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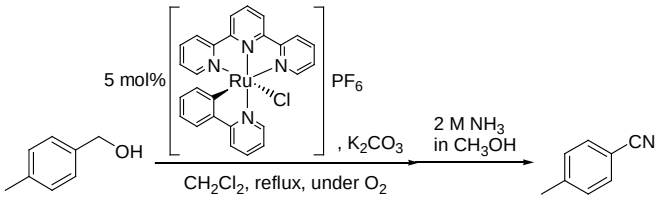

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Aerobic oxidative dehydrogenations of benzyl alcohols to benzaldehydes by using a cyclometalated ruthenium catalyst

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ABSTRACT

The ruthenium(III) complex bearing phenylpyridine as a cyclometalated ligand serves as an efficient catalyst for the aerobic oxidative dehydrogenation of benzyl alcohols to the corresponding benzaldehydes under mild conditions and for the one-pot synthesis of benzonitriles from benzyl alcohols with ammonia.

The development of catalytic systems employing aerial oxygen as an oxidant instead of classical toxic reagents is highly desired,[1] and there are a number of reports on ruthenium-catalyzed oxidative dehydrogenation.[2] We previously reported a new catalytic system in which a cyclometalated Ru(III) complex, [RuCl(ppy)(tpy)][PF_6] (**1a**)[3] (ppy = 2-phenylpyridine; tpy = 2,2':6',2"-terpyridine), served as an efficient catalyst for the aerobic oxidative dehydrogenation of imidazolines and benzylamines.[4,5] The ruthenium(III) complex bearing benzo[*h*]quinoline (bhq) as a cyclometalated ligand, [RuCl(bhq)(tpy)][PF_6] (**1b**), was synthesized and applied as a catalyst for aerobic oxidative dehydrogenation of benzylamines.[6] The key feature of catalysts **1a** and **1b** is the presence of a cyclometalated ligand and a Cl ligand. The σ-donor character of the cyclometalated ligand lowers the redox potential of the metal center, which enables the aerobic oxidation of the substrates. The *trans* effect of the cyclometalated ligand also assists in the dissociation of the Cl ligand followed by coordination of amines. This process provides a different catalytic reaction pathway for aerobic dehydrogenation from that of the common ruthenium-catalyzed aerobic oxidation of amines, including ruthenium hydride species.[2a-p] These observations persuaded us to explore coordinative substrates other than amines. The scope of this work is the aerobic oxidation of alcohols. The selective oxidation of primary alcohols to aldehydes is one of the most important reactions in organic chemistry. Although several excellent catalysts for the aerobic oxidation of alcohols to the corresponding carbonyl compounds have been developed,[1b-c,2] primary alcohols sometimes suffer from overoxidation, thus forming carboxylic acid. Therefore, selective oxidation that results in the formation of an aldehyde is desired. We report herein that the Ru complex **1a** serves as an efficient catalyst for the aerobic oxidative dehydrogenation of benzyl alcohols to benzaldehydes. The one-pot synthesis of benzonitriles from benzyl alcohols with ammonia is also described.

The oxidation of 4-methylbenzyl alcohol (**2a**) to 4-methylbenzaldehyde (**3a**) was carried out using **1a** as a catalyst in CH_2Cl_2 under reflux in air. The reaction was monitored by ^1H NMR spectroscopy using *p*-xylene as an internal standard. The desired product **3a** was obtained in 80% yield after 8 h (Table 1, entry 1). The yield was improved when the reaction was carried out under molecular oxygen (1 atm), whereas the same reaction under a nitrogen atmosphere gave only 5% yield (entries 2 and 3). The results indicate that molecular oxygen serves as an oxidant in the catalytic reaction. The yield of benzoic acid as a by-product was negligible (entry 2). When the reaction time was extended (10 h), the yield of **3a** decreased (87%) and the yield of benzoic acid slightly increased (3%). When CH_2Cl_2 and THF were used as solvents, yield of 92% and 82%, respectively, were obtained (entries 2 and 8). These solvents dissolved the substrate, the catalyst and a part of K_2CO_3

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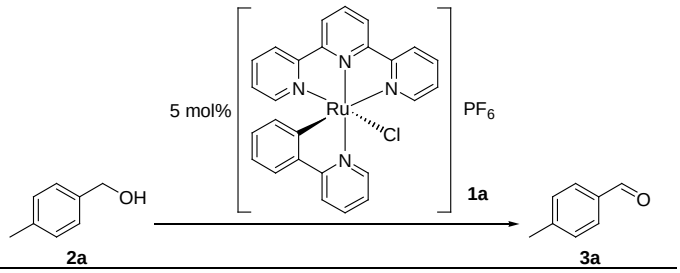
Table 1. Oxidative dehydrogenation of **2a** using **1a** as a catalyst[a]

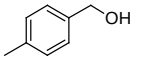
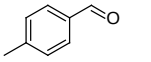
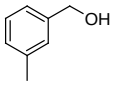
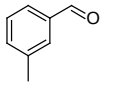
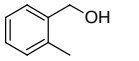
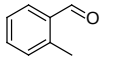
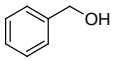
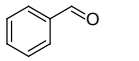
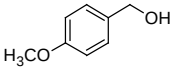
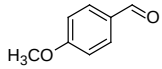
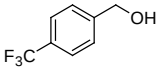
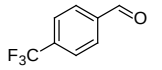
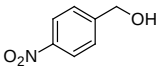
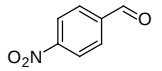
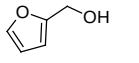
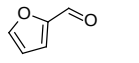
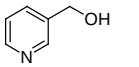
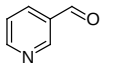
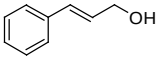
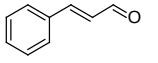
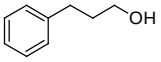
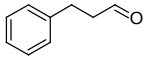
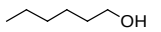
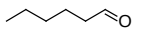
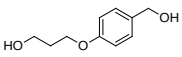
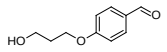
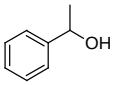
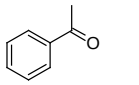
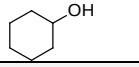
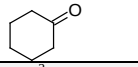


Entry	Conditions				Yield[b] (%)
1	K_2CO_3	CH_2Cl_2	reflux	Air	80
2	K_2CO_3	CH_2Cl_2	reflux	O_2	92
3	K_2CO_3	CH_2Cl_2	reflux	N_2	5
4	K_2CO_3	$CHCl_3$	60	O_2	46
5	K_2CO_3	$CHCl_2CHCl_2$	60	O_2	21
6	K_2CO_3	1,2-dichlorobenzene	60	O_2	27
7	K_2CO_3	DME	60	O_2	10
8	K_2CO_3	THF	60	O_2	82
9	K_2CO_3	CH_3OH	60	O_2	64
10	K_2CO_3	acetone	60	O_2	9
11	K_2CO_3	CH_3CN	60	O_2	6
12	–	CH_2Cl_2	reflux	O_2	0
13	Na_2CO_3	CH_2Cl_2	reflux	O_2	25
14	Cs_2CO_3	CH_2Cl_2	reflux	O_2	18
15	DBU	CH_2Cl_2	reflux	O_2	2
16	K_2CO_3 (0.5 eq)	CH_2Cl_2	reflux	O_2	82
17	K_2CO_3 (2.0 eq)	CH_2Cl_2	reflux	O_2	91
18[c)]	K_2CO_3	CH_2Cl_2	reflux	O_2	0
19[c)]	K_2CO_3	CH_2Cl_2	reflux	O_2	0

[a]Reaction conditions: **2a** (0.15 mmol), **1a** (7.5×10^{-3} mmol), base (0.15 mmol), solvent (1.0 mL), 8 h.
[b]Determined by ^{1}H NMR spectroscopy using *p*-xylene as an internal standard.
[c]Complex **1c** (entry 18) and **1d** (entry 19) were used as a catalyst instead of **1a**.

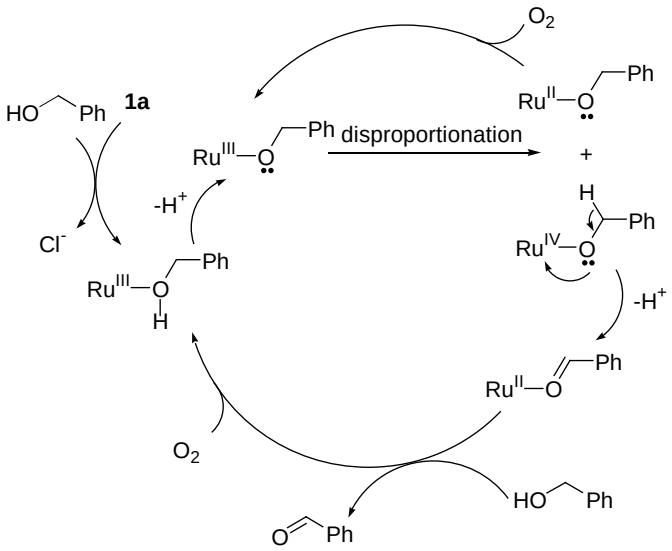
during the reactions. The reaction in methanol proceeded slowly because the substrate competed with the solvent (entry 9). Acetone and CH_3CN were ineffective solvents probably because of their coordinative ability to the metal center and the low solubility of K_2CO_3 (entries 10 and 11). The addition of inorganic bases accelerated the reaction (entries 2, 12-14); the best result was obtained when K_2CO_3 was used. The addition of organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was less effective probably because they coordinate to the ruthenium center instead of the substrate (entry 15). The reaction with two equivalent molar amounts of K_2CO_3 provided the better yield (91%) than that with 0.5 equivalent molar amount of K_2CO_3 (82%) (entries 2 and 16, 17).

Table 2. Oxidative dehydrogenation of **2a-2o** using **1a** as a catalyst[a]

Entry	Substrate		Product		Yield[b] (%)
1		**2a**		**3a**	92
2		**2b**		**3b**	93
3		**2c**		**3c**	70
4		**2d**		**3d**	90
5		**2e**		**3e**	82
6		**2f**		**3f**	84
7		**2g**		**3g**	86
8		**2h**		**3h**	81
9		**2i**		**3i**	2
10		**2j**		**3j**	89
11[c]		**2k**		**3k**	7
12[c]		**2l**		**3l**	3
13		**2m**		**3m**	82
14[c]		**2n**		**3n**	21
15[c]		**2o**		**3o**	10

[a]Reaction conditions: **2** (0.15 mmol), **1a** (7.5×10^{-3} mmol), K_2CO_3 (0.15 mmol), CH_2Cl_2 (1.0 mL), reflux, 8 h, O_2 atmosphere.
[b] Determined by ^{1}H NMR spectroscopy using *p*-xylene as an internal standard.
[c]Reaction time: 24 h.

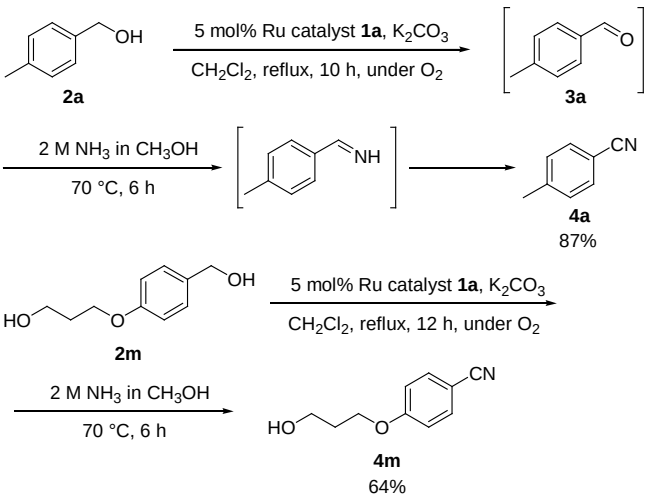
The aerobic oxidative dehydrogenation of various alcohols, **2b**-**2o**, was carried out under the optimized conditions (Table 1, entry 2). The substitution of phenyl groups with either electron-donating group or electron-withdrawing group was tolerated to afford the desired products (Table 2, entries 1-7). The reactions of furfuryl alcohol **2h** and allylic alcohol **2j** also gave the corresponding aldehydes in good yields (entries 8 and 10). In contrast, the reaction of 3-pyridinemethanol **2i** did not give the desired product (entry 9). The low yield of the product is attributed to the coordination of the pyridine moiety of **2i** to the ruthenium center. The progress of the reaction of the aliphatic alcohols without resonance stabilization was negligible (entries 11 and 12). The oxidation of 4-(3-hydroxypropoxy)benzyl alcohol (**2m**) gave 4-(3-hydroxypropoxy)benzaldehyde (**3m**) in a good yield, indicating that the benzylic hydroxy group of **2m** was selectively oxidized. Although the corresponding ketones were obtained from the reactions of secondary alcohols **2n** and **2o** (entries 14 and 15), the secondary alcohols were less reactive than the primary alcohols.



Scheme 1. Suggested reaction pathway for the aerobic oxidative dehydrogenation of benzyl alcohol.

To elucidate the reaction pathway, the related ruthenium complexes, $[Ru(ppy)(bpy)_2][PF_6]$ **1c** and $[RuCl(bpy)(tpy)][PF_6]$ **1d**, were examined as catalysts. The control experiments revealed that neither **1c** nor **1d** showed catalytic activity (Table 1, entries 18 and 19). The inactivity of **1c** indicates that the reaction proceeds only if the coordination of **2a** to the metal center takes place. This is consistent with the fact that the use of coordinative solvents, a base, and **2i** prevents the catalytic reaction. The secondary alcohols were less reactive than the primary alcohols as mentioned above (Table 2, entries 14 and 15). These results also indicate that secondary alcohols cannot coordinate easily to the ruthenium center because of their bulkiness. The inactivity of **1d** is owing to the high redox potential of the ruthenium center (Ru(III)/Ru(II); $E_{1/2}$: **1a** = 0.46 V versus NHE,[3] **1d** = 1.05 V versus NHE[7]); the low oxidation potential of **1a** is necessary for the aerobic oxidation of the ruthenium metal center. The addition of a radical scavenger such as 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) slightly affected the catalytic reactions, showing that free-radical intermediates such as a benzyl radical were not involved in this reaction.[2f] Since these results are consistent with the results of our previous reports on the oxidation of amines,[4,5] the catalytic reaction of **1a** is closely related to the aerobic oxidation of amines. A plausible reaction pathway for the reaction is shown in Scheme 1: the dissociation of the Cl ligand occurs easily owing to the *trans* effect of the cyclometalated ppy ligand. The coordination of benzyl alcohol to the metal center affords the Ru-alcohol complex. The Ru-alcohol complex is then converted to the Ru-aldehyde complex by aerobic oxidation involving the removal of two protons and two electrons; the reaction is likely to result from the disproportionation of the ruthenium intermediate to form a Ru(IV) species containing dissociable protons.[4,8] Finally, aldehyde is replaced by alcohol. The base induces deprotonation of the coordinated OH group because the reaction proceeded smoothly by using more than one molar equivalent of the base. Mayer *et al.* reported related ruthenium-promoted dehydrogenation of ligated substrates,[9] which was elucidated by a metal-mediated hydrogen atom transfer reaction. We consider that Mayer's and our pathways have little difference, if the resonance structures are taken into consideration (Scheme S1 and S2).

Because **1a** was an efficient catalyst for the aerobic oxidative dehydrogenation of benzyl alcohols to benzaldehydes, we applied **1a** as a catalyst for the one-pot synthesis of benzonitrile from benzyl alcohol with ammonia. There are only a few reports of the synthesis of benzonitriles directly from benzyl alcohols using aerobic oxidations.[10] This transformation is considered to proceed



Scheme 2. One-pot synthesis of benzonitrile **4a** and **4m**.

via the following three sequential reactions: 1) the oxidation of alcohol, 2) the condensation of aldehyde and ammonia, and 3) the oxidation of imine. We initially expected that the one-pot synthesis could be achieved by **1a** because **1a** was effective for the aerobic oxidation of amines as well as alcohols. However, when the oxidation of alcohol was carried out in the presence of ammonia, the desired product benzonitrile **4a** was obtained in a low yield (24 h, 18%). The highly coordinative ability of ammonia and **4a** prevented the aerobic oxidation of **2a**. However, **4a** was obtained in a high yield (87%) when the ammonia solution was added to the reaction mixture after the conversion of alcohol **2a** to aldehyde **3a** (Scheme 2). A similar reaction of diol **2m** gave 4-(3-hydroxypropoxy)benzonitrile (**4m**) in 64% yield, which was realized by using the difference in reactivity of the hydroxy groups. Because **4m** is known to be an intermediate for the syntheses of biologically active compounds and liquid crystal materials,[11] this reaction would be a promising method for the preparation of industrially important chemical products.

In summary, the cyclometalated ruthenium complex **1a** effectively catalyzed the oxidative dehydrogenation of benzyl alcohols to benzaldehydes under mild conditions. The scope of the aerobic oxidation was expanded to the one-pot synthesis of benzonitrile from benzyl alcohol because **1a** promotes the aerobic oxidation of amines as well as alcohols. Further studies on this catalytic system using **1a** are expected to contribute to the development of reactions with functional group selectivity.

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Supplementary data

Supplementary data (general experimental information and experimental detail) associated with this article can be found, in the online version, at doi:

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