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A Homogeneous Catalyst for Reduction of Optically Active Esters to the Corresponding Chiral Alcohols without Loss of Optical Purities

Wataru Kuriyama,[a,*] Yasunori Ino,[a] Osamu Ogata,[a] Noboru Sayo,[a] and Takao Saito[a]

[a] Takasago International Corporation, Corporate Research & Development Division, 4-11, 1-Chome, Nishi-Yawata, Hiratsuka City, Kanagawa 254-0073, Japan
Fax: (+81)-463-25-2093; e-mail: wataru_kuriyama@takasago.com

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Abstract: A ruthenium complex was found to catalyze the hydrogen reduction of esters under mild and neutral conditions. A variety of optically active esters can be reduced to the corresponding alcohols in excellent yield without loss of their optical purity or causing undesirable side reactions. Hydrogen reduction needs such simple operations – reaction, concentration, and purification – that the violent quench step and extraction step, which accompany conventional sodium borohydride or lithium aluminum hydride reduction, can be omitted.

Keywords: chiral alcohols; esters; homogeneous catalyst; hydrogenation; reduction; ruthenium

Chiral alcohols are versatile intermediates for physiologically active compounds.[1] A wide variety of chiral secondary alcohols having the hydroxy group on chiral centers are efficiently synthesized by asymmetric syntheses such as catalytic asymmetric hydrogenation or asymmetric biocatalytic reduction of the corresponding ketones.[2a–f] Another technique is dynamic kinetic resolution of racemic secondary alcohols by the combination of metal catalysts and enzymes.[2g] Chiral primary alcohols have often been obtained *via* stoichiometric metal hydride reduction of the corresponding chiral esters, which are generally easily available from the chiral pool or through asymmetric syntheses. Conventionally, sodium borohydride or lithium aluminum hydride reductions have been employed for this purpose. They are reliable in the laboratory, but an alternative method is desirable for large scale synthesis to avoid the use of extremely reactive metal hydride compounds, and to simplify the subsequent operations.

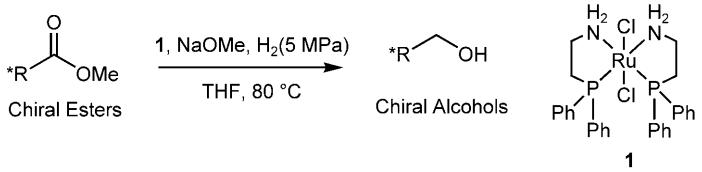
To the best of our knowledge, there are few published articles that refer to catalytic reduction of optically active esters to the corresponding chiral alcohols. In a recent article, a Nishimura catalyst, which consists of Rh/Pt oxide, catalyzed the hydrogenation of chiral α-hydroxy or α-amino esters at 25 °C under 10 MPa hydrogen pressure without racemization.[3] However, application of the catalyst was limited, because at the same time a phenyl group was hydrogenated to a cyclohexyl group.

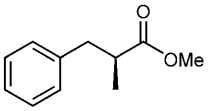
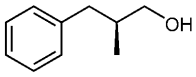
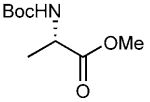
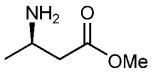
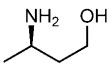
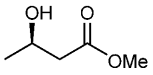
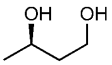
More recently, homogeneous ruthenium-aminophosphine complexes were reported to demonstrate excellent performance in the catalytic reduction of esters. They showed high activity and selectivity under basic and relatively mild conditions.[4] However the article gave no description of chiral esters and optical purity.

We began to develop a homogeneous catalytic system for the reduction of chiral esters because homogeneous catalysts seemed the most likely to have both activity and selectivity. Herein, we report a new ruthenium-catalyzed hydrogen reduction of various kinds of optically active esters to the corresponding chiral alcohols with virtually perfect retention of their optical purities.

We first investigated whether the reported highly active catalytic system, which employed the complex $RuCl_2$(aminophosphine)$_2$ and a base,[4a] could catalyze the reduction of chiral esters (Table 1). Unfortunately, the procedure did not work for that purpose. The catalyst reduced some kinds of chiral esters, but with a considerable loss in enantiomeric excess. Undesirable side reactions were also observed. This system showed higher catalytic activity for reduction of an α-

Table 1. Hydrogenation reduction of chiral esters with $RuCl_2$(aminophosphine)$_2$/base.[a]



Entry	Substrate	Product	Yield [%] (Δee)[b]
1[c]			93[d] (62)
2			70[d] (>98)
3			Trace[e] (–)
4			0[f] (–)

[a] *Standard reaction conditions:* substrate (5.0 mmol), **1** (0.05 mmol), and NaOMe (0.5 mmol) in THF (2 mL) under 5 MPa H_2 at 80 °C for 16 h.
[b] Δee = (*ee* of substrate) − (*ee* of product). *ee* of substrate/product; entry 1 (78.9/17.4), entry 2 (>99/1).
[c] **1** (0.01 mmol).
[d] Isolated yield.
[e] GC analysis.
[f] Only starting ester was detected by GC analysis.

alkylated ester, but a significant drop in optical purity was observed (entry 1, $\Delta ee = 62$). In the case of an α-amino acid ester protected by a Boc group, which is one of the most useful protecting groups for the amino moiety, the reduction itself proceeded, but optical purity was lost and a side reaction formed an oxazolidinone ring (entry 2).[5] When unprotected β-hydroxy and β-amino acid esters were examined, only traces or no product was obtained (entries 3 and 4). In entry 3, although the starting material was consumed, a trace of amino alcohol was obtained, probably because of its instability under basic conditions. Considering these results, we decided that more neutral conditions were required for the ester reduction to succeed.

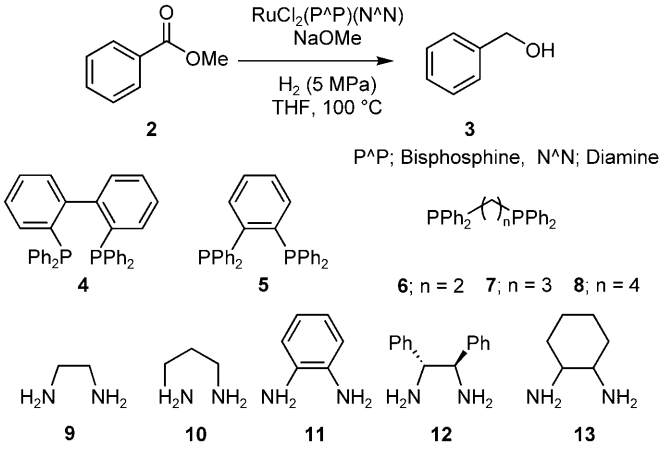
Milstein et al. reported a ruthenium complex which catalyzed hydrogen reduction of esters without addition of a base. They proposed that ester coordination to ruthenium is involved in the catalytic cycle.[6] Concerning metal-ligand bifunctional catalysts with the "N–H" effect,[7] Ru$H(\eta^1$-$BH_4)$(bisphosphine)(diamine) and Ru$H(\eta^1$-$BH_4)$(aminophosphine)$_2$ complexes have been reported to catalyze the asymmetric hydrogenation of ketones without addition of a base.[8] In this article, we focused on Ru$H(\eta^1$-$BH_4)$(bisphosphine)(diamine) complexes because the easy availability of various bisphosphine and diamine ligands would make it easy to tune the catalyst. We attempted to modify the catalytic system for hydrogen reduction of esters, although it was likely to be challenging because it was reported that the ester was not simultaneously hydrogenated.[8]

We conducted a screening test to investigate the ligand effect of precursor $RuCl_2$(bisphosphine)(diamine) complexes under basic conditions by using methyl benzoate as the substrate (Table 2).[9] Ligand combination strongly influenced catalyst activity. Among the combinations examined, dppp-dpen showed the best performance. Substituents on the ethylene moiety of ethylenediamine significantly improved the catalytic activity (entries 8 and 9). $RuCl_2$(dppp)(dpen)[10] was considered the precursor of choice.

The complex was converted according to a known method into Ru$H(\eta^1$-$BH_4)$(dppp)(dpen).[8a] Both complexes Ru$H(\eta^1$-$BH_4)$(dppp)[(*R*,*R*)-dpen] and Ru$H(\eta^1$-$BH_4)$(dppp)[(*S*,*S*)-dpen] were obtained in reasonable yields (Scheme 1).

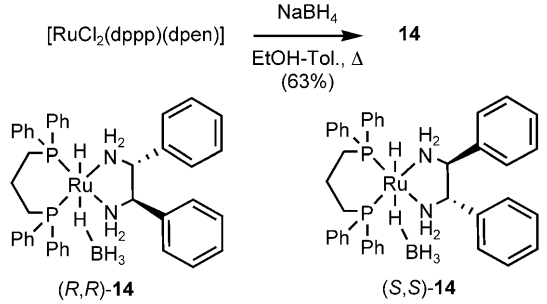
We first tried to apply these catalysts to the reduction of α-substituted chiral esters (Table 3). These complexes successfully catalyzed hydrogen reductions of various kinds of α-alkyl, substituted amino, and protected hydroxy esters without addition of a base. The corresponding chiral alcohols were produced in

Table 2. Hydrogen reduction of methyl benzoate with $RuCl_2$(bisphosphine)(diamine)/base.[a]



Entry	P^P	N^N	**3**[b]	**2**[b]
1	**4**	**9**	15	70
2	**5**	**9**	22	62
3	**6**	**9**	4	85
4	**7**	**9**	49	37
5	**8**	**9**	27	59
6	**7**	**10**	76	21
7	**7**	**11**	1	97
8	**7**	**12**	97	0
9	**7**	**13**[c]	97	Trace

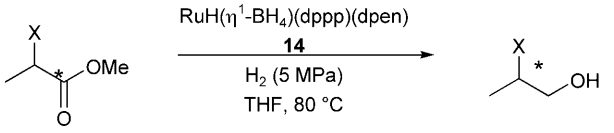
[a] *Standard reaction conditions:* methyl benzoate (4 mmol), $RuCl_2$(bisphosphine)(diamine) (0.008 mmol) and NaOMe (0.4 mmol) in THF (3 mL) under 5 MPa H_2 for 3 h.
[b] GC area %.
[c] Racemic mixture.

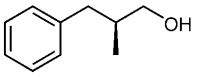
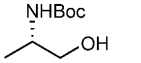
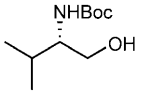
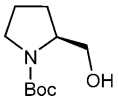
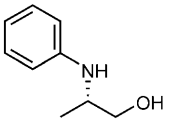
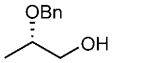
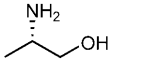
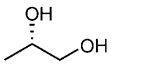


Scheme 1. Synthesis of [RuH(η^1-BH_4)(dppp)(dpen)].

excellent yields without loss of optical purity and undesirable side reactions. The *tert*-butoxycarbonyl moiety was tolerated. A variety of Boc-protected α-amino acid esters were reduced effectively (entries 2a, 2b, 3 and 4). *N*-Phenylalanine ester was also reduced (entry 5). The protected lactic acid ester gave the corresponding monoprotected diol without hydrogenolysis of the benzyl moiety (entries 6a and 6b). But no product or only moderate yields were obtained in the

Table 3. Hydrogen reduction of α-substituted chiral esters with ruthenium complex **14**.[a]



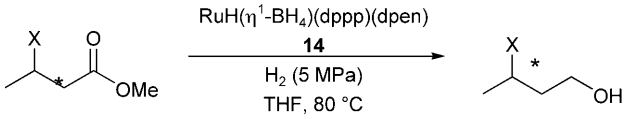
Entry	Product	Cat.	Yield [%] (Δ*ee*)[b]
1a		(*R*,*R*)-**14**	95 (<2)
1b		(*S*,*S*)-**14**	95 (1)
2a		(*R*,*R*)-**14**	92 (1)
2b		(*S*,*S*)-**14**	96 (<1)
3		(*S*,*S*)-**14**	94 (<1)
4		(*S*,*S*)-**14**	89 (<1)
5		(*S*,*S*)-**14**	89 (<1)
6a		(*R*,*R*)-**14**	95 (<1)
6b		(*S*,*S*)-**14**	90 (<1)
7a		(*R*,*R*)-**14**	0[c] (–)
7b		(*S*,*S*)-**14**	0[c] (–)
8a		(*R*,*R*)-**14**	30[d] (6) [<1][e]
8b		(*S*,*S*)-**14**	45[d] (5) [2][e]

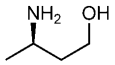
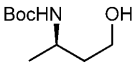
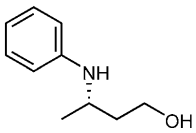
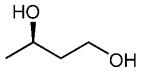
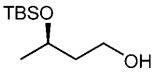
[a] *Standard reaction conditions:* substrate (5.0 mmol) and **14** (0.05 mmol) in THF (2 mL) under 5 MPa H_2 at 80 °C for 16 h. Purification: silica gel column chromatography.
[b] Δ*ee* = (*ee* of substrate) − (*ee* of product). *ee* of substrate/product; entry 1a (78.9/77.4), 1b (78.9/77.6), entry 2a (product 98.9), entry 2b (product 99.1), entry 3 (product 99.1), entry 4 (product > 99.8), entry 5 (61.3/61.3), entry 6a (98.5/98.3), entry 6b (98.5/98.3), entry 8a (99.0/93.4, remaining ester 98.3), entry 8b (99.0/93.7, remaining ester 97.7).
[c] GC analysis.
[d] GC area%.
[e] (*ee* of starting methyl lactate) − (*ee* of remaining substance).

case of the unprotected α-functionalized esters (entries 7a–8b). In comparison with the results with (*R*,*R*)-**14** and those with (*S*,*S*)-**14**, virtually no steric effect between non-racemic DPEN and chiral substrates was observed.

Next, β-substituted esters were examined (Table 4). In this case, even unprotected β-amino and β-hydroxy esters were reduced to the corresponding amino alcohols and diols (entries 1a, 1b, 4a and 4b). Although 100% conversion was obtained as determined by GC analysis in entries 1a and 1b, small-scale distillation produced only moderate yields (we expect that scal-

Table 4. Hydrogen reduction of β-substituted chiral esters with ruthenium complex **14**.[a]

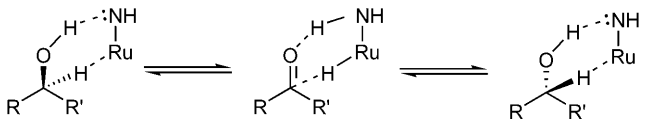


Entry	Alcohol	Cat.	Yield[b] [%]	Δ*ee*[c]
1a		(*R*,*R*)-**14**	64[d]	(<1)
1b		(*S*,*S*)-**14**	53[d]	(<1)
2a		(*R*,*R*)-**14**	96	(<1)
2b		(*S*,*S*)-**14**	92	(1)
3a		(*R*,*R*)-**14**	96	(<2)
3b		(*S*,*S*)-**14**	95	(<1)
4a		(*R*,*R*)-**14**	98	(19)
4b		(*S*,*S*)-**14**	95	(24)
5a		(*R*,*R*)-**14**	87	(<1)
5b		(*S*,*S*)-**14**	92	(<1)

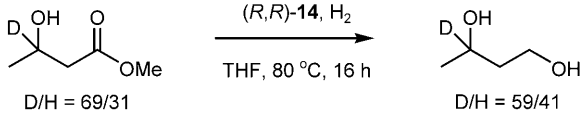
[a] *Standard reaction conditions:* substrate (5.0 mmol) and **14** (0.05 mmol) in THF (2 mL) under 5 MPa H_2 at 80 °C for 16 h. Purification; silica gel column chromatography.
[b] Isolated yield.
[c] Δ*ee* = (*ee* of substrate) − (*ee* of product). *ee* of substrate/product; entry 1a (product 99.6), entry 1b (product 99.7), entry 2a (product 99.7), entry 2b (product 98.7), entry 3a (87.7/86.2), entry 3b (87.7/87.0), entry 4a (98.9/80.2), entry 4b (98.9/75.1), entry 5a (98.9 max./98.8), entry 5b (98.9 max./98.8).
[d] Purification by distillation.

ing up the operation would improve the yield). Enantiomeric excesses were almost perfectly retained through the reaction process, except for the reduction of the unprotected β-hydroxy ester (entries 4a and 4b). This might be caused *via* the hydrogen transfer process shown in Scheme 2.[11] Once the hydroxy group was protected, no racemization was observed (entry 5).

To confirm the hypothesis, we reduced deuterium-labelled methyl β-hydroxybutyrate. Methyl β-hydroxybutyrate with 69% deuterium-labelling gave 1,3-butanediol with 59% deuterium-labelling. This result suggests that transfer hydrogenation occurred during the reduction (Scheme 3).

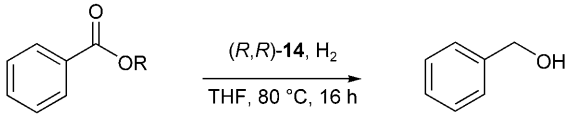


Scheme 2. Racemization process through transfer hydrogenation.



Scheme 3. Hydrogen reduction of deuterium-labelled methyl β-hydroxybutyrate

Table 5. Hydrogen reduction of benzoic acid esters with ruthenium complex (*R*,*R*)-**14**.[a]



2' **3**

Entry	R	**3**[b]	**2'**[b]
1	Me	97	<1
2	*i*-Pr	34	66
3	*t*-Bu	<1	>99
4	Ph	8	84

[a] *Standard reaction conditions:* benzoic acid ester (4 mmol), (*R*,*R*)-**14** (0.008 mmol) in THF (3 mL) under 5 MPa H_2 for 16 h.
[b] GC area %.

Last, we investigated the application of this catalytic system to variety of alkyl and aryl esters by using benzoic acid esters as the substrates (Table 5).

In the hydrogen reduction of methyl benzoate, 0.2 mol% of the catalyst afforded almost full conversion, however, as the steric bulkiness of the R group increased, the product ratio decreased (entry 1; Me group 97%, entry 2; *i*-Pr group 34%, entry 3; *t*-Bu <1%). In the reduction of phenyl benzoate, this catalyst gave a lower yield than methyl and isopropyl benzoate (entry 4).

To summarize, a new catalytic system for the hydrogen reduction of esters has been developed. This promising method was carried out without addition of a base to give various types of chiral alcohols from the corresponding esters, which are easy to obtain from the chiral pool or through asymmetric syntheses. In many cases, yields were excellent without loss of optical purity. Using this catalytic system, the troublesome and annoying operations incidental to ordinary metal hydride reduction can be avoided. The catalytic process could contribute to sustainable chemistry by reducing the waste generated and energy consumed during the reactions and subsequent operations.

Experimental Section

Catalyst Preparation

RuH(η^1-BH$_4$)(dppp)[(*S*,*S*)-dpen]: $RuCl_2$(dppp)(*S*,*S*)-dpen)[10] (2.0 g, 2.51 mmol) was placed in a 200-mL 3-neck flask

equipped with a Dimroth condenser. The atmosphere was replaced with nitrogen gas, followed by addition of a toluene and ethanol (30 mL) solution of $NaBH_4$ (2.4 g, 62.8 mmol). The mixture was stirred at 65 °C for 5 min., and at room temperature for 1 h. The reaction mixture was concentrated under vacuum, followed by addition of toluene (90 mL). The suspension was stirred at 40 °C for 10 min, and filtered through a Celite column and the column was washed with toluene (45 mL). The solution was concentrated under vacuum, until approximately 95 mL of toluene had been removed. To the mixture, was added hexane (70 mL). The precipitate was filtered off and washed with hexane (10 mL × 3) to afford RuH(η^1-BH_4)(dppp)[(*S*,*S*)-dpen] as light brown solid; yield: 1.25 g (63%). ^{1}H NMR (300 MHz, C_6D_6): $\delta =$ −14.98 (t, $J = 25.8$ Hz, 1H), −0.68 (br, 4H), 1.28–1.56 (m, 1H), 1.58–1.91 (m, 1H), 2.20–2.42 (m, 3H), 2.49–2.62 (m, 1H), 2.67–2.87 (m, 2H), 3.58–3.73 (m, 1H), 3.88–4.03 (m, 1H), 4.25–4.40 (m, 1H), 4.56–4.70 (m, 1H), 6.47–8.18 (m, 30H); ^{31}P NMR (121.5 MHz, C_6D_6): $\delta = 57.51$.

RuH(η^1-BH_4)(dppp)[(*R*,*R*)-dpen] was synthesized by a similar procedure.

General Procedure for Hydrogen Reduction of Chiral Esters

To a 100-mL stainless steel autoclave equipped with a Teflon-coated stirrer bar, was charged ruthenium complex **14** (0.05 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of a THF (2 mL) solution of the substrate ester (5 mmol). The vessel was purged three times with hydrogen gas (0.5 MPa), and then pressurized with hydrogen (5 MPa). The mixture was stirred at 80 °C for 16 h.

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