenation of Alcohols to Acids

To a 25 mL Schlenk tube were added **[Ru]-5** (1.4 mg, 0.0025 mmol), **L5** (3.6 mg, 0.010 mmol), KOH (1.35 g, 24 mmol), and dry toluene (2.0 mL), and the mixture was refluxed under an open argon flow for 1.5 h. Then alcohol **1** was added to the flask, and the suspension was refluxed for 12 h. Afterwards, water (5 mL) was added, and the aqueous layer was washed with diethyl ether (3 × 30 mL) before acidification. The water layer was then acidified with 3 N HCl (3 mL) and extracted with ethyl acetate (3 × 30 mL). The organic phase was dried with Na_2SO_4 , concentrated, and dried to obtain pure carboxylic acid **2**. In addition, the detailed methods for obtaining the NMR and isolated yield of all the acids followed our previous publication [33].

3.5. X-ray Crystallography

Diethyl ether was slowly evaporated into a solution of an NHC/Ru complex in CDCl_3 , affording the resulting single-crystal sample suitable for analysis. Diffraction data were collected with $\text{CuK}\alpha$ radiation ($\lambda = 1.54184 \text{ \AA}$), and numerical absorption corrections were applied. The structures were solved by direct methods and refined on F2 with anisotropic thermal parameters for all non-hydrogen atoms. Protons were refined at the calculated positions by using a riding model. CCDC-1959447 (corresponding

to [Ru]-3), CCDC-1959445 (corresponding to [Ru]-4), and CCDC-1959448 (corresponding to [Ru]-5) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

4. Conclusions

In summary, we designed and synthesized five benzimidazole-derived NHC/Ru complexes, incorporating distinct substituents on the NHC ligands. The effects of ancillary NHC ligands and an additional ligand were also extensively studied, followed by the screening of other reaction parameters. As a result, a combination of [Ru]-5 with an electron-poor ancillary NHC ligand and L5 as an additional ligand was verified to be highly efficient for the alcohol dehydrogenation to carboxylic acids. Under the optimized conditions, numerous carboxylic acids were efficiently synthesized from the corresponding aromatic or aliphatic alcohols. Notably, a low Ru loading of 125 ppm was enough to achieve satisfactory results. Furthermore, TONs up to 15,200 and TOFs up to 4800 were also achieved. It is worth mentioning that this work demonstrates the lowest catalyst loading as well as the highest TOF value ever reported for this catalytic process.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/10/1/10/s1>, Table S1: Comparison of this catalytic system with the reported Ru systems. Table S2: Comparison of this catalytic system with other metal-based systems. Table S3: Catalyst poisoning by the mercury test. ^a Figure S1: NMR reactions utilizing [Ru]-5 without an additional ligand. Figure S2: NMR reactions utilizing [Ru]-5 with L5 as an additional ligand. [Ru system]: [Ru]-5 (1.0 equiv.), L5 (4.0 equiv.), KOH (12 equiv.) and toluene-*d*₈ (0.6 mL) were heated at reflux for 1.5 h. ¹H NMR, ¹³C NMR, HRMS data as well as spectra of NHC precursor L5, NHC/Ru complexes [Ru]-3–[Ru]-5 and carboxylic acids 2a–2s. The single-crystal data of [Ru]-3–[Ru]-5.

Author Contributions: W.-Q.W., C.C., and F.V. discussed and designed the project. W.-Q.W., H.C., Y.-Q.H., and H.-J.W. performed the experiments. C.C. wrote the draft of the manuscript, then Y.Y., Z.-Q.W., W.S., and F.V. revised the manuscript. C.C. and F.V. together finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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