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Highly active bidentate N-heterocyclic carbene/ruthenium complexes performing dehydrogenative coupling of alcohols

Eight bidentate NHC/Ru complexes, namely [Ru]-1~[Ru]-8, were designed and prepared. Particularly, [Ru]-2 displayed extraordinary performance even in open air for the dehydrogenative coupling of alcohols and hydroxides. Notably, an unprecedentedly low catalyst loading of 250 ppm and the highest TON of 32800 and TOF of 3200 until now were obtained.

and hydroxides in open air

Transforming primary alcohols into the corresponding carboxylic acids is a fundamental process in organic chemistry.^{1,} ² Traditionally, direct oxidation of primary alcohols was utilized for the production of acids.³ However, stoichiometric amounts of strong and toxic oxidants were usually required and enormous by-products were generated as waste.⁴⁻⁶ Even though in some cases oxygen were used as the sole oxidant,⁷⁻¹⁷ problems may occur as oxygen could form explosive mixtures with various organic reagents and solvents. Therefore, it is of vital importance to develop green and sustainable alternatives for producing carboxylic acids. Recently, the dehydrogenative coupling of alcohols and water or hydroxides has been demonstrated as an environmental-benign and atom-economic transformation with the concomitant generation of dihydrogen (H₂) as the sole byproduct, showing a prosperous potential for synthetic applications. At the outset, Grützmacher et al. accomplished the catalytic dehydrogenative synthesis of carboxylic acids from primary alcohols promoted by hydrogen acceptors.18-20 The acceptorless version of this transformation was pioneered by Milstein and co-workers.²¹ In this work, 0.2 mol% of a PNN-type Ru pincer complex could realize this catalytic process without a hydrogen acceptor, thereby a number of primary alcohols were directly transformed into carboxylic acids in aqueous NaOH solution. Afterwards, a handful of Ru,²²⁻³¹ Rh,³² Pd,³³ Ir^{34, 35}, Ag,³⁶ Fe,³⁷ Mn,^{37, 38} and Zn³⁹ complexes were also reported for this catalysis. Especially, Ru complexes have been most accessed and investigated.

With catalyst loadings ranging from 0.1 mol% to 5.0 mol%, a number of Ru complexes were reported to be active for this approach. Among these catalysts, N-heterocyclic carbene (NHC)-based Ru complexes have attracted our growing interest owing to the attractiveness of NHCs as ligands in organometallic catalysis.⁴⁰⁻⁴⁴ Hence, two monodentate NHC/Ru complexes have also been developed and proven to be active for this transformation (Figure 1a).^{23, 26} Despite the above two NHC/Ru complexes, the discovery of versitile and highly active NHC/Ru complexes for this process is still in high demand. Inspired by the high activities of our previously presented bidentate NHC/Ru complexes in dehydrogenative amidation of alcohols⁴⁵ and by the recent developments for the dehydrogenative coupling of alcohols to form carboxylic acids, we thereby designed and synthesized several Ru complexes bearing C^{NHC}C bidentate NHC ligands (Figure 1b). Gratifyingly, selective formation of carboxylic acids was acheived through extensive screening of various conditions. Notably, one of these complexes ([Ru]-2) demonstrated outstanding efficiency, with the applied catalyst loading at a low level of 250 ppm. Moreover, the turnover number (TON) could be up to 32800 and the maximum turnover frequency (TOF) could be 3200. To the best of our knowledge, this is the lowest catalyst loading and highest TON and TOF ever reported for this reaction (as listed in Table S1 of the supporting information). In addition, this catalytic dehydrogenation was performed in open air and did not require special handling or purification, demonstrating great potential for its practical applications.

With the above considerations in mind, five bidentate NHC/Ru complexes (**[Ru]-1~[Ru]-5**, as shown in the scheme of Table 1) were easily prepared and purified from a mixture of $[RuCl_2(p-cymene)]_2$, a $C^{NHC}C$ bidentate NHC precursor and Cs_2CO_3 in refluxing THF. Then the acceptorless dehydrogenative coupling of benzyl alcohol (**1a**) and a hydroxide was selected as a typical reaction for optimization of reaction conditions. Varied hydroxides and solvents were screened, and KOH combined

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(a) Reported monodentate NHC/Ru complexes:



 $\sqrt{}$ as low as 250 ppm [Ru], TONs (TOFs) up to 32800 (3200) $\sqrt{}$ In open air and easy operation

Figure 1. The design strategy of this work.

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with *m*-xylene (at a refluxing temperature) were selected to be optimum (as detailed in Table S2 of the supporting information). In refluxing *m*-xylene, 94% of 2a was obtained after 6 h (entry 1). Interestingly, variation of the Ru loading from 0.1 mol% to 0.05 mol% and 0.025 mol% did not trigger substantial loss of the product yields (entries 2-3 vs. entry 1). With a Ru loading of 0.025 mol% (as listed in entry 3), the catalytic performance of the other four NHC/Ru complexes was also evaluated (as shown in entries 4-7). Compared with [Ru]-1, the imidazole-based analogue [Ru]-2 exhibited a similar activity (entry 4 vs. entry 3). For [Ru]-3 which was testified to be active for the dehydrogenative alcohol amidation with amines,45 а considerable decrease of the product yield was obtained (entry 5 vs. entry 3). With regard to the thiophene-containing [Ru]-4 and [Ru]-5, 52-70% yields of 2a were observed (entries 6-7). Therefore, [Ru]-1 and [Ru]-2 displayed outstanding activities at the current conditions (entries 3-4). In order to further examine the practical values of these two complexes and make a better comparison of their activities, reactions applying both complexes were conducted in open air (entries 8-9). The results indicated that [Ru]-2 afforded the product in 94% yield (entry 9). However, it seemed that air was detrimental to [Ru]-1 since the yield deteriorated to 76% for this complex in open air (entry 8). Furthermore, the superiority of the imidazole-based NHC ligand over the benzimidazole counterpart inspired us to conduct further optimization of NHC ligands. Different substituents were introduced on the imidazole framework of NHC ligands to afford [Ru]-6~[Ru]-8, which exhibited comparable activities with [Ru]-2 in open air (entries 10-12 vs. 9). In addition, the structures of [Ru]-4~[Ru]-8 were further confirmed by X-ray crystallography (as shown in Figure S1 of the supporting information). Accordingly, [Ru]-2 was selected as the optimal catalyst due to its high activity and robustness. In the absence of a Ru complex, only 5% of 2a was detected with



Entry	[Ru]	x	n	Yields of 2a (%) ^b	TON	TOF
1	[Ru]-1	0.10	6	94	940	157
2	[Ru]-1	0.05	6	93	1860	310
3	[Ru]-1	0.025	6	92	3680	640
4	[Ru]-2	0.025	6	91	3640	637
5	[Ru]-3	0.025	6	59	2360	393
6	[Ru]-4	0.025	6	70	2800	467
7	[Ru]-5	0.025	6	52	2080	347
8 ^c	[Ru]-1	0.025	6	76	3040	507
9°	[Ru]-2	0.025	6	94	3760	647
10 ^c	[Ru]-6	0.025	6	89	3560	593
11 ^c	[Ru]-7	0.025	6	91	3640	607
12 ^c	[Ru]-8	0.025	6	92	3680	613
13 ^c	-	-	6	5	-	-
14 ^{<i>c,d</i>}	[Ru]-2	0.025	24	90	3600	600
15 ^c	[Ru]-2	0.01	16	86	8600	538
16 ^{c,e}	[Ru]-2	0.0025	36 (1)	82 (8)	32800 (3200)	911 (3200)
17 ^{c,f}	[Ru]-2	0.025	6	87	3480	580

^{*a*} **Conditions: 1a** (1.00 equiv.), KOH (1.20 equiv.) and **[Ru]** (x mol%) at a refluxing *m*xylene under an open argon atmosphere; ^{*b*} NMR yields using 1,3,5trimethoxybenzene as an internal standard (average of two consistent runs); ^{*c*} in open air instead of argon; ^{*d*} under a neat condition; ^{*e*} KOH (2.00 equiv) was used; ^{*f*} the reaction was run at a scale of 100 mmol (10.4 g of **1a**).

the majority of **1a** remaining (entry 13), which excluded the pathway of base-promoted aerobic oxidation of primary alcohols.^{10, 13, 17} In addition, **[Ru]-2** could also efficiently catalyze the reaction under a neat condition, but a longer period of time was required (entry 14). Further reducing the catalyst loading to 0.01 mol% and 0.0025 mol% led to a maximum TON of 32800

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and a maximum TOF of 3200 (entries 15-16). Finally, a 10 gramscale reaction was also performed, leading to 87% of the desired product (entry 17). Therefore, the optimized parameters, recognized as 0.025 mol% (equal to 250 ppm) of **[Ru]-2**, 1.00 equiv. of **1a** and 1.20 equiv. of KOH in refluxing *m*-xylene for 6 h (as listed in entry 9 of Table 1), were used for further investigations.

With the optimized reaction conditions in hand, the substrate scope and limitations were thoroughly investigated (as depicted in Figure 2). First of all, a number of aromatic alcohols were subjected to this dehydrogenation, affording the corresponding carboxylic acids in moderate to good yields. Electron-rich benzyl alcohols 1b-1d gave acids 2b-2d in exellent yields, while the electron-deficient counterparts (1e-1h) generally afforded the corresponding acids in lower yields (45-73%) with longer reaction time (16 h) or a higher catalyst loading (500 ppm). Particularly, 1e (or 1f) not only produced expected product 2e (or 2f), but also yielded the dehalogenated acid 2a in 10% (or 12%) yield. Moreover, the substituent position on the phenyl ring was found to affect the yields of the products. Under the standard conditions, 3-methylbenzyl alcohols (1i) and 2methylbenzyl alcohol (1j) generated the acid products in 83% and 73% yields, respectively. Impressively, phenyl- and anilinecontaining alcohols 1k and 1l could also be tolerated to give acids 2k and 2l in 51% and 10% yields, respectively. Additionally, the reactions of substrates (1m and 1n) bearing a naphthyl group or a sulfur atom also proceeded smoothly. Except aromatic alcohols, we also extended this Ru-catalyzed protocol to aliphatic alcohols under analogous conditions. Sterically nonhindered alcohols including linear alcohols (10-1p), cyclopentylmethanol (1q), cyclohexylmethanol (1r) and 3phenylpropan-1-ol (1s) gave rise to aliphatic acid products (2o-2s) in 81-93% yields after 16 h. In addition, the bulky substrate 1-adamantanemethanol (1t) was efficiently converted to acid 2t in 65% yield, and 73-85% of the desired products (2u-2v) were given for heterocycle-containing substrates. For the reaction of KOH and hex-5-en-1-ol (1w) comprising a terminal C=C bond, a mixture of 57% of product 2w, 18% of 2w' generated by olefin isomerization of 2w, and 7% of the reduced product 2o were obtained. Substrate 1x, which contains both primary and secondary OH groups, was also attempted. It was indicated that acid 2x, with the secondary OH intact, was obtained in 48% yield. Finally, treatment of amino alcohols 1y-1z with KOH furnished the corresponding amino acids **2y-2z** in good yields.

Generally, it has been postulated that the generation of Ru hydride species is crucial for this Ru-catalyzed dehydrogenative transformation.^{21, 26, 30} Therefore, NMR studies deciphering the mechanistic insights were carried out. Expectedly, several hydride resonances were observed, which was probably indicative of the essential role of Ru-hydride species in the catalytic cycle (as detailed in Fig. S2 of the supporting information). Based on these experiments and the reported Ru catalysts for this transformation,^{21, 26, 30} we suggested a plausible pathway for this [**Ru**]-**2**-catalyzed protocol (as shown in Figure S3 of the supporting information). Initially, treatment of [**Ru**]-**2** with alcohol **1** and KOH gives key Ru-alkoxide





^[a] **1** (6.25 mmol), **KOH** (7.50 mmol), **[Ru]-2** (0.025 mol%) and *m*-xylene (1.5 mL) at reflux for 6 h under open air; Isolated yields (avarage of two consistent runs); ^[b] 500 ppm of **[Ru]-2**; ^[c] The yield of benzoic acid (**2a**); ^[d] 16 h; ^[e] KOH (12.5 mmol) was used; ^[f] under argon; ^[g] the yield of 4-hexenoic acid (**2u'**); ^[h] the yield of hexanoic acid (**2l**).

Figure 2. Synthesis of carboxylic acids from various alcohols and KOH catalyzed by [Ru]-2.

intermediate I and water molecule, which could solvate KOH to form the hydroxide ion (OH⁻).²⁶ Afterwards, I could probably undergo a similar pathway as proposed by our previous report for **[Ru]-3**-catalyzed dehydrogenative coupling of alcohols and amines, by replacing the amine nucleophile with H₂O (or OH⁻).⁴⁵ Through β-hydride elimination, intermediate I can be converted to a hydrido complex II bound with the corresponding aldehyde, which reacts with H₂O (or OH⁻) to produce intermediate III and liberate one molecule of H₂. Furthermore, III is accompanied with another β-hydride elimination to provide Ru monohydride species IV, followed by ligand substitution with **1** to deliver carboxylic acid **2** (which is converted to carboxylate **[2-H]**⁻ under basic condition) and hydrido complex V. Eventually, V eliminates another H₂ molecule to regenerate intermediate I, allowing for the fulfilment of the catalytic cycle.

In summary, we have successfully prepared eight Ru complexes bearing C^{NHC}C bidentate NHC ligands, namely [Ru]-

 1^{Ru} -[Ru]-8. Through a systematic investigation of these complexes and other parameters, optimized reaction conditions applying [Ru]-2 demonstrated excellent activities for the acceptorless dehydrogenative coupling of primary alcohols and KOH. Accordingly, numerous aromatic and aliphatic alcohols were efficiently transformed into the corresponding carboxylic acids. Interestingly, this catalytic process could be performed in open air, and no special handling or further purification was necessary to achieve satisfactory results. Notably, [Ru]-2 is effective for this transformation even at a low catalyst loading of 250 ppm. In addition, a TON of up to 32800 and a TOF of up to 3200 were obtained. It is worth mentioning that these values are superior over all the literature reports until now. Hopefully, this highly active complex will be of practical value for further interesting applications.

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Conflicts of interest

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There are no conflicts to declare.

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A highly active and robust bidentate NHC/Ru complex for the acceptorless dehydrogenative coupling of alcohols and hydroxides in open air.