Effective transfer hydrogenation of unsaturated compounds by ruthenium dihydride complex in propan-2-ol

Eiichiro Mizushima, Motowo Yamaguchi, Takamichi Yamagishi *

Department of Applied Chemistry, Graduate School of Engineering, Tokyo Metropolitan University, Minami-Ohsawa, Hachioji, Tokyo 192-0397, Japan

Abstract

Ruthenium(II)-hydride complexes were very effective catalysts for the transfer hydrogenation of ketones and imines using propan-2-ol as hydrogen donor in the presence of a base. By using the catalyst dihydridotetrakis(triphenylphosphine)-ruthenium(II), the reduction proceeded effectively in the absence of a base. This ruthenium dihydride catalyst also caused the transfer hydrogenation of benzonitrile to afford benzylamine derivatives albeit in a moderate yield. Isotope labeling experiments in the reaction of *N*-(2-naphthylmethylidene)benzylamine with this ruthenium dihydride catalyst revealed the hydride transfer from ruthenium hydride to the C=N bond of the substrate. In the case of the ruthenium monohydride species, no transfer hydrogenation occurred for ketones, imines and nitrile in the absence of a base except at the C=C double bond of conjugated carbonyl compounds. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Transfer hydrogenation; Ruthenium; Dihydride complex

1. Introduction

For the preparation of optically active compounds (chiral compounds), the reduction of unsaturated compounds is an effective methodology. Transfer hydrogenation using alcohol as the hydrogen source is a convenient method to reduce ketones and imines because of the simplicity in experimental aspects. $RuCl_2(PPh_3)_3$ was frequently used for the transfer hydrogenation of ketones and imines, but the dichloro complex requires the presence of a base such as KOH, NaOH or K_2CO_3 to proceed the reduction smoothly, and it is not clear what kind of

ruthenium species is the actual active species [1–5]. It was reported that a hydride complex is formed by the reaction of $RuCl_2(PPh_3)_3$ with an alkoxide [6]. Therefore, the real active species for transfer hydrogenation is assumed to be a hydridoruthenium species [7,8]. We have examined several hydridoruthenium species in the transfer hydrogenation and found that the ruthenium monohydride species hydridochlorotris(triphenylphosphine)ruthenium(II) **1** and the ruthenium dihydride species dihydridotetrakis(triphenylphosphine)ruthenium(II) **2** are much more active for the transfer hydrogenation of ketones and imines than $RuCl_2(PPh_3)_3$. Furthermore, $RuH_2(PPh_3)_4$ was active even in the absence of a base [9]. In this paper, we report the application of this ruthenium dihydride catalyzed trans-

* Corresponding author. Tel.: +81 426 77 2847; Fax: +81 426 77 2821; E-mail: yamagishi-takamichi@c.metro-u.ac.jp

fer hydrogenation to various unsaturated substrates (ketones, imines, nitrile and α,β-unsaturated carbonyl compounds) together with the results of mechanistic studies.

2. Experimental

2.1. General procedure

^{1}H and ^{31}P NMR spectra were recorded on a JEOL EX-270 spectrometers, with tetramethylsilane (Me$_4$Si) as an internal standard and 85% H$_3$PO$_4$ as an external standard, respectively. *J* values are given in Hz. Column chromatography was carried out on silica gel (Merck, 230–400 mesh) or alumina using ethyl acetate/n-hexane as eluent.

2.2. Preparation of ruthenium hydride complexes

Hydridochlorotris(triphenylphosphine)ruthenium(II) **1**, dihydridotetrakis(triphenylphosphine)ruthenium(II) **2** and dideuteridotetrakis(triphenylphosphine)ruthenium(II) were prepared by methods reported in literature [10–12]. These complexes were identified by ^{1}H and ^{31}P NMR spectra.

RuHCl(PPh$_3$)$_3$ **1**: A purple powder: δ_H(270 MHz, C$_6$D$_6$) −17.5 (q, *J* = 25.8, 1H); RuH$_2$-(PPh$_3$)$_4$ **2**: A yellow powder: δ_H(270 MHz, C$_6$D$_6$) −10.1 (m, 2H); δ_P{^{1}H} (109 MHz, C$_6$D$_6$) 41.7 (t, *J* = 13.9, 2P), 49.8 (t, *J* = 13.9, 2P); RuD$_2$(PPh$_3$)$_4$: A yellow powder: This complex was obtained as a mixture of RuD$_2$(PPh$_3$)$_4$, RuHD(PPh$_3$)$_4$ and RuH$_2$(PPh$_3$)$_4$. δ_P{^{1}H} (109 MHz, C$_6$D$_6$) 41.7 (m, 2P), 49.8 (m, 2P); the multiplet hydride signal was observed at δ_H −10.1. The average H/D ratio was 0.58/0.42.

2.3. General procedure for the ruthenium catalyzed transfer hydrogenation with propan-2-ol

2.3.1. Reaction in the presence of KOH

After the ruthenium hydride complex (0.1–0.5 mol%) was solved in propan-2-ol, substrate

and 5 mol% of KOH were added successively into the solution. The reaction was conducted at 85°C under nitrogen atmosphere. The ruthenium catalyst was removed by filtration over short silica gel or alumina column, the yield was determined by ^{1}H NMR analysis.

2.3.2. Reaction in the absence of KOH

After the ruthenium hydride complex (0.5–2 mol%) was solved in propan-2-ol, substrate was added into the solution. The reaction was conducted at 85°C under nitrogen atmosphere. The ruthenium catalyst was removed by filtration over short silica gel or alumina column, the yield was determined by ^{1}H NMR analysis.

2.3.3. Isotope labeling study

Three types of the ruthenium hydride or deuteride complex, **1**, **2** and Ru(A$_2$)(PPh$_3$)$_4$ (A$_2$ = D$_2$, HD or H$_2$, H/D = 0.58/0.42) were used. As hydrogen donor, CH$_3$OH and CD$_3$OD (D content 99.8%) were used. The reaction was performed in methanol/THF mixture at 65°C because of the solubility problems of the ruthenium complexes.

3. Results and discussion

3.1. Transfer hydrogenation of ketones and imines with RuHCl(PPh$_3$)$_3$ and RuH$_2$(PPh$_3$)$_4$

The transfer hydrogenation of several ketones proceeded very smoothly in propan-2-ol at reflux temperature when catalyzed by complexes RuHCl(PPh$_3$)$_3$ (**1**) and RuH$_2$(PPh$_3$)$_4$ (**2**) in the presence of KOH under nitrogen atmosphere
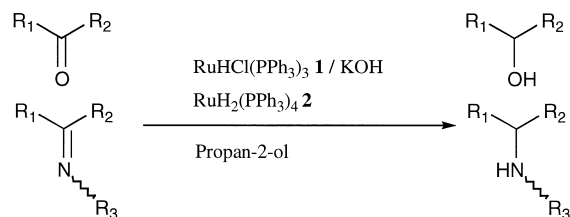
Scheme 1.

Table 1

Transfer hydrogenation of ketones catalyzed by ruthenium hydride complexes **1** and **2**[a]

Entry	Ketone substrate		Catalyst	Time (h)	Temp. (°C)	Yield (%)
	R_1	R_2				
1	Ph–	Me–	**1**	1	85	67 (48)[b]
2	Ph–	Et–	**1**	1	85	57 (18)[b]
3	Ph–	Et–	**2**	1	85	53
4	1-Nap–	Me–	**1**	1	85	96
5	2-Nap–	Me–	**1**	1	85	83
6[c]	2-Nap–	Me–	**1**	4	r.t.	50
7[c]	$-CH_2(CH_2)_3CH_2-$		**1**	1	r.t.	50 (57)[d]
8[c,d]	$-CH_2(CH_2)_3CH_2-$		**2**	1	r.t.	47

[a] Reaction was carried out in propan-2-ol at 85°C unless otherwise noted. **1** or **2**/Substrate/KOH = 1/1000/5.
[b] Values in parentheses refer to the results of the $[RuCl_2(PPh_3)_3]$ system [1].
[c] **1** or **2**/Substrate/KOH = 1/200/5.
[d] The reaction performed in propan-2-ol/THF mixture.

(Scheme 1). The catalytic activities of complexes **1** and **2** are much higher than that of $RuCl_2(PPh_3)_3$ (Table 1). The activity of the complex **2** was nearly the same as that of the complex **1**. The complex **1** could catalyze the transfer hydrogenation of 1- or 2-acetonaphthone very effectively in up to 96% yield within 1 h (entries 4 and 5). The transfer hydrogenation by the complex **1** proceeded even at room temperature in the presence of a base (entries 6, 7 and 8) while with a dihaloruthenium-phosphine catalyst, such as $RuCl_2(PPh_3)_3$ and the diphosphine complex $RuBr_2(P-P)_2$, the reaction of ketones required higher reaction temperatures [1,13].
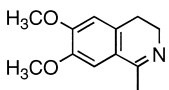
Imines were also reduced by the transfer hydrogenation using **1** or **2** in the presence of KOH in propan-2-ol at reflux temperature, though the imine reduction is slower than that of ketones. As shown in Table 2, aldimines are more easily reduced than ketimines [3] by complexes **1** and **2**. Cyclic imine was smoothly reduced by the catalyst **1** to afford a tetrahydroisoquinoline derivative in a good yield (entry 6).

As described above, catalysts **1** and **2** showed nearly the same activity in the presence of KOH co-catalyst. We have examined the reaction in the absence of a base and found that the catalyst **2** could cause the transfer hydrogenation of ketones and imines even in the absence of a base. In contrast, transfer hydrogenation did not proceed with the catalyst **1** in the absence of a base (Table 3, entries 2 and 5; Table 4, entry 3).

Table 2

Transfer hydrogenation of imines catalyzed by ruthenium hydride complexes **1** and **2**[a]

Entry	Imine Substrate			Catalyst	Time	Yield
	R_1	R_2	R_3		/h	/%
1	Ph-	H-	$PhCH_2-$	**1**	5	95 (93/18h)[b]
2	2-Nap-	H-	$PhCH_2-$	**1**	5	96 (91/18h)[b]
3	Ph-	Me-	$PhCH_2-$	**1**	18	84 (48/18h)[b]
4	Ph-	Me-	$PhCH_2-$	**2**	18	89
5	2-Nap-	Me-	$PhCH_2-$	**1**	18	95
6[c]				**1**	18	90

[a] Reaction was carried out in propan-2-ol at 85°C unless otherwise noted. **1** or **2**/Substrate/KOH = 1/200/5.
[b] Values in parentheses refer to the results of the $[RuCl_2(PPh_3)_3]$ system [3].
[c] Cyclic imine was used as substrate.

Table 3
Transfer hydrogenation of ketones catalyzed by ruthenium hydride complexes **1** and **2** without KOH[a]

Entry	Substrate		Catalysts	Time (h)	Yield (%)
	R_1	R_2			
1	Ph–	Me–	**2**	3	93
2	Ph–	Me–	**1**	3	0
3	2-Nap–	Me–	**2**	3	97
4[b]	2-Nap–	Me–	**2**	6	82
5	2-Nap–	Me–	**1**	3	0

[a]Reaction was carried out in propan-2-ol at 85°C. **1** or **2**/Substrate = 1/200.
[b]At 50°C.

The presence of KOH did not accelerate the catalytic activity of the catalyst **2** (Table 4, entries 1 and 2). These results suggest that the catalyst **2** is the true active species for the transfer hydrogenation of ketones and imines in propan-2-ol. Only a few examples of ruthenium catalyzed effective transfer hydrogenation of ketones and imines in alcohol without a base are reported [14]. [1,2] With this catalyst **2**, isomerization of ketimines to aldimines was observed in aprotic solvents [15]. This strongly suggests the addition of ruthenium hydride to the C=N double bond, followed by β-elimination. In an alcoholic solution, protonation of the intermediary ruthenium complex formed by the hydride addition will afford the reduced product.

As described before, a cyclic imine, a dihydroisoquinoline derivative, was reduced by the catalyst **1** in the presence of KOH to afford the cyclic amine effectively. With the complex **2** in the absence of KOH, this cyclic imine was not reduced at all, but an isoquinoline compound was obtained in a moderate yield by dehydrogenation (Table 4, entry 9), though the ordinary imines were readily reduced to amines by this

catalyst **2** in the absence of KOH. This striking difference in the reaction of the cyclic imine will indicate the different structures of the active species derived from **1**-KOH or **2** systems. The mechanism of dehydrogenation in the cyclic imine by **2** is not clear, but the contribution of zero-valent ruthenium species formed by the reductive elimination of dihydride may be possible [16,17].

3.2. Transfer hydrogenation of benzonitrile

We further applied this $RuH_2(PPh_3)_4$ catalyst to the reduction of nitrile, since the transfer hydrogenation of nitrile has not been reported yet. Murahashi et al. [18] reported the hydrolysis of nitriles to afford amides in the presence of the ruthenium dihydride complex. With $RuH_2(PPh_3)_4$ in the absence of a base, benzonitrile was converted in propan-2-ol to a mixture of benzylamine (6%), benylidenebenzylamine (20%) and dibenzylamine (25%) in 51% conversion (Scheme 2). Benzylamine was assumed to be formed by stepwise reductions via an imine, while dimeric product, benzylidenebenzylamine, was considered to be formed via transimination of the imine by benzylamine. Recently, similar dimerization is observed in the reduction of 2-cyanopyrrole with lithium aluminum hydride [19]. Using $RuHCl(PPh_3)_3$ as the catalyst and in the presence of KOH, the reaction afforded complex products in low yields.

3.3. Selective transfer hydrogenation of unsaturated carbonyl compounds

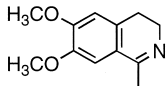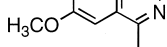In the ruthenium catalyzed transfer hydrogenation of α,β-unsaturated aldehydes or ketones using alcohol as hydrogen donor, the carbon–carbon double bond is more easily reduced than the carbonyl group [20,21]. In the present transfer hydrogenation (Scheme 3), $RuH_2(PPh_3)_4$ could reduce selectively the carbonyl group of the α,β-unsaturated aldehyde. For

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[1] Recently, Noyori et al. reported that the ruthenium(II)-arene complex with p-TsN(C_6H_5)CH(C_6H_5)CHNH ligand catalyzed the reduction of acetophenone without KOH.

[2] On the 43rd and 44th organometallic chemistry symposium of Japan, Yamamoto et al. also reported the transfer hydrogenation of benzylideneanilines in the absence of base with cationic monohydridoruthenium(II) catalysts.

Table 4
Transfer hydrogenation of imines catalyzed by ruthenium hydride complexes **1** and **2** without KOH[a]

Entry	Imine Substrate			Catalyst	Time	Yield
	R_1	R_2	R_3		/h	/%
1	Ph-	Me -	PhCH$_2$-	**2**	18	89
2[b]	Ph-	Me -	PhCH$_2$-	**2**-KOH	18	89
3[c]	Ph-	Me-	PhCH$_2$-	**1**	5	0
4	Ph-	Me-	PhCH$_2$-	**1**-KOH	18	84
5	2-Nap-	H-	PhCH$_2$-	**2**	5	95
6	Cy-	Me -	PhCH$_2$-	**2**	18	81
7	Ph-	H-	Ph(Me)CH-	**2**	18	36
8	Ph-	H-	Ph(Me)CH-	**1**-KOH	18	85
9				**2**	18	0[e]
10[b]				**1**-KOH	18	90

[a] Reaction was carried out in propan-2-ol at 85°C. **1** or **2**/Substrate = 1/200.
[b] Ru/KOH = 1/5.
[c] Ru/Substrate = 1/50.
[e] Aromatization occurred to afford the corresponding isoquinoline derivative in 21% yield.

α,β-unsaturated ketones, however, selective hydrogenation was not observed and saturated secondary alcohols were obtained [22]. With RuHCl(PPh$_3$)$_3$, only the C=C double bond was
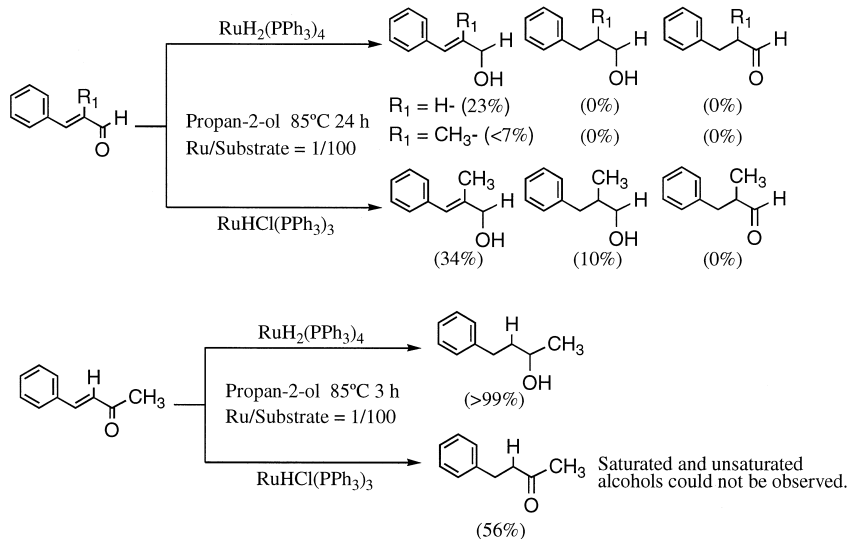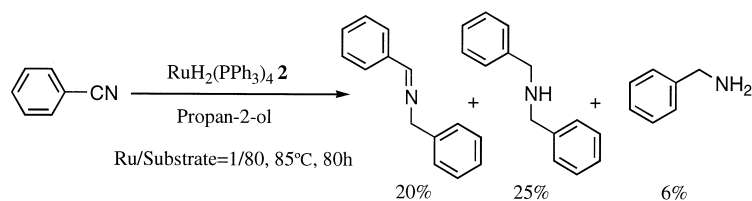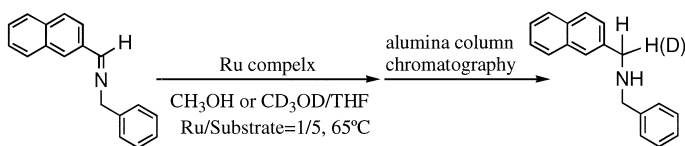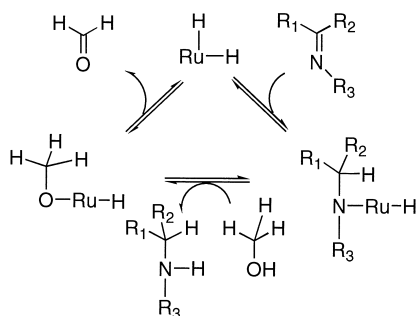

Scheme 2.

Scheme 3.

Scheme 4.

reduced to afford saturated ketone in the absence of a base.

3.4. Mechanistic study by isotope labeling

As to the mechanism of ruthenium catalyzed transfer hydrogenation in alcohols, two possibilities are considered [4]: (1) hydride transfer from ruthenium hydride to substrate, (2) direct hydrogen transfer from alkoxo ligand on ruthenium species formed in alcohol to substrate (Meerwein–Ponndorf–Verley type mechanism). The hydride transfer from $RuH_2(PPh_3)_4$ to olefins has been also reported by Komiya et al. [23]. More recently, Noyori et al. revealed that Ru(II) catalyzed asymmetric transfer hydrogenation in propan-2-ol proceeded by the hydride route involving the ruthenium monohydride complex as an intermediate [14] [1]. In order to clarify the transfer hydrogenation mechanism by ruthenium dihydride species in alcohol in the absence of a base, the reduction of an imine was performed with $RuH_2(PPh_3)_4$ in deuterated methanol(CD_3OD)/THF or with dideuterido ruthenium complex in methanol(CH_3OH)/THF (Scheme 4).

In the reaction of *N*-(2-naphthylmethylidene)-benzylamine with 20 mol% of **2** in methanol-d_4 (D content 99.8%)/THF mixture, the product amine was isolated and examined by ^{1}H NMR. The conversion was 5% and the turnover number by the catalyst was 0.25. The ratio of H/D introduced to the methylidene carbon was 0.94/0.06. At 7% conversion, H/D ratio was 0.86/0.14. These high ratios of H/D strongly support the addition of ruthenium hydride to the C=N bond of the substrate in alcohol without base (Scheme 5). Application of deuteride containing complex $RuA_2(PPh_3)_4$ ($A_2 = D_2$, HD or H_2, H/D = 0.58/0.42) to the reduction afforded the product with a H/D ratio of 0.67/0.33 both in methanol and methanol-d_4 (conversion was 4%). Introduction of deuteride to the methylidene carbon also supports the mechanism of ruthenium hydride addition to substrates. On the other hand, the reduction of the imine with **1**-CD_3ONa in methanol-d_4/THF mixture showed the introduction of deuteride to the methylidene carbon with a H/D ratio of

Scheme 5. Proposed mechanism via dihydrido complex **2** in methanol.

Table 5
The H/D transfer ratios to the naphthylmethylidene carbon[a]

Entry	Ru complex	Solvent	Time (h)	Conv. (%)	H/D[b]
1	$RuH_2(PPh_3)_4$	CD_3OD	0.5	5	94/6
2	$RuH_2(PPh_3)_4$	CD_3OD	3	7	86/14
3	$RuA_2(PPh_3)_4$[c]	CD_3OD	0.5	4	67/33
4	$RuA_2(PPh_3)_4$[c]	CH_3OH	0.5	4	67/33
5[d]	$RuHCl(PPh_3)_3$ $-CD_3ONa$	CD_3OD	3	4	63/37

[a]Reaction was carried out in methanol/THF mixture at 65°C. Ru/Substrate = 1/5.
[b]The ratio of H and D introduced at the methylidene carbon. Determined by ^{1}H NMR.
[c]$RuA_2(PPh_3)_4$: $A_2 = D_2$, HD or H_2, H/D in $A_2 = 0.58/0.42$.
[d]Ru/$CD_3ONa = 1/5$.

0.63/0.37 at 5% conversion. Incorporation of deuteride may suggest the contribution of the direct hydride transfer path from methoxo unit on ruthenium(II) for the reaction with **1**-CD_3ONa, but ruthenium hydride addition cannot be denied since it was reported that **1** was converted to ruthenium dihydride complex with CH_3ONa in methanol in about 50% yield [6]. (Table 5)

4. Conclusion

The ruthenium dihydride phosphine complex, $RuH_2(PPh_3)_4$, was effective for the transfer hydrogenation of ketones, imines and benzonitrile even in the absence of a base. This catalyst also caused the selective transfer hydrogenation of α,β-unsaturated aldehydes to afford unsaturated alcohols. By isotope labeling experiment, hydride transfer from ruthenium to an imine was revealed. We propose the hydridic mechanism by $RuH_2(PPh_3)_4$ for the transfer hydrogenation in alcohol.

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