CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200500539

Synthetic Scope and Mechanistic Studies of $Ru(OH)_x/Al_2O_3$-Catalyzed Heterogeneous Hydrogen-Transfer Reactions

Kazuya Yamaguchi,[a, b] Takeshi Koike,[a] Miyuki Kotani,[b] Mitsunori Matsushita,[a] Satoshi Shinachi,[a] and Noritaka Mizuno*[a, b]

Abstract: Three kinds of hydrogen-transfer reactions, namely racemization of chiral secondary alcohols, reduction of carbonyl compounds to alcohols using 2-propanol as a hydrogen donor, and isomerization of allylic alcohols to saturated ketones, are efficiently promoted by the easily prepared and inexpensive supported ruthenium catalyst $Ru(OH)_x/Al_2O_3$. A wide variety of substrates, such as aromatic, aliphatic, and heterocyclic alcohols or carbonyl compounds, can be converted into the desired products, under anaerobic conditions, in moderate to excellent yields and without the need for additives such as bases. A larger scale, solvent-free reaction is also demonstrated: the isomerization of 1-octen-3-ol with a substrate/catalyst ratio of 20000/1 shows a very high turnover frequency (TOF) of 18400 h^{-1}, with a turnover number (TON) that reaches 17200. The catalysis for these reactions is intrinsically heterogeneous in nature, and the $Ru(OH)_x/Al_2O_3$ recovered after the reactions can be reused without appreciable loss of catalytic performance. The reaction mechanism of the present $Ru(OH)_x/Al_2O_3$-catalyzed hydrogen-transfer reactions were examined with monodeuterated substrates. After the racemization of (*S*)-1-deuterio-1-phenylethanol in the presence of acetophenone was complete, the deuterium content at the α-position of the corresponding racemic alcohol was 91 %, whereas no deuterium was incorporated into the α-position during the racemization of (*S*)-1-phenylethanol-OD. These results show that direct carbon-to-carbon hydrogen transfer occurs via a metal monohydride for the racemization of chiral secondary alcohols and reduction of carbonyl compounds to alcohols. For the isomerization, the α-deuterium of 3-deuterio-1-octen-3-ol was selectively relocated at the β-position of the corresponding ketones (99 % D at the β-position), suggesting the involvement of a 1,4-addition of ruthenium monohydride species to the α,β-unsaturated ketone intermediate. The ruthenium monohydride species and the α,β-unsaturated ketone would be formed through alcoholate formation/β-elimination. Kinetic studies and kinetic isotope effects show that the Ru−H bond cleavage (hydride transfer) is included in the rate-determining step.

Keywords: heterogeneous catalysis • isomerization • racemization • reduction • ruthenium

Introduction

The kinetic resolution of racemic alcohols and amines is a practical method to produce enantiomerically pure chiral products, which are very important intermediates in the synthesis of agricultural chemicals and medicines.[1] However, the maximum yield is 50 % based on the starting racemate and this is still much too low. To overcome this disadvantage, racemization of an undesired enantiomer has been carried out so that this enantiomer can be recycled.[2] Furthermore, dynamic kinetic resolution, in which the substrates are continuously racemized with catalysts during an enzymatic kinetic resolution process, has been performed to overcome this disadvantage.[3] Although many methods for the homogeneous racemization of secondary alcohols and amines catalyzed by transition-metal complexes, especially

---

[a] Dr. K. Yamaguchi, T. Koike, M. Matsushita, S. Shinachi,
Prof. Dr. N. Mizuno
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81) 3-5841-7220
E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp

[b] Dr. K. Yamaguchi, M. Kotani, Prof. Dr. N. Mizuno
Core Research for Evolutional Science and Technology (CREST)
Japan Science and Technology Agency
4-1-8 Honcho, Kawaguchi, Saitama, 332-0012 (Japan)

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

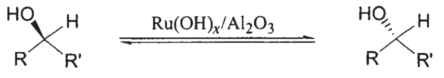
ruthenium complexes, have been developed,[4] these systems often need additives such as hydrogen acceptors and/or bases to promote the reaction. As far as we know, there are only five examples of the heterogeneously catalyzed racemization of alcohols.[2b,d,g,4j,k]

The reduction of carbonyl compounds to alcohols is a fundamental functional transformation and the Meerwein–Ponndorf–Verley (MPV) reduction, in which a ketone is reduced by an alcohol in the presence of an alcoholate of a main-group element, is a long established method.[5] Recently, many transition-metal-catalyzed MPV-type reductions have been developed.[6] Enantioselective reductions have also been achieved in extremely high enantiomeric excesses (*ee*s) using transition-metal catalysts with chiral BINAP and DuPhos ligands.[7]

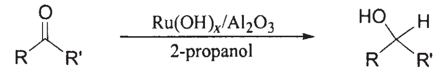
The transformation of allylic alcohols to the corresponding saturated ketones has potential for use in organic synthesis and is usually performed with a two-step sequential or two-pot reaction involving dehydrogenation (or hydrogenation) of allylic alcohols followed by the hydrogenation (or dehydrogenation). However, protection and deprotection steps are sometimes required for such a transformation. From the standpoint of reaction efficiency, the one-pot isomerization of allylic alcohols to the corresponding saturated ketones (theoretical atom economy = 100 %) is highly desirable. Many homogeneous catalytic systems have been developed for this transformation.[8] For example, $[HRuCl(PPh_3)_3]$,[8a] $[RuCp(PPh_3)(CH_3CN)_2]PF_6$,[8e] $[RuCp(PPh_3)_2]Cl/Et_3NPF_6$,[8b,c] a [Cp*Ru(PN)] complex,[8h] Shvo's diruthenium complex,[8d] and nPr$_4$NRuO$_4$/2-undecanol[8f] can catalyze the direct isomerization of allylic alcohols in the presence of bases (in some cases). However, efficient heterogeneous catalysts for the isomerization of allylic alcohols have not been reported so far.

In the manufacture of large-scale petrochemicals as well as in laboratory-scale syntheses, environmentally unfriendly processes should be replaced with greener catalytic ones. In the past few decades, many efficient catalytic hydrogen-transfer reactions have been developed.[2–8] However, especially in the case of racemization of chiral alcohols and isomerization of allylic alcohols, most of them are homogeneous systems and there are few excellent heterogeneous systems that use solid (supported) catalysts, in spite of the significant advantages from environmental and economical standpoints, such as easy catalyst/product separation and recycling of catalysts.[9] Another significant advantage of using heterogeneous catalysts is their high thermal stability.

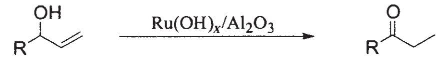
We have recently developed an efficient heterogeneous aerobic oxidation of alcohols,[10a,c] amines,[10b,c] alkylarenes,[10e] phenols[10f] and naphthols,[10f] and hydration of nitriles[10d] by a supported ruthenium hydroxide catalyst ($Ru(OH)_x/Al_2O_3$). In 2002, we reported that a hydrogen-transfer reaction from 2-propanol to acetophenone takes place in the presence of $Ru(OH)_x/Al_2O_3$ under anaerobic conditions during an investigation of the mechanism of the aerobic oxidation of alcohols.[10a,11] Herein, we report the synthetic scope of three kinds of heterogeneously catalyzed hydrogen-transfer reactions, namely the racemization of chiral secondary alcohols [Eq. (1)], the reduction of carbonyl compounds to alcohols with 2-propanol as the hydrogen donor [Eq. (2)], and the isomerization of allylic alcohols to saturated ketones [Eq. (3)], in the presence of $Ru(OH)_x/Al_2O_3$. Furthermore, we have also investigated the reaction mechanism of the present $Ru(OH)_x/Al_2O_3$-catalyzed hydrogen-transfer reactions with monodeuterated substrates.



(1)



(2)



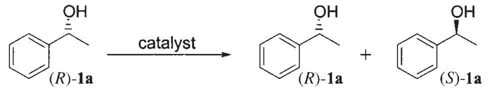
(3)

Results and Discussion

Racemization of chiral secondary alcohols: First, the catalytic activity and selectivity for the racemization of (R)-1-phenylethanol ((R)-**1a**) were compared for various catalysts. The results are shown in Table 1. No racemization proceeded in the absence of the catalyst or in the presence of Al_2O_3 alone (Table 1, entries 20 and 21). In the case of $RuCl_3 \cdot nH_2O$, the selectivity for the racemization was very low (6 %) because of the formation of 1-phenyl-1-tolylethane and 1,1′-(oxydiethylidene)dibenzene as by-products (Table 1, entry 12). Among the various ruthenium catalysts tested, $Ru(OH)_x/Al_2O_3$ showed the highest catalytic activity for the racemization of (R)-**1a**, giving the corresponding alcohol **1a** in 31 % *ee* with a small amount of acetophenone (**1b**) (Table 1, entry 1). The racemization rate increased with an increase in the reaction temperature (333–383 K), and the TOF reached 68 h^{-1} at 383 K, while the selectivity for the racemization was slightly decreased from 92 % (at 353 K) to 80 % (at 383 K). The TOF value was higher than that of the active homogeneous catalyst nPr$_4$NRuO$_4$ (3.7 h^{-1}, entry 18) and that of the active heterogeneous catalyst Ru–hydroxyapatite (RuHAP) (1.0 h^{-1}, Table 1, entry 11).[2c,12,13] Although other ruthenium catalysts such as $[RuCl_2(PPh_3)_3]$, $[RuCl_2(bpy)_2]$, and $[RuCl_2(DMSO)_4]$ have been reported to be active for the racemization in the presence of bases such as NaOH and Na_2CO_3,[2] they were completely inactive in the absence of bases under the present reaction conditions (Table 1, entries 13–15). Similarly, $K_2RuCl_6 \cdot nH_2O$, $[Ru(acac)_3]$, and $[Ru_3(CO)_{12}]$ were completely inactive under the present conditions (Table 1, entries 16, 17, and 19).

Among the solvents tested, nonpolar toluene, isooctane, and p-xylene were found to be good solvents and gave 31, 47, and 59 % *ee* for **1a** (Table 1, entries 1–3), respectively, for the racemization of (R)-**1a** under the conditions described in Table 1. On the other hand, polar 1,4-dioxane and

Table 1. Racemization of (*R*)-1-phenylethanol ((*R*)-**1a**).[a]



Entry	Catalyst	Solvent	*ee* [%][b]	Select. [%]	TOF [h^{-1}][c]
1	$Ru(OH)_x/Al_2O_3$	toluene	31	92	23
2	$Ru(OH)_x/Al_2O_3$	isooctane	47	96	15
3	$Ru(OH)_x/Al_2O_3$	*p*-xylene	59	94	11
4	$Ru(OH)_x/Al_2O_3$	chlorobenzene	74	97	6.0
5	$Ru(OH)_x/Al_2O_3$	THF	76	96	5.5
6	$Ru(OH)_x/Al_2O_3$	1,2-dichloroethane	79	98	4.7
7	$Ru(OH)_x/Al_2O_3$	1,4-dioxane	80	95	4.4
8	$Ru(OH)_x/Al_2O_3$	acetonitrile	98	98	0.4
9	$Ru(OH)_x/Al_2O_3$	water	NR	–	
10[d]	RuHAP	toluene	95	98	1.0
11	RuO_2 (anhydrous)	toluene	NR	–	
12	$RuCl_3{\cdot}nH_2O$	toluene	1	6[e]	–
13	$[RuCl_2(PPh_3)_3]$	toluene	NR	–	
14	$[RuCl_2(bpy)_3]$	toluene	NR	–	
15	$[RuCl_2(DMSO)_4]$	toluene	NR	–	
16	$[Ru(acac)_3]$	toluene	NR	–	
17	$K_2RuCl_6{\cdot}nH_2O$	toluene	NR	–	
18	$n\mathrm{Pr}_4NRuO_4$	toluene	83	88	3.7
19	$[Ru_3(CO)_{12}]$	toluene	NR	–	
20[f]	Al_2O_3	toluene	NR	–	
21	none	toluene	NR	–	

[a] Reaction conditions: (*R*)-**1a** (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol %), solvent (3 mL), 353 K, 5 h, under 1 atm of Ar. The enantiomeric excess of (*R*)-**1a** and selectivity for racemization were determined by GC analysis (Rt β-CDEXM column) using an internal standard technique. The main by-product was acetophenone. Each carbon balance was more than 95 %. [b] NR = no reaction. [c] The TOF values were calculated by the following recursion formula: TOF [h^{-1}] = {log(*ee*/100)}/{log(1−(*x*/100))}/*t*, where *ee*, *x*, and *t* are the enantiomeric excess [%], amount of catalyst [mol %], and reaction time [h], respectively. [d] Prepared according to the literature procedure (Ru content: 1.9 wt %, ref. [12]). [e] 1-Phenyl-1-tolylethane and 1,1′-(oxydiethylidene)bisbenzene were formed as by-products. [f] Al_2O_3 (37 mg).

acetonitrile were found to be poor solvents (Table 1, entries 7 and 8), and the racemization did not proceed at all in water (Table 1, entry 9).

To verify whether the observed catalysis is due to solid $Ru(OH)_x/Al_2O_3$ or leached ruthenium species, a catalytic racemization of (*R*)-**1a** was carried out under the conditions described in Table 1 and then the $Ru(OH)_x/Al_2O_3$ was removed from the reaction mixture by filtration at the reaction temperature. The filtrate was used again for the reaction. As shown in Figure 1, no racemization of (*R*)-**1a** was observed after the removal of $Ru(OH)_x/Al_2O_3$. Furthermore, it was confirmed by ICP-AES analysis that no ruthenium was present in the filtrate (below detection limit of 7 ppb). The $Ru(OH)_x/Al_2O_3$ catalyst recovered after the racemization of (*R*)-**1a** could be recycled without appreciable loss of the original catalytic activity (entry 2 in Table 2). These facts rule out any contribution to the observed catalysis from ruthenium species that leach into the reaction solution and signify that the observed catalysis is intrinsically heterogeneous.[14]

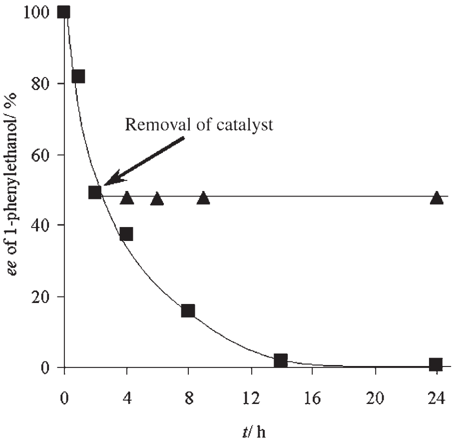
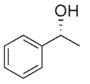
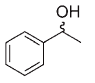
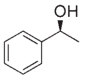
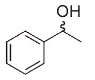
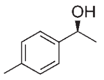
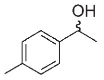
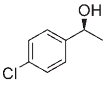
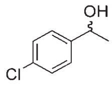
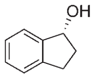
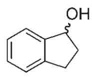
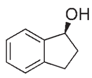
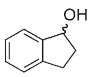
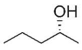
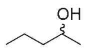
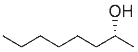
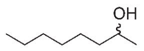
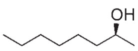
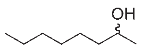


Figure 1. Effect of removal of $Ru(OH)_x/Al_2O_3$ on the racemization of (*R*)-**1a**. Without removal of $Ru(OH)_x/Al_2O_3$ (■); an arrow indicates the removal of $Ru(OH)_x/Al_2O_3$ (▲). Reaction conditions: (*R*)-**1a** (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol %), toluene (3 mL), 353 K.

Table 2 shows the results of racemization of various chiral secondary alcohols with 1 mol % of the $Ru(OH)_x/Al_2O_3$ catalyst at 353 K under anaerobic conditions. $Ru(OH)_x/Al_2O_3$ has high catalytic activity for the racemization of nonactivat-

Table 2. Racemization of various chiral secondary alcohols catalyzed by $Ru(OH)_x/Al_2O_3$.[a]

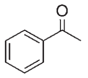
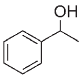
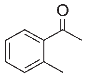
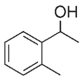
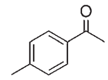
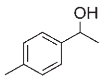
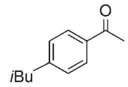
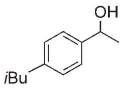
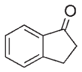
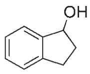
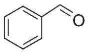
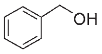
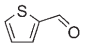
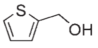
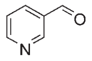
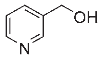
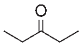
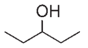
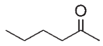
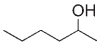
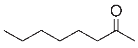
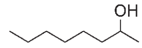
Entry	Substrate	Product	*ee* [%]	Select. [%]
1 2[b]	 (*R*)-**1a**	 **1a**	2 9	87 92
3	 (*S*)-**1a**	 **1a**	2	86
4	 (*S*)-**2a**	 **2a**	6	90
5	 (*S*)-**3a**	 **3a**	51	94
6	 (*R*)-**4a**	 **4a**	1	57
7	 (*S*)-**4a**	 **4a**	<1	65
8	 (*R*)-**5a**	 **5a**	2	91
9	 (*R*)-**6a**	 **6a**	4	92
10	 (*S*)-**6a**	 **6a**	2	91

[a] Reaction conditions: Substrate (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol %), toluene (3 mL), 353 K, 24 h, under 1 atm of Ar. The enantiomeric excess and selectivity to racemization were determined by GC (Rt β-CDEXM column) or HPLC (Chiralcel-OD column) analyses using an internal standard technique. The main by-products were the corresponding ketones. Each carbon balance was more than 95 %. [b] Recycling experiment. The reaction conditions were the same as those for the first run.

ed chiral secondary alcohols as well as activated ones. Phenylethanols (*R*)-**1a**, (*S*)-**1a**, and (*S*)-**2a** were smoothly converted into the corresponding racemic alcohols with good *ee* values and selectivities (Table 2, entries 1, 3, and 4). On the other hand, the racemization of (*S*)-**3a**, which contains an electron-withdrawing substituent, was much slower than that of (*S*)-**2a**, which contains an electron-donating substituent (Table 2, entries 4 and 5). The racemization of indanols (*R*)-**4a** and (*S*)-**4a** proceeded efficiently with the formation of indanone (Table 2, entries 6 and 7). Both aromatic alcohols and less-reactive aliphatic alcohols such as (*R*)-**5a**, (*R*)-**6a**, and (*S*)-**6a** could be racemized to the corresponding alcohols (Table 2, entries 8–10).

Reduction of carbonyl compounds to alcohols: The transition-metal-catalyzed hydrogen-transfer reaction from 2-propanol to carbonyl compounds is convenient in large-scale production processes because it is not necessary to use high-pressure molecular hydrogen or hazardous reduction reagents such as $LiAlH_4$ and $NaBH_4$. Various kinds of ketones and aldehydes could be reduced to the corresponding alcohols in high yields with 2-propanol as the hydrogen donor (solvent) in the presence of $Ru(OH)_x/Al_2O_3$ under similar conditions to those of the racemization.[15] The results are summarized in Table 3. The present system does not need any bases and the reduction proceeds under relatively mild reaction conditions with a small amount of the catalyst (typically 1–3 mol%). A major advantage of using $Ru(OH)_x/Al_2O_3$ is its heterogeneous nature, which was confirmed by the fact that the reaction did not proceed after removal of the solid catalyst. Acetophenones **1b**, **7b**, **2b**, and **8b** were smoothly converted into the corresponding 1-phenylethanols in excellent yields (more than 88%, Table 3, entries 1–4). $Ru(OH)_x/Al_2O_3$ also catalyzes the reduction of sulfur- or nitrogen-containing carbonyl compounds to the corresponding alcohols in moderate yields (Table 3, entries 7 and 8). Both aromatic ketones and less-reactive aliphatic ketones such as **6b**, **12b**, and **13b** could be reduced to the corresponding aliphatic secondary alcohols in excellent yields (more than 95%, Table 3, entries 9–11).

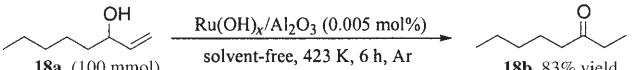
Table 3. Reduction of various ketones and aldehyde using 2-propanol as a hydrogen donor catalyzed by $Ru(OH)_x/Al_2O_3$.[a]

Entry	Substrate	Product	Yield [%]	Select. [%]
1	 **1b**	 **1a**	93	>99
2	 **7b**	 **7a**	98	>99
3	 **2b**	 **2a**	91	>99
4	 **8b**	 **8a**	88	>99
5	 **4b**	 **4a**	61	>99
6	 **9b**	 **9a**	86	>99
7[b]	 **10b**	 **10a**	70	95
8[c]	 **11b**	 **11a**	50	99
9	 **12b**	 **12a**	96	>99
10[b]	 **13b**	 **13a**	97	>99
11[b]	 **6b**	 **6a**	95	>99

[a] Reaction conditions: Substrate (1 mmol), $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol%), 2-propanol (3 mL), 363 K, 24 h, under 1 atm of Ar. Yields and selectivities were determined by GC analysis (DB-WAX column) using an internal standard technique. Each carbon balance was more than 95%. [b] $Ru(OH)_x/Al_2O_3$ (Ru: 3 mol%). [c] $Ru(OH)_x/Al_2O_3$ (Ru: 5 mol%).

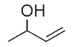
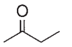
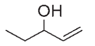
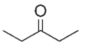
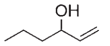
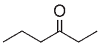
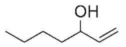
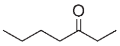
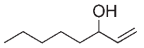
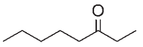
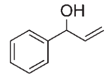
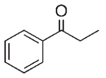
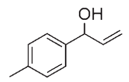
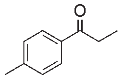
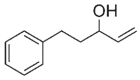
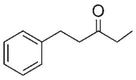
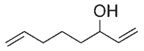
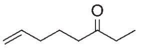
Isomerization of allylic alcohols: The scope of the present $Ru(OH)_x/Al_2O_3$-catalyzed isomerization of various kinds of allylic alcohols was also examined.[16] The results are summarized in Table 4. Trace amounts of the corresponding α,β-unsaturated ketones (ca. 1%) were detected as by-products in some cases. The aliphatic terminal allylic alcohols **14a**–**18a** were completely isomerized to the corresponding aliphatic saturated ketones **14b**–**18b** at 363 K in 3 h (more than 98%, Table 4, entries 1–5). The aromatic terminal allylic alcohols **19a**–**21a** were also isomerized to the corresponding aromatic ketones **19b**–**21b** in high yields (more than 80%, Table 4, entries 7–9). In the case of dienol **22a**, the hydrogen atoms were only transferred to the allylic double bond to afford the corresponding enone **22b** as the sole product (Table 4, entry 10). In the present system, the isomerization of internal allylic alcohols such as 2-cyclohexen-1-ol and 3-penten-2-ol[17] and homoallylic alcohols such as 1-hexen-4-ol and 4-phenyl-1-buten-4-ol did not proceed. The $Ru(OH)_x/Al_2O_3$ catalyst could be reused with the maintenance of the high catalytic performance; the aliphatic allylic alcohol **18a** was converted almost quantitatively into **18b** at the same reaction rate as that for the first run (Table 4, entry 6). The heterogeneous nature of the $Ru(OH)_x/Al_2O_3$ catalyst was examined by filtration experiments; no isomerization proceeded in the filtrate after removal of the catalyst.

The heterogeneous isomerization of allylic alcohols *without any organic solvents* would be more important for industry. We therefore demonstrated that $Ru(OH)_x/Al_2O_3$ efficiently catalyzes the isomerization of **18a** *without solvents.* Thus, the solvent-free reaction of **18a** was carried out at 423 K with a substrate/catalyst molar ratio of 20000/1; a TOF of 18400 h^{-1} (determined by the initial rate) and TON (after 6 h) of 17200 were achieved [Eq. (4)].[18]



18a, (100 mmol) 86% conv. — **18b**, 83% yield TOF = 18400 h^{-1} (4)

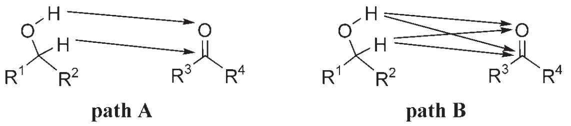
Table 4. Isomerization of various allylic alcohols catalyzed by Ru(OH)$_x$/Al$_2$O$_3$.[a]

Entry	Substrate	Product	Yield [%]	Select. [%]
1	 **14a**	 **14b**	98	>99
2	 **15a**	 **12b**	>99	>99
3	 **16a**	 **16b**	>99	>99
4	 **17a**	 **17b**	99	99
5	 **18a**	 **18b**	98	99
6[b]			96	99
7[c]	 **19a**	 **19b**	94	>99
8[c]	 **20a**	 **20b**	80	99
9[c]	 **21a**	 **21b**	89	>99
10[d]	 **22a**	 **22b**	91	99

[a] Reaction conditions: Substrate (1 mmol), Ru(OH)$_x$/Al$_2$O$_3$ (Ru: 1 mol%), toluene (3 mL), 363 K, 3 h, under 1 atm of Ar. Yields and selectivities were determined by GC analysis (DB-WAX column) using an internal standard technique. Traces of the α,β-unsaturated ketones (<1%) were detected in some cases. Each carbon balance was more than 95%. [b] Recycling experiment. The reaction conditions were the same as those for the first run. The reaction rate for the recycling experiment was almost the same as that for the first run with new catalyst. [c] 393 K. [d] **22a** (0.5 mmol), Ru(OH)$_x$/Al$_2$O$_3$ (Ru: 2 mol%), [D$_8$]toluene (1.5 mL), 393 K, 15 h. Yield and selectivity were determined by GC and ^{1}H NMR analysis.

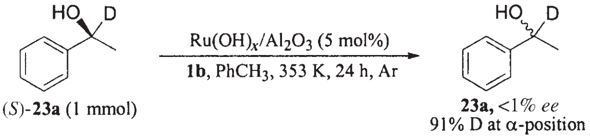
The TOF and TON values are higher than those reported to date for the isomerization of allylic alcohols: [Cp*Ru(PN)]/KO*t*Bu (**19a**, TOF and TON of 2500 h^{-1} and 100, respectively),[8h] [RuCp(PPh$_3$)(CH$_3$CN)$_2$]PF$_6$ (**18a**, 2000 h^{-1}, 100),[8e] Shvo's diruthenium complex (**18a**, 1000 h^{-1}, 500),[8d] [HRuCl(PPh$_3$)$_3$] (**18a**, 287 h^{-1}, 287),[8a] Fe(CO)$_5$/$h\nu$ (**18a**, 95 h^{-1}, 95),[8g] [RuCp(PPh$_3$)$_2$]Cl/Et$_3$NPF$_6$ (**20a**, 8 h^{-1}, 16),[8b,c] and n-Pr$_4$NRuO$_4$/2-undecanol (**19a**, not reported, 17).[8f]

Mechanism of racemization and reduction of carbonyl compounds to alcohols: According to the literature,[2e,f] the racemization of chiral secondary alcohols and reduction of carbonyl compounds to alcohols can proceed through the one of two mechanisms. The first is a direct hydrogen transfer, which involves a six-membered cyclic transition state and is reported to occur in the case of main-group elements,[2,3,19] and the other is the metal hydride mechanism using transition-metal catalysts.[2,3,7c] Since the detailed mechanistic studies of Ru(OH)$_x$/Al$_2$O$_3$-catalyzed aerobic oxidation of alcohols suggest the formation of a ruthenium hydride,[10a,c] the present racemization and reduction probably proceed by the metal hydride mechanism. Two different pathways have been reported for the metal hydride mechanism depending on the nature of the metal hydride species:[2e] a metal monohydride species can be formed only from the α-hydrogen of an alcohol substrate, while a metal dihydride species can be formed from both the α-hydrogen and hydroxy proton of an alcohol substrate. In the case of the monohydride mechanism, the α-hydrogen is directly transferred to the carbonyl carbon of a hydrogen acceptor (path A in Scheme 1), whereas two hydrogens are completely scrambled and lose their identity in the case of the dihydride mechanism (path B in Scheme 1).



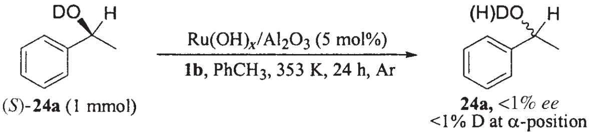
Scheme 1. Possible pathways for hydrogen transfer.[2e]

To clarify the origin of the hydride species, the racemization of enantiomerically pure (*S*)-1-deuterio-1-phenylethanol ((*S*)-**23a**) was carried out with an equimolar amount of acetophenone (**1b**) according to a similar method to that reported by Bäckvall and co-workers.[2e] As shown in Equation (5), the deuterium content at the α-position of the racemic alcohol **23a** was high (91%) after complete racemization of (*S*)-**23a**.



(5)

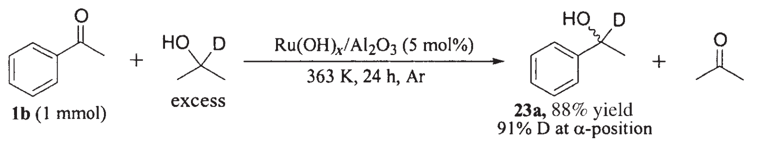
Furthermore, when racemization of (*S*)-**24a** was carried out with an equimolar amount of **1b**, no deuterium was found at the α-position of the racemic alcohol **24a** and the deuterium content in the hydroxy group was high (>80%) [Eq. (6)].



(6)

These results show that the α-hydrogen atom of the alcohol is transferred to the carbonyl carbon atom and that the hydroxy proton is transferred to the carbonyl oxygen in the present Ru(OH)$_x$/Al$_2$O$_3$-catalyzed hydrogen-transfer reactions.

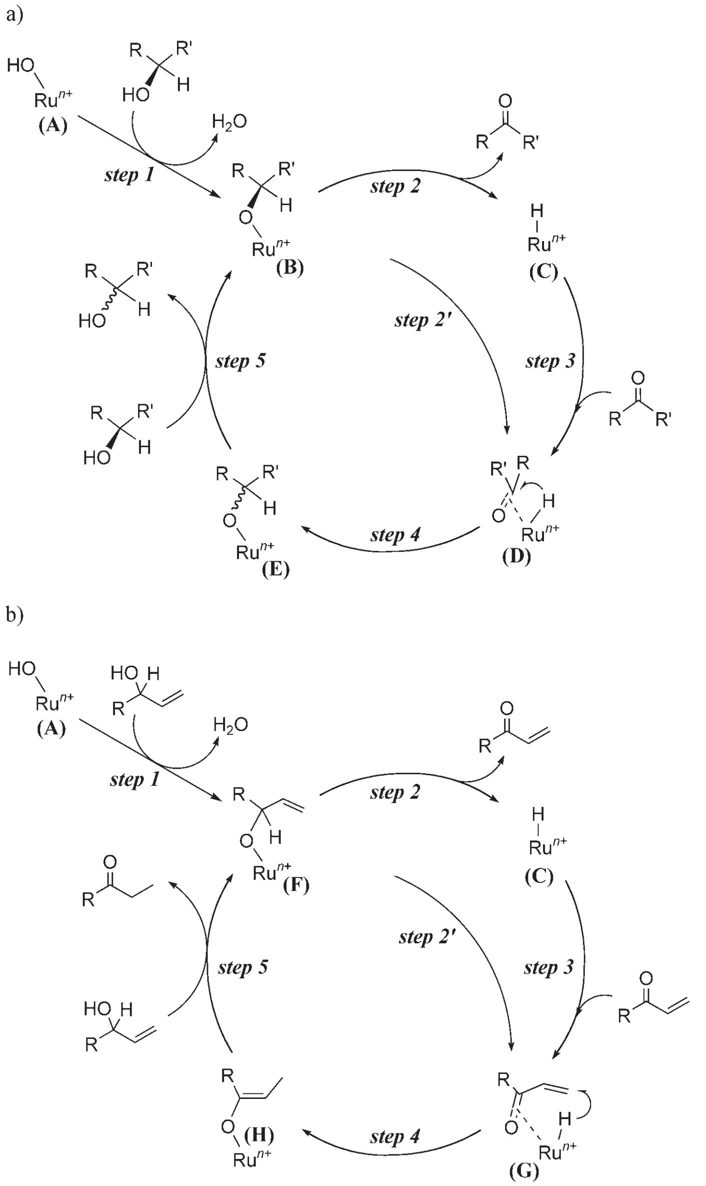
On the basis of these results, we can propose a possible reaction mechanism for this Ru(OH)$_x$/Al$_2$O$_3$-catalyzed racemization (Scheme 2a). Initially, the ruthenium alcoholate species **B** is formed by ligand exchange between ruthenium hydroxide **A** and the alcohol (step 1). The alcoholate **B** then undergoes β-hydride elimination to afford the corresponding carbonyl compound and the ruthenium monohydride species **C** (step 2). The direct formation of the ketone–hydride intermediate **D** from **B** may be possible (step 2′). The re-addition of the hydride species **C** to the carbonyl carbon gives the isomeric alcoholate species **E** (steps 3 and 4). Finally, intermolecular ligand exchange between the alcoholate **E** and the alcohol leads to the racemic alcohol (step 5). When the reduction of **1b** was carried out using 2-deuterio-2-propanol under similar conditions to those described in Table 3, the α-deuterium of 2-deuterio-2-propanol was transferred to the carbonyl carbon of **1b** to give racemic 1-deuterio-1-phenylethanol (**23a**) as the main product (88% yield, 91% D at α-position) [Eq. (7)].



(7)

This fact suggests that the reduction of carbonyl compounds to alcohols using 2-propanol also proceeds by the same mechanism as that for the racemization.

A kinetic isotope effect (k_H/k_D) of 3.3 was observed for the racemization of (*S*)-**1a** and (*S*)-**23a** at 353 K.[20] On the other hand, no kinetic isotope effect ($k_H/k_D = 1.0$) was observed for the racemization of (*S*)-**1a** and (*S*)-**24a**. These kinetic isotope effects show that the O–H bond cleavage is not part of the rate-determining step and that the C–H (β-elimination) or Ru–H bond cleavage (hydride transfer) is part of the rate-determining step. The Arrhenius plots for the racemization of (*R*)-**1a** (the pseudo-first-order rate constant k_{app} versus T^{-1} between 333 and 383 K) are shown in Figure 2. The good linearity of these plots gives the following activation parameters: $E_a = 11.9$ kcal mol^{-1}, $\Delta H^{\ddagger}_{353} = 11.2$ kcal mol^{-1}, $\Delta S^{\ddagger}_{353} = -46.5$ eu, and $\Delta G^{\ddagger}_{353} = 27.5$ kcal mol^{-1}. The large negative value of the activation entropy ($\Delta S^{\ddagger}_{353}$) suggests that a bimolecular transition state, where two molecules (or more) are converted into a single transition state molecule, is probably included in the rate-determining step.[21] Therefore, we conclude that Ru–H bond cleavage (hydride transfer, step 4) is the rate-determining step for this racemization.



Scheme 2. Proposed reaction mechanisms for the Ru(OH)$_x$/Al$_2$O$_3$-catalyzed racemization of chiral secondary alcohols (a) and isomerization of allylic alcohols (b).

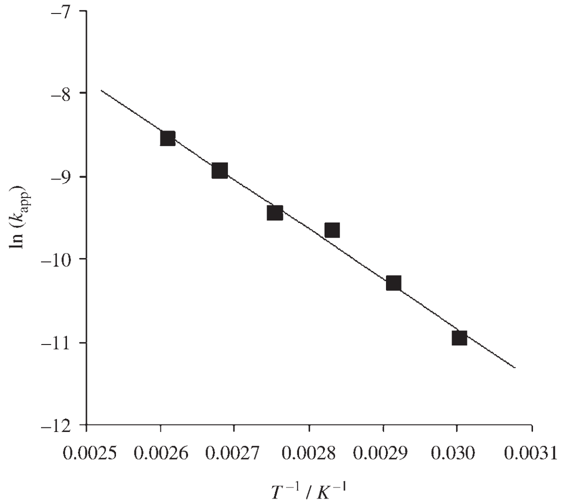
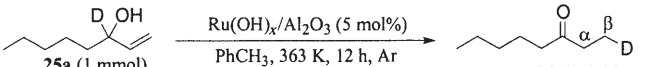


Figure 2. Arrhenius plots for the racemization of (*R*)-**1a**. The apparent pseudo-first-order rate constants (k_{app}) were determined from the initial part of the reactions. Reaction conditions: (*R*)-**1a** (1 mmol), Ru(OH)$_x$/Al$_2$O$_3$ (Ru: 1 mol%), toluene (3 mL), 333–383 K. Line fit: $\ln(k_{app}) = 7.1 - 5977.1/T$ ($R^2 = 0.99$). The following activation parameters were obtained from the line fit of the Arrhenius plots: $E_a = 11.9$ kcal mol^{-1}, $\Delta H^{\ddagger}_{353} = 11.2$ kcal mol^{-1}, $\Delta S^{\ddagger}_{353} = -46.4$ eu, and $\Delta G^{\ddagger}_{353} = 27.5$ kcal mol^{-1}.

Mechanism of isomerization of allylic alcohols: The isomerization of the allylic acetate of 3-acetoxy-1-octene and homoallylic alcohols such as 1-hexen-4-ol and 4-phenyl-1-buten-4-ol does not proceed under the same conditions as those described in Table 4. In addition, the hydrogen-transfer reaction does not take place at the isolated double bond in the case of a dienol (entry 10 in Table 4). Therefore, both an allylic hydroxy function and a double bond are necessary for the present isomerization. When 1 mol% of $Ru(OH)_x/Al_2O_3$ was used for the isomerization of **18a**, the corresponding α,β-unsaturated ketone was initially produced and the yield was less than 1% in the conversion range 0–99%.

A monodeuterated allylic alcohol, namely 3-deuterio-1-octen-3-ol (**25a**), was used as a mechanistic probe.[8c,h] The isomerization of **25a** for 12 h under similar conditions of Table 4 gave a monodeuterated saturated ketone (MS: *m*/*z* 129.20 [M^+], 7.25% of base peak). The deuterium is only present at the β-position of this ketone [Eq. (8)], therefore, the present $Ru(OH)_x/Al_2O_3$ can distinguish between the hydrogen in the hydroxy group and from the α-hydrogen, probably because of their relocation at the α- and β-carbon atoms of the corresponding ketone.[22]



25a (1 mmol)
>99% conv.

25b, 98% yield
<1% D transfer to α-position
99% D transfer to β-position

(8)

On the basis of the above results, we can propose the following reaction mechanism for this $Ru(OH)_x/Al_2O_3$-catalyzed isomerization of allylic alcohols (Scheme 2b). The initial two steps (steps 1 and 2) are probably the same as those for the racemization and reduction: the ruthenium alcoholate species **F** is formed by ligand exchange between ruthenium hydroxide **A** and an allylic alcohol (step 1), followed by the formation of the ruthenium monohydride species **C** and the corresponding α,β-unsaturated ketone by β-hydride elimination (step 2). The direct formation of the enone–hydride intermediate **G** from **F** may also be possible (step 2′). Then, 1,4-addition of **C** to the α,β-unsaturated ketone gives the σ-enolate intermediate **H** (steps 3 and 4).[8f,23] Finally, intermolecular ligand exchange between **H** and the allylic alcohol leads to the corresponding saturated ketone (step 5).

A kinetic isotope effect (k_H/k_D) of 2.5 was observed for the isomerization of **18a** and **25a** at 353 K, whereas no kinetic isotope effect ($k_H/k_D = 1.0$) was observed for the isomerization of **18a** and deuterated 1-octen-3-ol (**26a**). For the isomerization of **18a**, an activation entropy ($\Delta S^{\ddagger}_{363}$) of −30.5 eu was observed,[24] which suggests that a bimolecular transition state is included in the rate-determining step.[21] These results show that the Ru−H bond cleavage (hydride transfer, step 4) is the rate-determining step for this isomerization.

Conclusion

$Ru(OH)_x/Al_2O_3$ acts as an efficient heterogeneous catalyst for three kinds of hydrogen-transfer reactions. This ability raises the prospect of using this type of simple supported catalyst for organic syntheses and industrial processes because of 1) its applicability to a wide range of substrates, 2) its high turnover frequency and turnover number, 3) simple workup procedures, that is, product/catalyst separation, and 4) its reusability. The mechanistic investigations using monodeuterated substrates have shown that the ruthenium monohydride species formed from an alcohol and a ruthenium hydroxide species on the catalyst is a key intermediate for these $Ru(OH)_x/Al_2O_3$-catalyzed hydrogen-transfer reactions, for which Ru−H bond cleavage (hydride transfer) is included in the rate-determining step.

Experimental Section

General: NMR spectra were recorded on a JEOL JNM-EX-270 spectrometer. ^1H and ^{13}C NMR spectra were measured at 270 and 67.8 MHz, respectively, in [D_1]chloroform or [D_3]acetonitrile with TMS as an internal standard. ^2H NMR spectra were measured at 41.25 MHz using [D_6]benzene as an external standard. GC analyses were performed on a Shimadzu GC-17 A using a flame ionization detector equipped with an Rt β-CDEXM capillary column (internal diameter = 0.25 mm, length = 30 m) or a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). HPLC analyses were performed on Shimadzu LC-10 A with a UV detector equipped with a Chiralcel-OD column (internal diameter = 46 mm, length = 25 cm) and with *n*-hexane/2-propanol (95/5 v/v) as the eluent. Mass spectra were recorded on a Shimadzu GCMS-QP2010 equipped with a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m) at an ionization voltage of 70 eV. Reagents, solvents, and substrates, except for **21a**, **22a**, (*S*)-**23a**, (*S*)-**24a**, **25a**, and **26a**, which were synthesized according to the literature procedures (see Supporting Information),[8c,25–27] were purchased from Tokyo Kasei, Aldrich, and Fluka (reagent grade) (the solvents in particular must be carefully purified). Alumina (KHS-24, BET surface area: 160 m^2g^{-1}) was supplied by Sumitomo Chemical Co., Ltd. All products were identified by comparison of their GC retention time, mass spectra, and ^1H and ^{13}C NMR spectra with authentic samples. The $Ru(OH)_x/Al_2O_3$ catalyst was prepared according to a procedure reported previously (See Supporting Information).[10]

Procedure for the $Ru(OH)_x/Al_2O_3$-catalyzed hydrogen-transfer reactions: All operations were carried out in a glove box under argon. A typical procedure is as follows. $Ru(OH)_x/Al_2O_3$ (Ru: 1 mol%), (*R*)-**1a** (1 mmol), and toluene (3 mL) were successively placed into a Pyrex-glass vial. A Teflon-coated magnetic stir-bar was then added, and the reaction mixture was vigorously stirred (800 rpm) at 353 K under 1 atm of argon. After 24 h, the catalyst and the product(s) were separated by filtration (or centrifugation), and the solid mixture was washed with toluene. Then, diphenyl (internal standard, 0.3 mmol) was added to the combined organic solution and the solution was analyzed by chiral GC. The separated $Ru(OH)_x/Al_2O_3$ was washed with an aqueous solution of NaOH (1 M) and water, and then dried in vacuo before being recycled.

Procedure for the $Ru(OH)_x/Al_2O_3$-catalyzed deuterium transfer reactions: The reactions of (*S*)-**23a**, (*S*)-**24a**, and **25a** were carried out following the same procedure as for the hydrogen-transfer reactions. The location and content of deuterium in the products were determined by ^1H, ^2H, and ^{13}C NMR analyses (see Supporting Information).

Acknowledgements

This work was supported by the Core Research for Evolutional Science and Technology (CREST) program of the Japan Science and Technology Agency (JST) and Grants-in-Aid for Scientific Research ((A) and Priority Area "Molecular Nano Dynamics") from the Ministry of Education, Culture, Sports, Science, and Technology.

---

[1] a) R. A. Sheldon, *Chirotechnology, Industrial Synthesis of Optically Active Compounds*, Dekker, New York, **1993**; b) C. H. Wang, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Elsevier, Amsterdam, **1994**.

[2] a) J. H. Koh, H. M. Jeong, J. Park, *Tetrahedron Lett.* **1998**, *39*, 5545; b) W.-H. Kim, R. Karvembu, J. Park, *Bull. Korean Chem. Soc.* **2004**, *25*, 931; c) S. Wuyts, D. E. De Vos, F. Verpoort, D. Depla, R. De Gryse, P. A. Jacobs, *J. Catal.* **2003**, *219*, 417; d) U. T. Strauss, U. Felfer, K. Faber, *Tetrahedron: Asymmetry* **1999**, *10*, 107; e) O. Pàmies, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052; f) D. Klomp, T. Maschmeyer, U. Hanefeld, J. A. Peters, *Chem. Eur. J.* **2004**, *10*, 2088; g) D. W. House, *US Patent*, 5,476,964, **1995**.

[3] a) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.* **2003**, *103*, 3247; b) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321.

[4] a) B. A. Persson, A. L. E. Larsson, M. Le Ray, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 1645; b) O. Pàmies, A. H. Éll, J. S. M. Samec, N. Hermanns, J.-E. Bäckvall, *Tetrahedron Lett.* **2002**, *43*, 4699; c) O. Pàmies, J.-E. Bäckvall, *J. Org. Chem.* **2002**, *67*, 1261; d) J. H. Koh, H. M. Jung, M.-J. Kim, J. Park, *Tetrahedron Lett.* **1999**, *40*, 6281; e) J. H. Choi, Y. H. Kim, S. H. Nam, S. T. Shin, M.-J. Kim, J. Park, *Angew. Chem.* **2002**, *114*, 2479; *Angew. Chem. Int. Ed.* **2002**, *41*, 2372; f) M.-J. Kim, Y. Chung, Y. K. Choi, H. K. Lee, D. Kim, J. Park, *J. Am. Chem. Soc.* **2003**, *125*, 11494; g) R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport, L. A. Cuccia, *J. Org. Chem.* **1991**, *56*, 2656; h) P. M. Dinh, J. A. Howarth, A. R. Hudnott, J. M. J. Williams, W. Harris, *Tetrahedron Lett.* **1996**, *37*, 7623; i) A. Dijksman, J. M. Elzinga, Y.-X. Li, I. W. C. E. Arends, R. A. Sheldon, *Tetrahedron: Asymmetry* **2002**, *13*, 879; j) M. T. Reetz, K. Schimossek, *Chimia* **1996**, *50*, 668; k) S. Wuyts, K. De Temmerman, D. De Vos, P. Jacobs, *Chem. Commun.* **2003**, 1928; l) M. Ito, A. Osaku, S. Kitahara, M. Hirakawa, T. Ikariya, *Tetrahedron Lett.* **2003**, *44*, 7521.

[5] a) H. Meerwein, R. Schmidt, *Justus Liebigs Ann. Chem.* **1925**, *444*, 221; b) A. Verley, *Bull. Soc. Chim. Fr.* **1925**, *37*, 537; c) W. Ponndorf, *Angew. Chem.* **1926**, *38*, 138; d) K. Nishida, M. Noda, *Chirality* **2002**, *14*, 759; e) J. F. de Graauw, J. A. Peters, H. van Bekkum, J. Huskens, *Synthesis* **1994**, 1007, and references therein.

[6] a) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051; b) T. Naota, H. Takaya, S.-I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599; c) J.-E. Bäckvall, R. L. Chowdhury, U. Karlsson, *J. Chem. Soc. Chem. Commun.* **1991**, 473; d) A. Aranyos, G. Csjernyik, K. J. Szabó, J.-E. Bäckvall, *Chem. Commun.* **1999**, 351.

[7] a) R. Noyori, *Chem. Soc. Rev.* **1989**, *18*, 187; b) R. Noyori, *Science* **1990**, *248*, 1194; c) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345; d) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97; e) M. J. Palmer, M. Will, *Tetrahedron: Asymmetry* **1999**, *10*, 2045, and references therein.

[8] a) Y. Sasson, G. L. Rempel, *Tetrahedron Lett.* **1974**, *15*, 4133; b) B. M. Trost, R. J. Kulawiec, *Tetrahedron Lett.* **1991**, *32*, 3039; c) B. M. Trost, R. J. Kulawiec, *J. Am. Chem. Soc.* **1993**, *115*, 2027; d) J.-E. Bäckvall, U. Andresson, *Tetrahedron Lett.* **1993**, *34*, 5459; e) C. Slugovc, E. Ruba, R. Schmid, K. Kirchner, *Organometallics* **1999**, *18*, 4230; f) I. E. Markó, A. Gautier, M. Tsukazaki, A. Llobet, E. Plantalech-Mir, C. J. Urch, S. M. Brown, *Angew. Chem.* **1999**, *111*, 2126; *Angew. Chem. Int. Ed.* **1999**, *38*, 1960; g) H. Cherkaoui, M. Soufiaoui, R. Grée, *Tetrahedron* **2001**, *57*, 2379; h) M. Ito, S. Kitahara, T. Ikariya, *J. Am. Chem. Soc.* **2005**, *127*, 6172.

[9] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, **1998**; b) P. T. Anastas, L. B. Bartlett, M. M. Kirchhoff, T. C. Williamson, *Catal. Today* **2000**, *55*, 11; c) J. H. Clark, *Green Chem.* **1999**, *1*, 1; d) R. A. Sheldon, *Green Chem.* **2000**, *2*, G1; e) R. A. Sheldon, H. van Bekkum, *Fine Chemicals through Heterogeneous Catalysis*, Wiley, Weinheim, **2001**.

[10] a) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2002**, *114*, 4720; *Angew. Chem. Int. Ed.* **2002**, *41*, 4538; b) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2003**, *115*, 1517; *Angew. Chem. Int. Ed.* **2003**, *42*, 1479; c) K. Yamaguchi, N. Mizuno, *Chem. Eur. J.* **2003**, *9*, 4353; d) K. Yamaguchi, M. Matsushita, N. Mizuno, *Angew. Chem.* **2004**, *116*, 1602; *Angew. Chem. Int. Ed.* **2004**, *43*, 1576; e) K. Kamata, J. Kasai, K. Yamaguchi, N. Mizuno, *Org. Lett.* **2004**, *6*, 3577; f) M. Matsushita, K. Kamata, K. Yamaguchi, N. Mizuno, *J. Am. Chem. Soc.* **2005**, *127*, 6632.

[11] During the preparation of this manuscript, Park and co-workers reported the racemization of secondary alcohols with a $Ru(OH)_x/Al_2O_3$ catalyst. See reference [2b].

[12] K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc.* **2000**, *122*, 7144.

[13] Ikariya and co-workers have reported an efficient homogeneous racemization using [Cp*RuCl(cod)] as the catalyst. In the presence of $Ph_2P(CH_2)_2NH_2$ and KO*t*Bu as base, the turnover frequency for the racemization of (*R*)-**1a** reached 479 h^{-1}. See reference [4l].

[14] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485.

[15] The reduction of **1b** in methanol, ethanol, and 2-propanol was carried out under the conditions of Table 3 and gave the corresponding alcohol **1a** in 1, 5, and 93 % yield, respectively.

[16] The catalytic activity and selectivity for this isomerization were compared for various catalysts in the absence of bases using **18a** as a model substrate. The effect of solvents was also examined. See Table S1 in the Supporting information.

[17] It has been reported that the reactivity of internal allylic alcohols decreases with an increase in the steric constraints of the catalysts because the steric hindrance around the double bond of internal allylic alcohols imposes a steric barrier to coordination to the metal center(s). See reference [8].

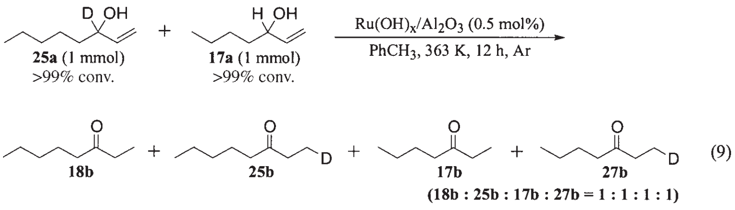
[18] We confirmed that no reaction proceeded under the same reaction conditions without the $Ru(OH)_x/Al_2O_3$ catalyst.

[19] a) W. N. Molton, R. E. Van Atta, R. R. Rich, *J. Org. Chem.* **1960**, *25*, 290; b) V. J. Shiner, D. Whittaker, J. Whittaker, *J. Am. Chem. Soc.* **1969**, *91*, 394.

[20] A kinetic isotope effect (k_H/k_D) of 5.3 was observed for the reduction of **1b** in 2-propanol and 2-deuterio-2-propanol.

[21] K. A. Connors, *Chemical Kinetics, The Study of Reaction Rates in Solution*, VCH Publishers: New York, **1990**.

[22] In the reaction of a 1:1 mixture of the two allylic alcohols **25a** and **17a** with $Ru(OH)_x/Al_2O_3$, an equimolar mixture of ketones **18b**, **25b**, **17b**, and **27b** was obtained [Eq. (9)], thus showing the intermolecularity of the present hydrogen transfer.



(9)

[23] For a related 1,4-addition of ruthenium species to α,β-unsaturated ketones, see: a) Y. Ishii, K. Osakada, T. Ikariya, M. Saburi, S. Yoshikawa, *J. Org. Chem.* **1986**, *51*, 2034; b) R. Guo, R. H. Morris, D. Song, *J. Am. Chem. Soc.* **2005**, *127*, 516; c) M. Watanabe, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2003**, *125*, 7508; d) T. Ikariya, H. Wang, M. Watanabe, K. Murata, *J. Organomet. Chem.* **2004**, *689*, 1377; e) H. Wang, M. Watanabe, T. Ikariya, *Tetrahedron Lett.* **2005**, *46*, 963.

[24] The Arrhenius plots for the isomerization of **18a** (333–373 K) are shown in Figure S1 in the Supporting Information. The following ac-

tivation parameters were obtained from the line fit of the Arrhenius plots: $E_a = 16.5$ kcal mol^{-1}, $\Delta H^{\ddagger}_{363} = 15.8$ kcal mol^{-1}, $\Delta S^{\ddagger}_{363} = -30.5$ eu, and $\Delta G^{\ddagger}_{363} = 26.8$ kcal mol^{-1}.

[25] C. Spino, N. Barriault, *J. Org. Chem.* **1999**, *64*, 5292.

[26] H. L. Holland, F. M. Brown, M. Conn, *J. Chem. Soc. Perkin Trans. 2* **1990**, 1651.

[27] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974.

Received: May 16, 2005