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Selective aerobic oxidations by supported ruthenium hydroxide catalysts

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Abstract

Aerobic oxidations of various alcohols, diols, and amines are efficiently promoted by the easily prepared inexpensive supported ruthenium hydroxide catalysts. A wide variety of substrates including aromatic, aliphatic, and heterocyclic ones can be converted into the desired products in moderate to excellent yields without the need for additives such as bases and electron/hydrogen transfer reagents. The catalysis for these reactions was intrinsically heterogeneous, and supported ruthenium hydroxide catalysts recovered after these reactions could be reused without appreciable loss of the catalytic performances. A reaction mechanism involving ruthenium alkoxide (amide) formation/β-elimination has been proposed for the present catalytic oxidations.

Keywords: Alcohols; Amines; Molecular oxygen; Oxidation; Ruthenium hydroxide

1. Introduction

Oxidations of alcohols and amines are of paramount importance in organic syntheses in laboratory as well as chemical industries because of their versatile use of the products such as carbonyl compounds and nitriles as important intermediates for medicines, agricultural chemicals, and fragrances [1–4]. They have been traditionally oxidized in non-catalytic procedures with stoichiometric oxidants such as chromium and manganese compounds in the presence of mineral acids, which produce large amounts of toxic metal salts as wastes. In order to minimize wastes, the catalytic method is a reliable solution [5–9]. In the manufacture of large-scale petrochemicals as well as the laboratory-scale syntheses, the environmentally unfriendly processes should be replaced with greener oxidant of molecular oxygen in combination with catalysts [5–9].

Many soluble transition metal-based homogeneous catalysts have been developed for the above-mentioned reactions [10–22]. They are usually dissolved in reaction solutions making all catalytic sites accessible to substrates and show high catalytic activity and selectivity. Despite these advantages, homogeneous catalysts have a share of only ca. 20% in industrial processes [9] because catalyst/product(s) separation (problem of product contamination) and reuse of expensive catalysts (economical aspect) are very difficult. In this concern, the development of easily recoverable and recyclable heterogeneous catalysts has received a particular research interest and a number of solid supported catalysts such as ruthenium, palladium, platinum and gold have been investigated [23–29].

We have recently developed efficient heterogeneous aerobic oxidations [30–35], hydrogen transfer reactions [36] and nitrile hydration [37] by supported ruthenium hydroxide catalysts. In this paper, we extend the scope of aerobic oxidations and discuss the reaction mechanism in more detail.

2. Experimental

2.1. General

GC analyses were carried out on Shimadzu GC-17A with a flame ionization detector equipped with a DB-WAX, FFAP or TC-1 capillary column (internal diameter = 0.25 mm, length = 30 m). Mass spectra were recorded on Shimadzu GCMS-QP2010 at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). NMR spectra were recorded on JEOL JNM-EX-270. ^{1}H and ^{13}C NMR spectra were measured at 270 and 67.8 MHz, respectively, with TMS as an internal standard. ^{2}H NMR spectra were measured at 41.25 MHz using C_6D_6 as an

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external standard. XPS measurements were carried out on JEOL JPS-90 using monochromated Al Kα radiation ($h\nu = 1486.6$ eV). The X-ray anode was run at 200 W and the voltage was kept at 10 kV. The pass energy was fixed at 20.0 eV to ensure sufficient resolution to determine peak positions accurately. The XRD patterns were measured with Rigaku Multiflex (Cu Kα radiation, 40 kV, 50 mA). The IR spectra were measured on JASCO FT/IR-460 Plus. The ICP-AES measurements were performed on Hitachi P-4010. The heterolytic benzylic C–H bond dissociation energies of *p*-substituted benzyl alcohols were calculated at the B3LYP/6-311++G(d, p) level theory with Gaussian 03 program package [38]. Substrates, reagents, and solvents were commercially obtained from Tokyo Kasei, Aldrich, and Fluka (reagent grade). Al_2O_3 (KHS-24, BET surface area: 160 $m^2\,g^{-1}$) and Fe_3O_4 (Cat. No. 310069, CAS 1317-61-9, BET; 6.8 $m^2\,g^{-1}$) were obtained from Sumitomo Chemical Co. Ltd. and Aldrich, respectively.

2.2. Preparation of supported ruthenium hydroxide catalysts

The powder Al_2O_3 (2.0 g) calcined at 550 °C for 3 h was vigorously stirred with 60 mL of an aqueous solution of $RuCl_3$ (8.3 mM) at room temperature. After 15 min, the pH of the solution was adjusted to 13.2 by addition of an aqueous solution of NaOH (1 M) and the resulting slurry was stirred for 24 h at room temperature (ca. 20 °C). The solid was then filtered off, washed with a large amount of water, and dried in vacuo to afford 2.1 g of $Ru(OH)_x/Al_2O_3$ as a dark green powder (Ru content: 2.1 wt%). The content of ruthenium is controllable by changing the concentration of the starting ruthenium solution. The XRD pattern of $Ru(OH)_x/Al_2O_3$ was the same as that of the parent Al_2O_3 support and no signal due to Ru metal (clusters) and RuO_2 was observed. XPS shows that binding energies of Ru $3d_{5/2}$ and Ru $3p_{3/2}$ of $Ru(OH)_x/Al_2O_3$ were detected at 281.8 (full width at the half maximum, FWHM 2.4 eV) and 463.5 eV (FWHM 4.7 eV), respectively, showing that the oxidation state of ruthenium species on $Ru(OH)_x/Al_2O_3$ is likely +3 [39]. The IR spectrum showed a very broad ν(OH) band in the range of 3000–3700 cm^{-1}. These facts suggest that ruthenium(III) hydroxide is highly dispersed on Al_2O_3. Ruthenium hydroxide catalyst supported on Fe_3O_4 (Ru content: 2.6 wt%) were prepared by a similar procedure to that for $Ru(OH)_x/Al_2O_3$.

2.3. Synthesis of deuterium labeled compounds

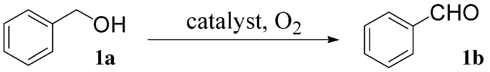
(*S*)-α-Deuterio-1-phenylethanol (**(*S*)-αD-6a**) was synthesized by the following procedures. First, racemic α-deuterio-1-phenylethanol (**αD-6a**) was synthesized by the reduction of acetophenone (**6b**) using lithium aluminum deuteride (LAD) [40]. A solution of **6b** (4.6 g, 38.4 mmol) in dry ether (10 mL) was added dropwise to a solution of LAD (1 g, 23.8 mmol) in dry ether (20 mL) at 0 °C and then the resulting mixture was allowed to warm to room temperature (ca. 20 °C). The mixture was stirred vigorously under argon atmosphere at room temperature. After 3 h, the mixture was cooled to 0 °C, and water (20 mL) and 15% aqueous solution of NaOH (5 mL) were added to the mixture. The resulting white solid was removed by the filtration and washed with dichloromethane (50 mL), and the filtrate was extracted with dichloromethane (30 mL × 5). The combined extract was dried with calcium chloride and distilled to give 4.3 g of pure **αD-6a** as a colorless oil (91% yield based on **6b**). Then, **αD-6a** (3.1 g, 25.2 mmol) was dissolved in vinyl acetate (15 mL). The temperature of the mixture was raised to 32 °C and supported lipase (PS-C Amano II, 1 g) was added to the mixture. After 2 h, the supported lipase was removed by the filtration and the solution was concentrated by the evaporation. The two products, **(*S*)-αD-6a** and (*R*)-acetate, were separated by silica gel column chromatography (initial: *n*-hexane only, after the acetate was eluted: *n*-hexane/ether = 3/1, v/v), giving 0.97 g of enantio pure **(*S*)-αD-6a** as a colorless oil (31% yield based on **αD-6a**). **(*S*)-αD-6a**: ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.41$ (s, 3H), 2.62 (brs, 1H), 7.18–7.31 (m, 5H). ^{2}H NMR (41.25 MHz, benzene, 25 °C, C_6D_6): $\delta = 4.57$ (s, 1D). ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 25.3$, 70.2 (t, ^1J(C,D) = 21.8 Hz), 125.8, 127.7, 128.8, 146.2. MS (70 eV, EI): *m/z* (%): 123 (36), 108 (100), 80 (91), 78 (33), 77 (24).

α-Deuterio-*p*-methylbenzyl alcohol (**αD-2a**) and *N*-phenyl-α-deuterio-4-methylbenzylamine (**αD-43a**) were synthesized by the similar procedures for the synthesis of **αD-6a**. **αD-2a**: ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.25$ (d, 1H ^3J(H,H) = 4.80 Hz), 2.33 (s, 3H), 4.54 (s, 1H), 7.13 (d, 2H, ^3J(H,H) = 7.10 Hz), 7.21 (d, 2H, ^3J(H,H) = 7.82 Hz). ^{2}H NMR (41.25 MHz, benzene, 25 °C, C_6D_6): $\delta = 4.54$ (s, 1D). ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 21.1$, 64.7 (t, ^1J(C,D) = 25.7 Hz), 127.1, 129.1, 137.2, 137.8. MS (70 eV, EI): *m/z* (%): 124 (19), 123 (100), 121 (18), 108 (84), 106 (44), 94 (54), 93 (43), 92 (54), 91 (77), 80 (77), 78 (52), 77 (70), 65 (52). **αD-43a**: ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.29$ (s, 3H), 3.80 (s, 1H), 4.16 (s, 1H), 6.66 (d, 2H, ^3J(H,H) = 7.92 Hz), 6.67 (t, 1H, ^3J(H,H) = 7.26 Hz), 7.21–7.08 (m, 6H). ^{2}H NMR (41.25 MHz, benzene, 25 °C, C_6D_6): $\delta = 4.16$ (s, 1D). ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 21.1$, 47.6 (t ^1J(C,D) = 20.8 Hz), 112.7, 117.3, 127.4, 129.1, 129.2, 136.2, 136.7, 148.1. MS (70 eV, EI): *m/z* (%):198 (10), 106 (100), 104 (11), 78 (11), 77 (22).

2.4. Catalytic aerobic oxidation

A suspension of the supported ruthenium hydroxide catalyst in a solvent was stirred for 5 min. Then, a substrate was added and molecular oxygen was passed through the suspension. The mixture was stirred (800 rpm) at reaction temperature under 1 atm of molecular oxygen (equipped with a balloon or flow). The conversion and product selectivity were periodically determined by GC analysis. All products have been identified by comparison of their ^{1}H and ^{13}C NMR, and mass spectra with the literature data. The recovered catalyst was washed with an aqueous solution of NaOH (1 M) and water, and then dried in vacuo before being recycled.

Table 1
Aerobic oxidation of benzyl alcohol



Entry	Catalyst	Conversion of **1a** (%)	Selectivity to **1b** (%)
1	$Ru(OH)_x/Al_2O_3$	>99	>99
2	$Ru(OH)_3 \cdot nH_2O$	2	>99
3	RuO_2 anhydrous	No reaction	
4	$RuCl_3 \cdot nH_2O$	>99	<1[a]
5	$RuCl_2(PPh_3)_3$	5	>99
6	$Ru(acac)_3$	No reaction	
7	$RuCl_2(DMSO)_4$	No reaction	
8	$RuCl_2(bpy)_2$	No reaction	
9	$[RuCl_2(p\text{-cymene})]_2$	No reaction	
10[b]	Al_2O_3	No reaction	
11	None	No reaction	

Reaction conditions: **1a** (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 2.5 mol%), $PhCF_3$ (1.5 mL), 83 °C, under 1 atm of molecular oxygen.

[a] Benzyltrifluorotoluenes were exclusively formed.

[b] Al_2O_3 (0.2 g).

3. Results and discussion

3.1. Scope of the aerobic oxidations by supported ruthenium hydroxide catalysts

First, the catalytic activity and selectivity for the oxidation of benzyl alcohol with 1 atm of molecular oxygen as a model reaction were compared among various ruthenium catalysts (Table 1). The reaction conditions were optimized by changing the reaction temperature, solvent, and scale. Among various ruthenium catalysts tested, supported ruthenium hydroxide catalyst of $Ru(OH)_x/Al_2O_3$ showed the highest catalytic activity and selectivity for the oxidation of benzyl alcohol (**1a**) to benzaldehyde (**1b**) without formation of benzoic acid and benzyl benzoate (entry 1). The reaction hardly proceeded in the presence of $Ru(OH)_3$ (entry 2) and anhydrous RuO_2 (entry 3). In the case of catalyst precursor of $RuCl_3 \cdot nH_2O$, Friedel–Crafts type reaction proceeded exclusively to afford *o*-, *m*-, and *p*-benzyltrifluorotoluenes (entry 4). $RuCl_2(PPh_3)_3$ gave only stoichiometric amounts of **1b** (entry 5) and ruthenium complexes such as $Ru(acac)_3$ (entry 6), $RuCl_2(DMSO)_4$ (entry 7), $RuCl_2(bpy)_2$ (entry 8) and $[RuCl_2(p\text{-cymene})]_2$ (entry 9) were completely inactive. No oxidation proceeded in the presence of Al_2O_3 (entry 10) or in the absence of the catalyst (entry 11).

In the presence of $Ru(OH)_x/Al_2O_3$, oxidation of various kinds of structurally diverse alcohols was examined (Table 2). Primary (**1a**–**5a**) and secondary (**6a**–**8a**) benzylic alcohols were oxidized to give the corresponding benzaldehydes and acetophenones, respectively, in quantitative yields (entries 1–8). It has been reported that **7a** gave the corresponding ketone **7b** with two-electron transfer oxidants and that one-electron transfer oxidants (radical mechanism) gave **1b** and *tert*-butyl radical as primary products [41]. In the present system, **7a** yielded the corresponding ketone **7b** as a sole product and no **1b** was detected (entry 7). The oxidation of **8a** with the unstable cyclopropane ring exclusively produced the corresponding ketone **8b** without formation of the ring-opened products (entry 8). The present system was not affected by the presence of carbon–carbon double bonds in the substrates. For example, primary (**9a** and **10a**) and secondary (**11a**) α,β-unsaturated alcohols afforded the corresponding α,β-unsaturated aldehydes and ketones, respectively, without the intramolecular hydrogen transfer and geometrical isomerization of carbon–carbon double bonds (entries 9–11). The present system could also oxidize linier (**12a**–**14a**) and cyclic aliphatic (**15a**–**17a**) alcohols in high yields (entries 15–20). Sterically hindered cyclic alcohols such as **18a** and **19a** were also efficiently oxidized to the corresponding ketones in excellent yields (entries 18 and 19). $Ru(OH)_x/Al_2O_3$ well catalyzed the oxidation of alcohols containing heteroatoms such as sulfur (**20a**) and nitrogen (**21a**) to the corresponding aldehydes in high yields (entries 20 and 21), while oxidations of these alcohols hardly proceed in the presence of homogeneous complexes due to the strong coordination to the metal centers.

The present procedure was further applied to the oxidation of various kinds of diols (Table 3). The product selectivities were dependent on their structures and substituents. The oxidation of α,ω-primary diol of 1,4-benzenedimethanol (**22a**) gave terephthalaldehyde (**22b**) (entry 1) while a lactonization proceeded in the case of 1,2-benzenedimethanol (**23a**) (entry 2). For vicinal diols with phenyl rings at α-positions (**24a** and **25a**), the carbon–carbon bond cleavage proceeded exclusively (entries 3 and 4). For aliphatic linier vicinal diol of 1,2-octanediol (**26a**), the carbon–carbon bond cleavage to give *n*-heptanal (**26b**) dominantly occurred with the formation of significant amounts of 2,4-dihexyl-1,3-dioxolane (**26c**) by acetalyzation of *n*-heptanal with starting **26a** (entry 5). The oxidation of *cis*-1,2-cyclooctanediol (**27a**) afforded 1,2-diketone (**27b**) and the carbon–carbon bond cleaved product (**27c**) (entry 6). It is noted that the oxidation of the primary-secondary diol of 4-(1-hydroxyethyl)benzyl alcohol (**28a**) gave chemoselectively 4-(1-hydroxyethyl)benzaldehyde (**28b**) in 94% selectivity at >99% conversion (entry 7). In addition to the intramolecular competitive oxidation of primary and

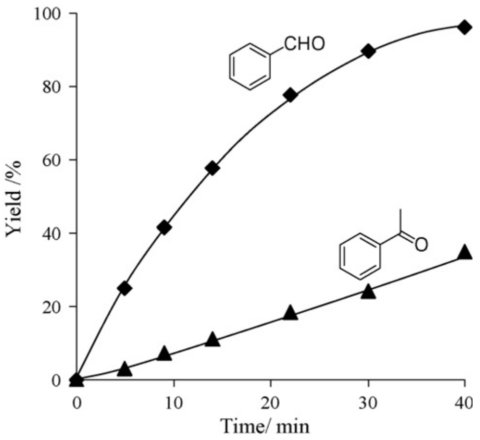
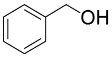
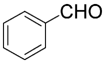
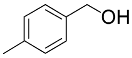
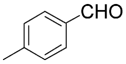
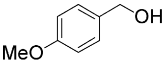
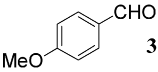
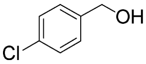
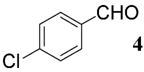
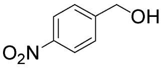
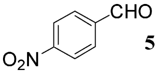
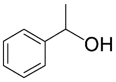
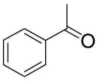
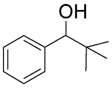
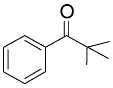
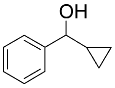
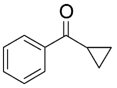
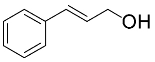
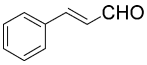
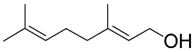
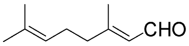
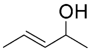
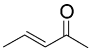
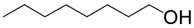
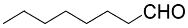
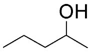
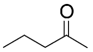
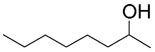
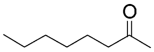
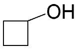
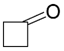
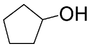
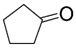
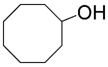
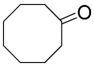
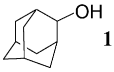
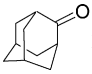
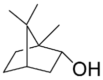
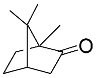
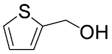
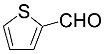
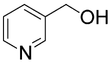
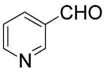


Fig. 1. Reaction profiles of the competitive oxidation of benzyl alcohol (1a) and 1-phenylethanol (**6a**). Reaction conditions: **1a** (0.5 mmol), **6a** (0.5 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 2.5 mol%), $PhCF_3$ (1.5 mL), 83 °C, under 1 atm of molecular oxygen.

Table 2
Aerobic oxidation of various alcohols by $Ru(OH)_x/Al_2O_3$

Entry	Substrate	Time (h)	Conversion (%)	Product	Selectivity (%)
1	 **1a**	1	>99	 **1b**	>99
2	 **2a**	1	>99	 **2b**	>99
3	 **3a**	1	>99	 **3b**	>99
4	 **4a**	1	>99	 **4b**	>99
5	 **5a**	3	97	 **5b**	>99
6	 **6a**	1	>99	 **6b**	>99
7	 **7a**	1.5	>99	 **7b**	>99
8	 **8a**	1	>99	 **8b**	>99
9	 **9a**	1.5	>99	 **9b**	98
10	 **10a**	6	89	 **10b** 97	97
11[a]	 **11a**	6	84	 **11b**	>99
12[a,b]	 **12a**	4	87	 **12b**	98
13	 **13a**	5	90	 **13b**	>99
14	 **14a**	2	91	 **14b**	>99
15[a]	 **15a**	8	85	 **15b**	99
16[a]	 **16a**	8	92	 **16b**	>99
17[a]	 **17a**	6	81	 **17b**	>99
18[a]	 **18a**	7	>99	 **18b**	>99
19	 **19a**	2	>99	 **19b**	99
20	 **20a**	1.5	>99	 **20b**	>99
21[a]	 **21a**	2	93	 **21b**	>99

Reaction conditions: alcohol (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 2.5 mol%), $PhCF_3$ (1.5 mL), 83 °C, under 1 atm of molecular oxygen.

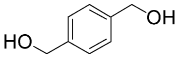
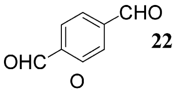
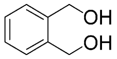
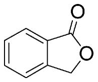
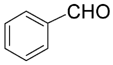
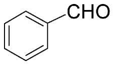
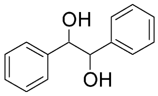
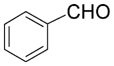
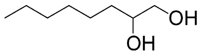
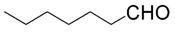
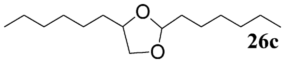
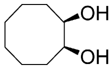
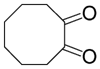
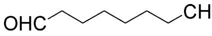
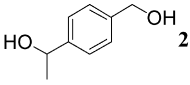
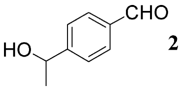
[a] $Ru(OH)_x/Al_2O_3$ (Ru: 5 mol%).

[b] Hydroquinone (1 equiv. with respect to Ru) was added.

secondary OH functions, the same phenomenon was observed for the intermolecular competitive oxidation of **1a** and **6a** (Fig. 1).

Next, the scope of the present $Ru(OH)_x/Al_2O_3$-catalyzed aerobic oxidation of various amines was examined (Table 4). Primary benzylic amines (**29a**–**34a**) were converted into the corresponding benzonitriles in high yields (entries 1–6). For **35a**, the carbon–carbon double bond was intact under the reaction conditions in a similar way to that for the alcohol oxidation and only the NH_2 function was dehydrogenated to the corresponding nitrile **35b** (entry 7). Although it is reported that less reactive aliphatic amines give low yields of the corresponding nitriles in homogeneous ruthenium catalysts such as *trans*-$[Ru^{VI}(tmp)(O_2)]$ (H_2tmp = 5,10,15,20-tetramesitylporphyrin) [19] and $RuCl_2(PPh_3)_3$ [20], the present $Ru(OH)_x/Al_2O_3$-catalyzed oxidation of primary aliphatic amines (**36a** and **37a**) effectively proceeded to give the corresponding nitriles in excellent yields (entries 8 and 9). Not

Table 3
Aerobic oxidation of various diols by $Ru(OH)_x/Al_2O_3$

Entry	Substrate	Time (h)	Conversion (%)	Product	Selectivity (%)
1	 **22a**	2	>99	 **22b**	>99
2	 **23a**	2	>99	 **23b**	98
3	 **1b**	16	>99	 **1b**	90
4	 **25a**	2	>99	 **1b**	92
5	 **26a**	24	80	 **26b**	26
				 **26c**	60
6	 **27a**	6	98	 **27b**	59
				 **27c**	30
7[a]	 **28a**	1	>99	 **28b**	94

Reaction conditions: diol (0.5 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 4 mol%), toluene (3 mL), 100 °C, under 1 atm of molecular oxygen.

[a] Reaction conditions: diol (0.25 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 10 mol%), DMSO (3 mL), 83 °C, under 1 atm of molecular oxygen.

only primary amines but also secondary and heterocyclic amines were selectively oxidized. In the case of secondary amines (**38a** and **39a**), the corresponding imines were obtained in high yields (entries 10 and 11). Heterocyclic amines of indoline (**40a**) and 1,2,3,4-tetrahydroquinoline (**41a**) gave indole (**40b**) and quinoline (**41b**) in >99 and 95% yields, respectively (entries 12 and 13). Interestingly, an intramolecular competitive oxidation of 4-(aminomethyl)benzyl alcohol (**42a**) afforded chemoselectively 4-cyanobenzyl alcohol (**42a**) (entry 14). Further, the same phenomenon was observed for the intermolecular competitive oxidation of amines and alcohols: when an equimolar mixture of **36a** and **12a** was used as substrates, the oxidation of **36a** occurred exclusively as shown in Fig. 2. It is likely that the NH_2 function coordinates more strongly to a ruthenium center than the OH one.

3.2. Heterogeneous catalysis and reuse

The use of solid catalysts can make the workup procedures very simple; catalysts can easily be recovered after the reaction and can be reused without the significant loss of the catalytic activity and selectivity [5–9]. However, leaching and/or deactivation problems of heterogeneous catalysts are responsible for severe drawbacks and are frequently observed in some cases. Therefore, the aerobic oxidations of **1a** and **6a** (for alcohol oxidation), **23a** and **41a** (for amine oxidation) and **32a** (for diol oxidation) as model substrates were carried out with supported ruthenium catalysts in order to verify whether the observed catalysis is caused by solid $Ru(OH)_x/Al_2O_3$ rather than leached ruthenium species. The catalysts were separated by filtration (or centrifugation) around 50% conversion at the reaction temperature and the reaction was again carried out with the filtrate under the same conditions. In all cases, no further consumptions of the substrates were observed, showing that the oxidation was completely stopped by the removal of the catalyst. Furthermore, it was confirmed by the ICP-AES analysis that no ruthenium species was found in the filtrate (below the detection limit of 7 ppb). Therefore, the nature of the observed catalysis is truly heterogeneous [42].

Recently, magnetic materials have attracted much attention because of their wide applications to supports of catalysts and

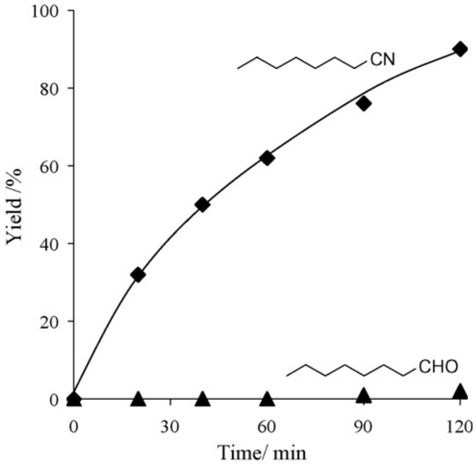
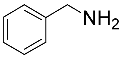
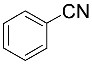
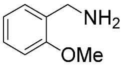
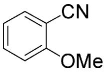
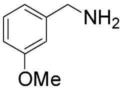
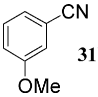
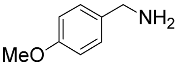
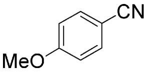
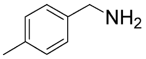
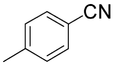
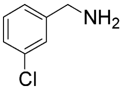
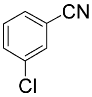
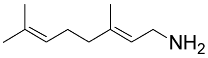
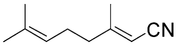
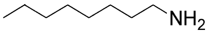
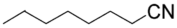
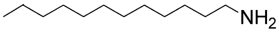
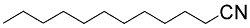
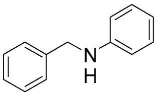
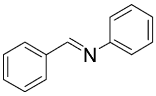
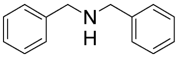
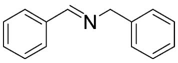
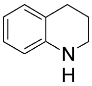
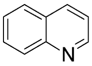
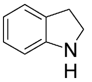
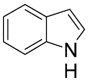
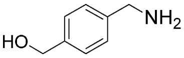
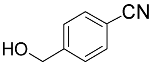


Fig. 2. Reaction profiles of the competitive oxidation of *n*-octylamine (36a) and 1-octanol (**12a**). Reaction conditions: **36a** (1 mmol), **12a** (1 mmol), $Ru(OH)_x/Al_2O_3$ (2.8 mol%), $PhCF_3$ (5 mL), 100 °C, under 1 atm of molecular oxygen.

Table 4
Aerobic oxidation of various amines by $Ru(OH)_x/Al_2O_3$

Entry	Substrate	Time (h)	Conversion (%)	Product	Selectivity (%)
1	 **29a**	1	>99	 **29b**	82
2	 **30a**	1	>99	 **30b**	97
3	 **31a**	1	94	 **31b**	93
4	 **32a**	1	>99	 **32b**	96
5	 **33a**	1	>99	 **33b**	93
6[a]	 **34a**	1	>99	 **34b**	90
7	 **35a**	10	98	 **35b**	90
8	 **36a**	2	>99	 **36b**	>96
9	 **37a**	3	84	 **37b**	90
10	 **38a**	15	85	 **38b**	94
11	 **39a**	16	85	 **39b**	84
12	 **40a**	7	95	 **40b**	>99
13	 **41a**	2	>99	 **41b**	>99
14	 **42a**	2	>99	 **42b**	78

Reaction conditions: amine (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 2.8 mol%), $PhCF_3$ (5 mL), 100 °C, under 1 atm of molecular oxygen.
[a] *p*-Xylene (5 mL), 130 °C.

enzymes, drug delivery, and biosensors [43–46]. Especially, the magnetic properties make possible the complete recovery of the catalyst by means of an external magnetic field, which is an important advantage of the use of a magnetically separable catalyst. We immobilized ruthenium hydroxide on magnetic particles ($Ru(OH)_x/Fe_3O_4$). The $Ru(OH)_x/Fe_3O_4$ catalyst also showed high catalytic performance for the above-mentioned oxidations [47]. In this case, the catalyst/product(s) separation was extremely simple: after the reaction, a permanent magnet was attached on an outside wall of the glass reactor in order to place the catalyst (Fig. 3) and the reaction solution including products was simply decanteted off. More than 99% of $Ru(OH)_x/Fe_3O_4$ catalyst could usually be recovered for each reaction [47].

The XRD patterns of the catalysts recovered after the above-mentioned oxidations were the same as that of the fresh catalysts, showing that the ruthenium species and supports keep the original structure during the oxidations. The catalyst could be reused several times (at least three times) without a significant loss of the catalytic activity and selectivity for both

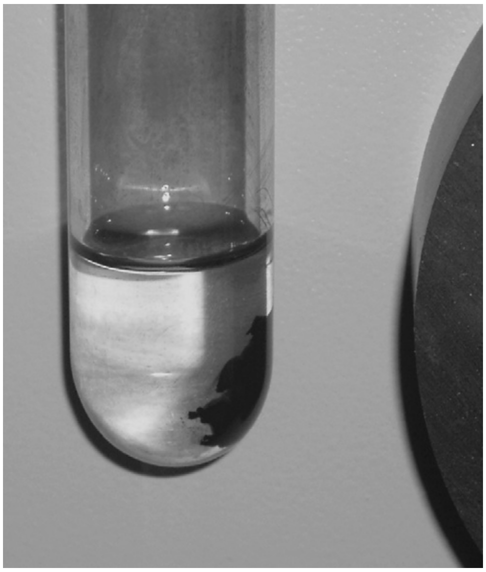
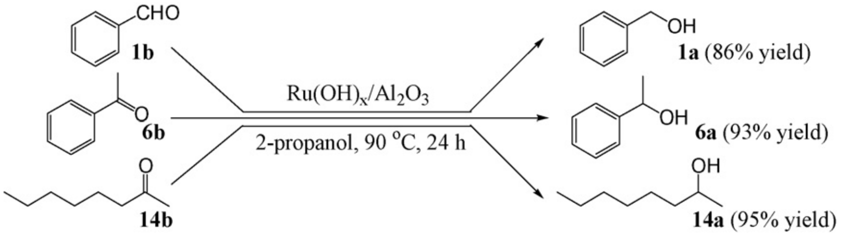
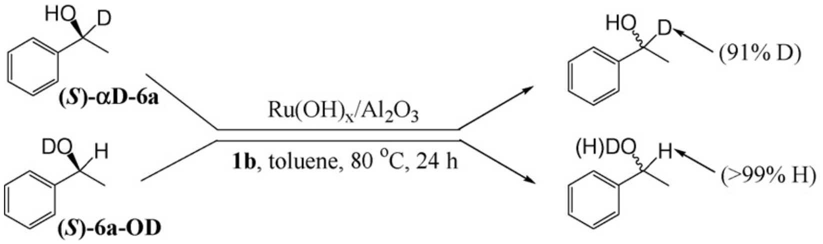


Fig. 3. The picture of the response of $Ru(OH)_x/Fe_3O_4$ to an external magnet.



Scheme 1. $Ru(OH)_x/Al_2O_3$-catalyzed reduction of carbonyl compounds with 2-propanol. Reaction conditions: substrate (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol%), 2-propanol (3 mL), 90 °C (bath temperature), 24 h, under 1 atm of argon.



Scheme 2. Hydrogen transfer racemization of (*S*)-α-deuterio-1-phenylethanol (**(*S*)-αD-6a**) and (*S*)-1-phenylethanol-OD (**(*S*)-6a-OD**) in the presence of acetophenone (**1b**). Reaction conditions: substrate (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 5 mol%), **1b** (1 mmol), toluene (3 mL), 80 °C, 24 h, under 1 atm of argon.

the above-mentioned oxidations. Furthermore, the catalysts have been reused for different types of reactions in sequence.

3.3. Reaction mechanism

A reaction mechanism for aerobic oxidation of alcohols was examined. The addition of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol and hydroquinone (2.5 mol% with respect to **1a**) did not affect the reaction rates as well as the product selectivity for the oxidation of **1a** under the conditions in Table 1. Further, the oxidations of **7a** and **8a** exclusively produced the corresponding ketones. These results show that free-radical intermediates are not involved in the present alcohol oxidation. As mentioned above, the oxidation of primary alcohols proceeded much faster than secondary ones in both intra- and intermolecular competitive oxidations. The faster oxidations of primary alcohols support the formation of ruthenium alkoxide via the ligand exchange of a ruthenium hydroxide species on supported ruthenium hydroxide catalysts with an alcohol. The formation of metal alkoxide species is well known for the selective oxidation of the primary hydroxyl group [48,49].

Next, the competitive oxidations of *p*-substituted benzyl alcohols were examined. The order of reactivity was as follows: *p*-CH_3O ($R_X/R_H = 2.27$) > *p*-CH_3 (1.55) > *p*-H (1.00) > *p*-Cl (0.96) > *p*-NO_2 (0.45), where the values in the parentheses were the relative rates and the rate for **1a** was taken as a unity. When the relative rates ($\log(R_X/R_H)$) were plotted against the heterolytic benzylic C–H bond dissociation energies of *p*-substituted benzyl alcohols calculated at the B3LYP/6-311 ++G(d, p) level theory [38], the good correlation was observed

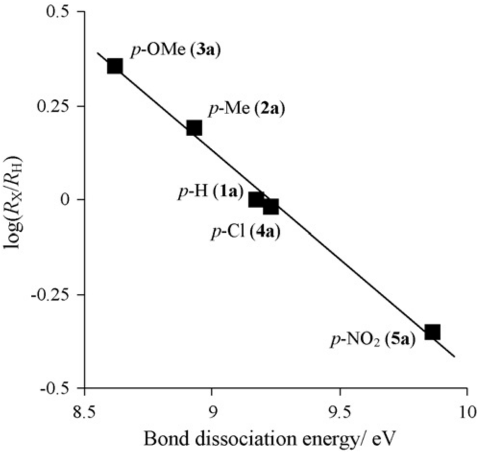
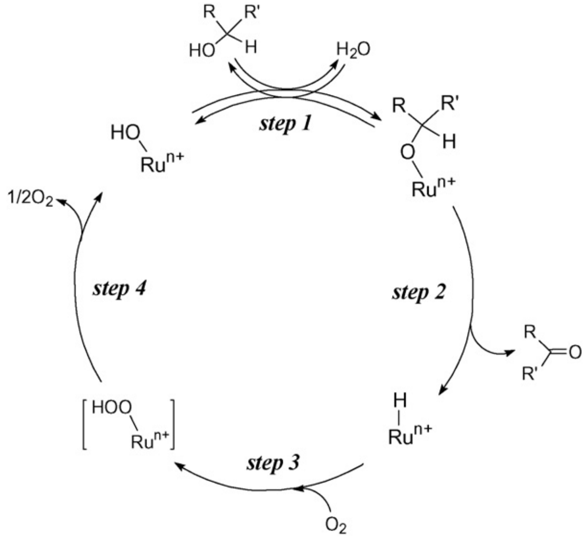
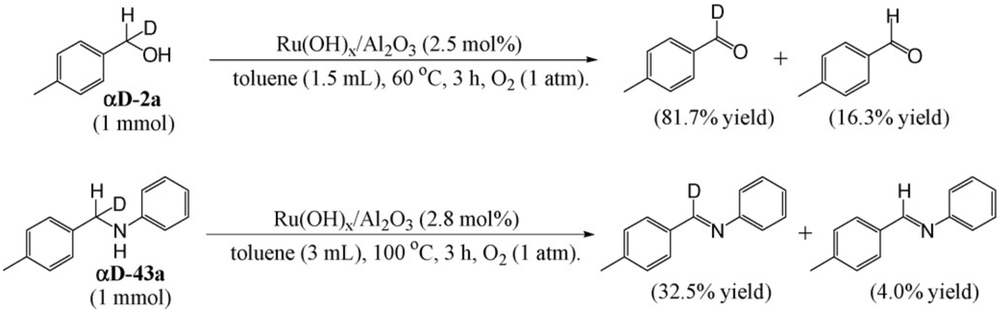


Fig. 4. Relationship between the relative rates ($\log(R_X/R_H)$) and the heterolytic benzylic C–H bond dissociation energies of *p*-substituted benzyl alcohols. Reaction conditions: benzyl alcohol (0.5 mmol), *p*-substituted benzyl alcohol (0.5 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol%), $PhCF_3$ (1.5 mL), 60 °C, under 1 atm of molecular oxygen.



Scheme 3. A possible reaction mechanism for $Ru(OH)_x/Al_2O_3$-catalyzed aerobic oxidation of alcohols. The value of *n* is possibly 3.



Scheme 4. $Ru(OH)_x/Al_2O_3$-catalyzed oxidation of α-deuterio-*p*-methylbenzyl alcohol (**α**D-2a) and *N*-phenyl-α-deuterio-4-methylbenzylamine (**αD-43a**).

as shown in Fig. 4, suggesting that the formation of carbocation-type transition state via the hydride abstraction, in which electron-donating substituents stabilize a carbocation transition state.

When carbonyl compounds were treated in 2-propanol under argon atmosphere, the corresponding alcohols were produced in excellent yields (Scheme 1). This suggests the formation of ruthenium hydride species as an intermediate. In order to clarify the origin of hydride species, the hydrogen-transfer racemization of enantiomerically pure (*S*)-α-deuterio-1-phenylethanol ((***S***)**-αD-6a**) was carried out with an equimolar amount of **1b** according to a similar method to that reported by Pàmies and Bäckvall [50]. In the case of monohydride mechanism, the α-deuterium of (***S***)**-αD-6a** is directly transferred to the carbonyl carbon of **1b** to form racemic **αD-6a** and the α-deuterium is completely preserved at the carbonyl carbon. In contrast, the α-deuterium and OH hydrogen are completely scrambled and lose their identity in the case of dihydride mechanism. As shown in Scheme 3, the deuterium content at the α-position of the racemic alcohol was high (91%) after complete racemization of (***S***)**-αD-6a**. Further, when racemization of (*S*)-α-phenylethanol-OD ((***S***)**-6a-OD**) was carried out with an equimolar amount of **1b**, no deuterium was found at the α-position of the racemic alcohol and the deuterium content in the hydroxyl group was high (>80%, Scheme 2). These results show that the α-hydrogen of an alcohol is transferred to the carbonyl carbon and that the hydroxyl proton is transferred to the carbonyl oxygen in the present $Ru(OH)_x/Al_2O_3$-catalyzed hydrogen-transfer racemization, suggesting the formation of monohydride species during the reaction.

On the basis of the above results, a possible reaction mechanism is proposed in Scheme 3. The present alcohol oxidation includes the formation of ruthenium alkoxide species (step 1) followed by the typical β-elimination to afford the corresponding carbonyl compound and ruthenium monohydride species (step 2). The monohydride species is then reoxidized by molecular oxygen (step 3). Monitoring the O_2 uptake for the oxidation of **1a** revealed that the amount of O_2 consumption was ca. half that of **1b** produced. The 1:2 (O_2:product) stoichiometry shows that the simple dehydrogenation does not proceed and support the reaction mechanism above described. Amine oxidation likely proceeds in a similar way; the formation of ruthenium amide species followed by β-elimination [31]. The kinetic isotope effects (k_H/k_D) were 5.0 ± 0.2 and 8.1 ± 0.3 for the oxidation of α-deuterio-*p*-methylbenzyl alcohol (**αD-2a**, for alcohol oxidation) and *N*-phenyl-α-deuterio-4-methylbenzylamine (**αD-43a**, for amine oxidation), respectively (Scheme 4), showing that the β-elimination is rate-determining step in the present aerobic oxidation [51].

4. Conclusions

We could successfully develop the efficient heterogeneous catalysts for aerobic oxidations of various substances including alcohols, diols, and amines. The performance would raise a prospect of using these types of simple supported catalysts for laboratory-scale organic syntheses as well as industrial applications because of (i) their applicability to a wide range of substrates, (ii) simple workup procedures, that is, products/catalyst separation and (iii) reusability of the catalysts. Detailed mechanistic studies indicate that the present alcohol oxidation includes the formation of ruthenium alkoxide species followed by the typical β-elimination. Further application of these types of supported catalysts to various organic syntheses is in progress.

Acknowledgements

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References

[1] R.A. Sheldon, J.K. Kochi, Metal Catalyzed Oxidation of Organic Compounds, Academic Press, New York, 1981.
[2] C.L. Hill, in: A.L. Baumstark (Ed.), Advances in Oxygenated Processes, vol. 3, JAI Press Inc., London, 1998, p. 1.
[3] M. Hudlucky, Oxidations in Organic Chemistry, ACS Monograph Series, American Chemical Society, Washington, DC, 1990.
[4] A. Madin, in: B.M. Trost, I. Fleming, S.V. Ley (Eds.), Comprehensive Organic Synthesis, vol. 7, Pergamon Press, Oxford, 1991, p. 251.
[5] P.T. Anastas, J.C. Warner, Green Chemistry: Theory and Practice, Oxford University Press, London, 1998.
[6] R.A. Sheldon, Green Chem. 2 (2000) G1.
[7] P.T. Anastas, L.B. Bartlett, M.M. Kirchhoff, T.C. Williamson, Catal. Today 55 (2000) 11.

[8] R.A. Sheldon, H. van Bekkum, Fine Chemical Through Heterogeneous Catalysis, Wiley, Weinheim, 2001.
[9] J. Hagen, Industrial Catalysis: A Practical Approach, Wiley-VCH, Weinheim, 1999.
[10] T. Mallat, A. Baiker, Chem. Rev. 104 (2004) 3037.
[11] R. Lenz, S.V. Ley, J. Chem. Soc., Perkin Trans. 1 (1997) 3291.
[12] A. Hanyu, E. Takezaki, S. Sakaguchi, Y. Ishii, Tetrahedron Lett. 39 (1998) 5557.
[13] A. Dijksman, A. Marino-González, A. Mairata i Payeras, I.W.C.E. Arends, R.A. Sheldon, J. Am. Chem. Soc. 123 (2001) 6826.
[14] G. Csjernyik, A.H. Ell, L. Fadini, B. Pugin, J.-E. Bäckvall, J. Org. Chem. 67 (2002) 1657.
[15] G.-J. ten Brink, I.W.C.E. Arends, R.A. Sheldon, Science 287 (2000) 1636.
[16] I.E. Markó, P.R. Giles, M. Tsukazaki, S.M. Brown, C.J. Urch, Science 274 (1996) 2044.
[17] I.E. Markó, P.R. Giles, M. Tsukazaki, I. Chellé-Regnaut, C.J. Urch, S.M. Brown, J. Am. Chem. Soc. 119 (1997) 12661.
[18] I.E. Markó, A. Gautier, R. Dumeunier, K. Doda, F. Philippart, S.M. Brown, C.J. Urch, Angew. Chem. Int. Ed. 43 (2005) 1588.
[19] A.J. Bailey, B.R. James, Chem. Commun. (1996) 2343.
[20] F. Porta, C. Crotti, S. Cenini, J. Mol. Catal. 50 (1989) 333.
[21] R. Tang, S.E. Diamond, N. Neary, F. Mares, J. Chem. Soc., Chem. Commun. (1978) 562.
[22] Y. Maeda, T. Nishimura, S. Uemura, Bull. Chem. Soc. Jpn. 76 (2003) 2399.
[23] K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, J. Am. Chem. Soc. 122 (2000) 7144.
[24] K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, Chem. Commun. (2001) 461.
[25] K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, J. Am. Chem. Soc. 124 (2002) 11573.
[26] Y. Uozumi, R. Nakao, Angew. Chem. Int. Ed. 42 (2003) 194.
[27] Y.M.A. Yamada, T. Arakawa, H. Hocke, Y. Uozumi, Angew. Chem. Int. Ed. 46 (2007) 704.
[28] A. Abad, P. Concepción, A. Corma, H. García, Angew. Chem. Int. Ed. 42 (2003) 194.
[29] D.I. Enache, J.K. Edwards, P. Landon, B. Solsona-Espriu, A.F. Carley, A.A. Herzing, M. Watanabe, C.J. Kiely, D.W. Knight, G.J. Hutchings, Science 311 (2006) 362.
[30] K. Yamaguchi, N. Mizuno, Angew. Chem. Int. Ed. 41 (2002) 4538.
[31] K. Yamaguchi, N. Mizuno, Angew. Chem. Int. Ed. 42 (2003) 1480.
[32] K. Yamaguchi, N. Mizuno, Chem. Eur. J. 9 (2003) 4353.
[34] K. Kamata, J. Kasai, K. Yamaguchi, N. Mizuno, Org. Lett. 6 (2004) 3577.
[35] M. Matsushita, K. Kamata, K. Yamaguchi, N. Mizuno, J. Am. Chem. Soc. 127 (2005) 6632.
[36] K. Yamaguchi, T. Koike, M. Kotani, M. Matsushita, S. Shinachi, N. Mizuno, Chem. Eur. J. 11 (2005) 6574.
[37] K. Yamaguchi, M. Matsushita, N. Mizuno, Angew. Chem. Int. Ed. 43 (2004) 1576.
[38] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, et al., Gaussian 03, Revision D.02, Gaussian Inc., Wallingford, CT, 2004.
[39] D. Briggs, M.P. Seah, Practical Surface Analysis by Auger and X-ray Photoelectron Spectroscopy, John Wiley & Sons, Chichester, 1983
[40] H.L. Holland, F.M. Brown, M. Conn, J. Chem. Soc., Perkin Trans. 2 (1990) 1651.
[41] I.V. Kozhevnikov, V.E. Tarabanko, K.I. Matveev, Kinet. Katal. 22 (1981) 619.
[42] R.A. Sheldon, M. Wallau, I.W.C.E. Arends, U. Schuchardt, Acc. Chem. Res. 31 (1998) 485.
[43] J. Zhang, Y. Wang, H. Ji, Y. Wei, N. Wu, B. Zuo, Q. Wang, J. Catal. 299 (2005) 114.
[44] H.M.R. Gardimalla, D. Mandal, P.D. Stevens, M. Yen, Y. Gao, Chem. Commun. (2005) 4432.
[45] J. Lee, D. Lee, E. Oh, J. Kim, Y.-P. Kim, S. Jin, H.-S. Kim, Y. Hwang, J.H. Kwak, J.-G. Park, C.-H. Shin, J. Kim, T. Hyeon, Angew. Chem. Int. Ed. 44 (2005) 7432.
[46] T.-J. Yoon, J.S. Kim, B.G. Kim, K.N. Yu, M.-H. Cho, J.-K. Lee, Angew. Chem. Int. Ed. 44 (2005) 1068.
[47] M. Kotani, T. Koike, K. Yamaguchi, N. Mizuno, Green Chem. 8 (2006) 735.
[48] K.B. Sharpless, K. Akashi, K. Oshima, Tetrahedron Lett. 17 (1976) 2503.
[49] S. Kanemoto, S. Matsubara, K. Takai, K. Oshima, K. Utimoto, H. Nozaki, Bull. Chem. Soc. Jpn. 61 (1988) 3607.
[50] O. Pàmies, J.-E. Bäckvall, Chem. Eur. J. 7 (2001) 5052.
[51] K.A. Connors, Chemical Kinetics, The Study of Reaction Rates in Solution, VCH Publishers Inc., New York, 1990.