Pergamon

TETRAHEDRON LETTERS

Aerobic oxidative dehydrogenation of benzylamines catalyzed by a cyclometalated ruthenium complex

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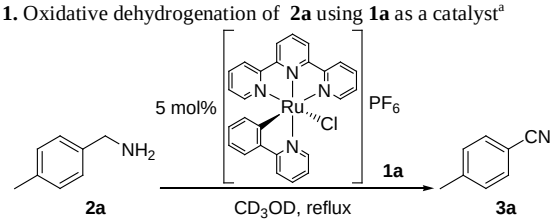
Abstract—The ruthenium(III) complex bearing phenylpyridine as a cyclometalated ligand serves as an efficient catalyst for the aerobic oxidative dehydrogenation of benzylamines to the corresponding benzonitriles under mild conditions. Keywords: Dehydrogenation; Homogeneous catalysis; Ruthenium; Amine

Nitriles are useful intermediates in the synthesis of biologically active compounds and pharmaceutical substances.[1] Since nitriles have been generally synthesized by the nucleophilic substitution of halides with inorganic cyanides and the oxidation of amines with a stoichiometric amount of oxidants,[2] the oxidative dehydrogenation of primary amines by molecular oxygen in air is more desirable for the synthesis of nitriles. Therefore, the development of efficient catalytic systems has recently been investigated for the aerobic oxidative dehydrogenation of amines.[3]

We previously reported that a cyclometalated ruthenium complex, [RuCl(ppy)(tpy)][PF_6] (**1a**)[4] (ppy = 2-phenylpyridine; tpy = 2,2':6',2''-terpyridine), serves as an efficient catalyst for the aerobic oxidative dehydrogenation of imidazoline derivatives.[5] The key feature of catalyst **1a** is to have a cyclometalated ligand and a Cl ligand because the catalytic reaction is considered to proceed as follows: i) The σ-donor character of the cyclometalated ligand lowers the redox potential of the metal center, which enables the aerobic oxidation of the ruthenium center. ii) Since the Cl ligand is easy to dissociate, imidazoline can coordinate to the ruthenium center. The ligated imidazoline is converted to imidazole by dehydrogenation involving the removal of two protons and two electrons. We thus envisioned that the complex **1a** would be an effective catalyst for the aerobic oxidative dehydrogenation of primary amines, since the oxidative dehydrogenation of amines and alcohols has been promoted by their coordination to transition-metal complexes.[3,6,7] However, the aerobic oxidation of primary amines to nitriles is considered to be more challenging than that of imidazoline because it requires the removal of four protons and four electrons. We report herein that the

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



Entry	Conditions			Time (h)	Yield[b] (%)
1		K_2CO_3	Air	12	90
2		K_2CO_3	O_2	1	87
3		K_2CO_3	N_2	1	0
4		–	O_2	1	16
5		Na_2CO_3	O_2	1	65
6		Cs_2CO_3	O_2	1	73
7		KO*t*Bu	O_2	1	69
8		DBU	O_2	1	16
9		Et_3N	O_2	1	19
10[c]		K_2CO_3	O_2	24	83
11[d]		K_2CO_3	O_2	1	2
12[e]		K_2CO_3	O_2	1	80
13[f]	**1b**	K_2CO_3	O_2	1	0
14[f]	**1c**	K_2CO_3	O_2	1	0

[a]The reaction was carried out in 1 mL solvent with **2a** (0.15 mmol), **1a** (7.5×10^{-3} mmol) and base (0.15 mmol).

[b]Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard.

[c]The reaction was performed at room temperature.

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[d]CD_3CN was used as the solvent instead of CD_3OD.

[e]The reaction was carried out in 4 mL solvent with **2a** (1.0 mmol), **1a** (5.0×10^{-2} mmol) and base (1.0 mmol).

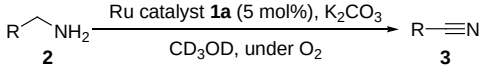
[f]**1b** (entry 13) and **1c** (entry 14) were used as the catalyst instead of **1a**.

cyclometalated complex **1a** is an efficient catalyst for the aerobic oxidative dehydrogenation of benzylamines, affording their corresponding benzonitriles under mild conditions.

The oxidation of 4-methylbenzylamine (**2a**) to 4-methylbenzonitrile (**3a**) was carried out using **1a** as a catalyst in methanol under reflux in air. The reaction was monitored by ^{1}H NMR spectroscopy. The desired product **3a** was obtained in 90% yield after 12 h (Table 1, entry 1). The reaction proceeded much faster using molecular oxygen (1 atm), and no catalytic reaction was observed under a nitrogen atmosphere (entries 2 and 3). These results indicate that molecular oxygen serves as the oxidant in the catalytic reaction. The addition of inorganic bases accelerated the reaction; the best result was obtained when K_2CO_3 was employed (entries 2, 4-7). The addition of organic bases is less effective because they probably coordinate to the ruthenium center instead of benzylamine (entries 8 and 9). The reaction proceeded even at room temperature; **3a** was obtained in good yield (entry 10). Acetonitrile, a solvent with a higher boiling point, was ineffective owing to its coordinative property and the low solubility of K_2CO_3 (entry 11). Methanol shows good solubilities for the substrate, the catalyst and base. The reaction could be also carried out in 1.0 mmol scale without any problem to give **3a** in good yield (entry 12).

Under the optimized conditions, the aerobic dehydrogenation of various benzylamines, **2a**-**2g**, was carried out. The corresponding benzonitriles, **3a**-**3g**, were obtained in each case, as shown in Table 2. When electron-withdrawing group-substituted benzylamines were used as the substrate, the yield was low presumably owing to the overreaction, forming by-products such as amide.[8] 4-Trifluoromethylbenzamide was detected by GC-MS and ^{1}H NMR as one of the by-products (10% yield) (entry 7). The

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

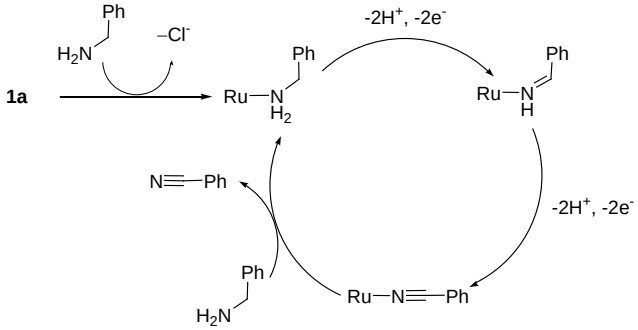


2 **3**

Entry	R		Temp. (°C)	Time (h)	Yield[b] (%)
1	*p*-MeC_6H_4	**a**	reflux	1	87
2	*m*-MeC_6H_4	**b**	reflux	1	75
3	*o*-MeC_6H_4	**c**	reflux	1	83
4	*p*-$MeOC_6H_4$	**d**	reflux	1	86
5	Ph	**e**	reflux	1	73
6	*p*-ClC_6H_4	**f**	30	24	61
7	*p*-$F_3CC_6H_4$	**g**	30	24	38
8	2-PhC_2H_4	**h**	reflux	1	0
9	3-PhC_3H_6	**i**	reflux	1	0

[a]The reaction was carried out in 1 mL solvent with **2** (0.15 mmol), **1a** (7.5×10^{-3} mmol) and base (0.15 mmol).

[b]Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard.



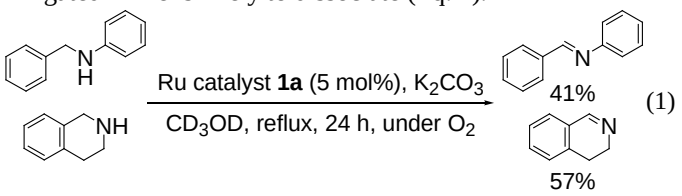
Scheme 1. Suggested reaction pathway for the aerobic oxidative dehydrogenation of benzylamine.

reaction of aliphatic amines **2h** and **2i** did not produce the desired nitriles under the standard conditions (entries 8 and 9).

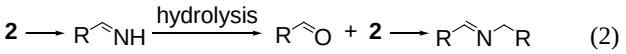
To elucidate the reaction pathway, comparable ruthenium complexes, $[RuCl(bpy)(tpy)][PF_6]$ (**1b**) and $[Ru(ppy)(bpy)_2][PF_6]$ (**1c**, bpy = 2,2'-bipyridine), were also examined (Table 1, entries 13 and 14). As shown in entries 13 and 14, in neither case was any **3a** detected. These results indicate that the redox potential of **1b** is not sufficiently low for the aerobic oxidation of the ruthenium center (Ru(III)/Ru(II); $E_{1/2}$: **1a** = 0.46 V vs. NHE,[4] **1b** = 1.05 V vs. NHE[9]). The inactivity of **1c** indicates that the reaction proceeds only if the coordination of **2a** to the metal center takes place. These results are consistent with results of our previous study;[5] the catalytic reaction is closely related to the aerobic oxidation of a ligated imidazoline.[10] The most commonly proposed mechanisms for ruthenium-induced oxidative dehydrogenation include a β-hydrogen elimination step from the ligated amine to produce an imine.[3a-d,6] However, the complex **1a** is unlikely to form ruthenium hydride species through β-hydrogen elimination because **1a** and the intermediates are coordinatively saturated. A plausible pathway of the reaction is shown in Scheme 1. Since the Ru-Cl bond length of **1a** (2.4431(13) Å)[4] is longer than that of **1b** (2.3969(6) Å, see Supplementary Material) owing to the *trans* influence of the cyclometalated ppy ligand, the dissociation of the Cl ligand followed by the coordination of benzylamine proceeds. The Ru-amine complex is converted to the Ru-imine complex by the aerobic oxidation involving the removal of two protons and two electrons.[7] The dehydrogenation of the imine to the nitrile takes place in the same way. Finally, benzonitrile is replaced by benzylamine. Although further investigation of the mechanistic details is needed, it can be considered that the base induces deprotonation of the NH group of the coordinated substrate because the reaction is accelerated under basic conditions. Molecular oxygen causes the oxidation of the Ru center with the dehydrogenation of the coordinated substrate, and H_2O is generated.

When the reaction was carried out using secondary amines, i.e., *N*-benzylaniline and 1,2,3,4-tetrahydroisoquinoline, under reflux for 24 h, *N*-benzylideneaniline and 3,4-dihydroisoquinoline were

obtained in 41% and 57% yields, respectively (Eq. 1). These results suggest that the reaction proceeds via the imine intermediate. Since trace amounts of *N*-benzylbenzaldimines have been observed in the reaction of **2a**-**2g**, which are formed by the condensation reaction of benzylamines with aldehydes through imine hydrolysis, the ligated imine is likely to dissociate (Eq. 2).



(1)



(2)

In summary, the cyclometalated ruthenium complex **1a** effectively catalyzed the oxidative dehydrogenation of benzylamines to benzonitriles under mild conditions. Since **1a** provides a new catalytic reaction pathway for the aerobic dehydrogenation of benzylamines, the method discussed in this paper is expected to pave the way for the development of efficient catalyst systems. An investigation of the reaction mechanism and other applications of the complex **1a** in oxidative dehydrogenation is now in progress.

Acknowledgments

The authors are grateful to Dr. J. Kuwabara of our laboratory for useful discussion. We thank to the Chemical Analysis Center of University of Tsukuba for the measurements of NMR spectra and X-ray analysis.

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Supplementary Material

Supplementary data (general experimental information, experimental detail, and X-ray data of **1b**) associated with this Letter can be found in the online version, at doi: