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Asymmetric hydrogenation of an α,β-unsaturated ketone by diamine(ether–phosphine)ruthenium(II) complexes and lipase-catalyzed kinetic resolution: a consecutive approach

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Abstract—The $RuCl_2(\eta^1\text{-}Ph_2PCH_2CH_2OCH_3)_2$(diamine) complexes **2L$_1$**–**2L$_5$** have been prepared in high yields from the reaction of equimolar amounts of $RuCl_2(\eta^2\text{-}Ph_2PCH_2CH_2OCH_3)_2$ **1** with various kinds of chelating diamines **L$_1$**–**L$_5$** to form five-membered chelates with ruthenium. These novel ruthenium(II) complexes have been used as catalysts in the asymmetric hydrogenation of the prochiral ketone *trans*-4-phenyl-3-butene-2-one **3**, using 2-propanol and different types of cocatalysts. Whereas complexes with achiral diamines afforded the racemic alcohols, complexes with chiral diamines (*R*,*R* or *S*,*S*) allowed the formation of the corresponding enantiomerically enriched secondary alcohol (*S* or *R*) with ee values of 45%. In order to obtain the secondary alcohol with ee of >99%, the kinetic resolution of enantiomerically enriched *trans*-4-phenyl-3-butene-2-ol **3** was performed in a consecutive approach using either the lipase-catalyzed enantioselective transesterification of the alcohol with isopropenyl acetate as the acyl donor in toluene or the enantioselective hydrolysis of the corresponding acetate in buffer. The determination of the enantiomeric excess (ee) of the resulting enantiomerically enriched secondary alcohols was performed by gas chromatography using heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin as the chiral stationary phase. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Despite the impressive progress in asymmetric synthesis, catalysis with chiral ruthenium complexes is still considered to be one of the most fascinating topics in organic chemistry.[1–5] Enantiomerically pure and enriched secondary alcohols are useful chiral building blocks for many natural products.[6] Accordingly, there is considerable interest in highly efficient routes to this class of compounds. They are usually synthesized in enantiomerically pure form by kinetic resolution of the racemates using either asymmetric enzymatic acylation;[7] or a dynamic approach based on a lipase/ruthenium combination[8] and the asymmetric reduction of prochiral ketones which can be performed either biologically using biocatalytic systems,[9] or chemically via stereoselective reduction using either a catalytic system[10] or a stoichiometric amount of a reducing agent.[11]

Transition metal-catalyzed hydrogenations of carbonyl groups represent a good method to access secondary alcohols.[1–6,12–16] However, some of the reported processes have to be improved for practical purposes due to their low catalytic activity and low molar substrate/catalyst ratio. An excellent catalytic performance in the asymmetric hydrogenation of ketones to secondary alcohols with 2-propanol as solvent has been reported using ruthenium(II) complexes attached to C_2-symmetrical chiral diamines as ligands.[2–5,12,17–19] Unfortunately, the conditions applied, e.g. reaction time of approximately 15 h or more, and a hydrogen pressure of 8–10 bar, limit their practical use in asymmetric synthesis.

Recently, ruthenium(II) complexes with ether–phosphine and diamine ligands were already successfully tested in the catalytic hydrogenation of unsaturated ketones.[20] These reactions have been performed under moderate conditions (35–40°C, low hydrogen pressures of 2–3 bar), and a molar substrate/catalyst ratio (S/C) between 1000–4000 resulting in the formation of unsaturated secondary alcohols in up to 99% yield. It has to be emphasized that the hemilabile character of ether–

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phosphines facilitates the formation of diamine(ether–phosphine)ruthenium(II) complexes through the presence of the oxygen donor which is considered to behave as an intramolecular solvent.[21]

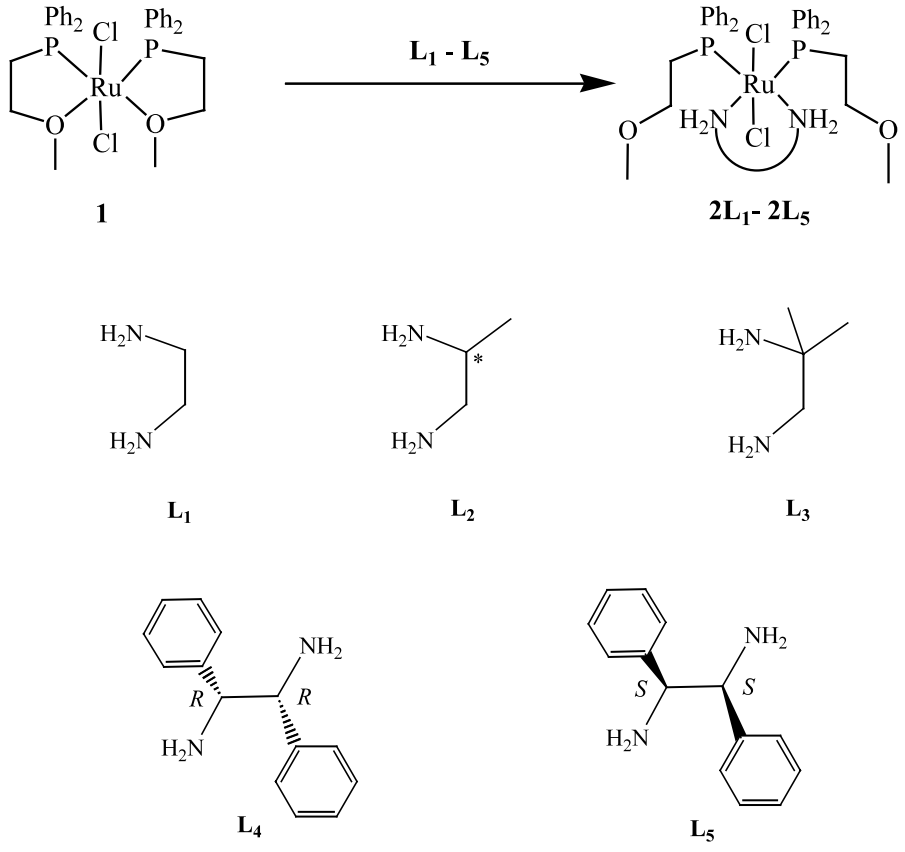
Herein, we report on the application of the diamine–bis(ether–phosphine)ruthenium(II) complexes **2L$_1$**–**2L$_5$** in the selective hydrogenation of an α,β-unsaturated ketone. Particular interest is directed to complexes with the chiral diamines **L$_4$** and **L$_5$**, which are able to perform the asymmetric hydrogenation of ketones affording enantiomerically enriched secondary alcohols. In a consecutive approach, the enantiomerically pure alcohol (>99% ee) was obtained by lipase-catalyzed transesterification of the enantiomerically enriched secondary alcohol or lipase-catalyzed hydrolysis of the corresponding acetate.

2. Results and discussion

2.1. Synthesis of the complexes 2L$_1$–2L$_5$ and X-ray structural determination of 2L$_4$

The synthesis of the diamine–bis(ether–phosphine)ruthenium(II) complexes **2L$_1$**–**2L$_5$** has already been described in the literature (Scheme 1).[20,21] However, to date, no structural information for a corresponding chiral ruthenium(II) complex has been presented.[20] Therefore, a structural investigation of complex **2L$_4$**, was performed. The crystal structure is shown in Figure 1.

Complex **2L$_4$** crystallizes with two independent molecules in the unit cell of the chiral, non-centrosymmetric monoclinic space group $P2_1$. Both molecules 1 and 2 are *trans*-chloro-*cis*-phosphine isomers of only approximate C_2 symmetry and differ in the orientation of the substituents at phosphorus relative to the conformation of the diamine ligand. Common to both molecules is the regular octahedral coordination geometry about ruthenium, only perturbed by the phosphine groups pushing the chlorine ligands from their axial positions toward the diamine chelate, as expressed by the deviation of the Cl–Ru–Cl angles from linearity, 165.65(7) and 166.34(7)°.[20,21] As expected, the phenyl substituents at the diamine carbon chain favor equatorial positions. Because of the fixed *R*,*R*-configuration of the diamine, the chelate ring formation with twist conformation results in the predetermined λ configuration. In the case of molecule 2, this twist conformation is actually slightly distorted toward an envelope conformation with C(75) at the tip: C(75) is displaced from the N–Ru–N plane by 0.53 Å, while C(76), C(31), and C(32) show smaller deviations in the range 0.27–0.39 Å.



Scheme 1. Synthesis of the complexes **2L$_1$**–**2L$_5$**.

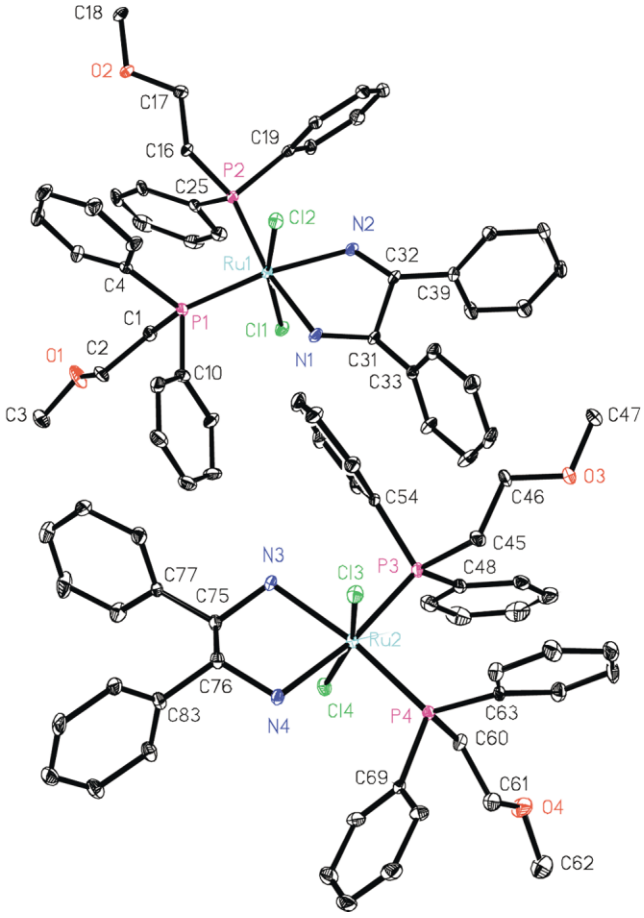


Figure 1. ORTEP plot with atom-numbering scheme showing the two independent molecules in the crystal structure of $\mathbf{2L_4}$. Thermal ellipsoids are shown at the 20% probability level, hydrogen atoms have been omitted for clarity.

2.2. Catalytic activity of the ruthenium(II) complexes $\mathbf{2L_1}$–$\mathbf{2L_5}$ in the selective hydrogenation of an α,β-unsaturated ketone

The catalytic activity of the ruthenium(II) complexes $\mathbf{2L_1}$–$\mathbf{2L_5}$ has been studied in the hydrogenation of *trans*-4-phenyl-3-butene-2-one **3**. This substrate was selected as a model, since three different possibilities of hydrogenation are expected to form (*RS*)-**4**, (*RS*)-**5**, and **6** (Scheme 2). Adding to that, it has been reported that the reduction of **3** can lead to the formation of (*RS*)-**4** (5 mol%), (*RS*)-**5** (5 mol%), **6** (55 mol%), and (*RS*)-**7** (45 mol%) in a whole cell bioconversion process[9] (Scheme 2).

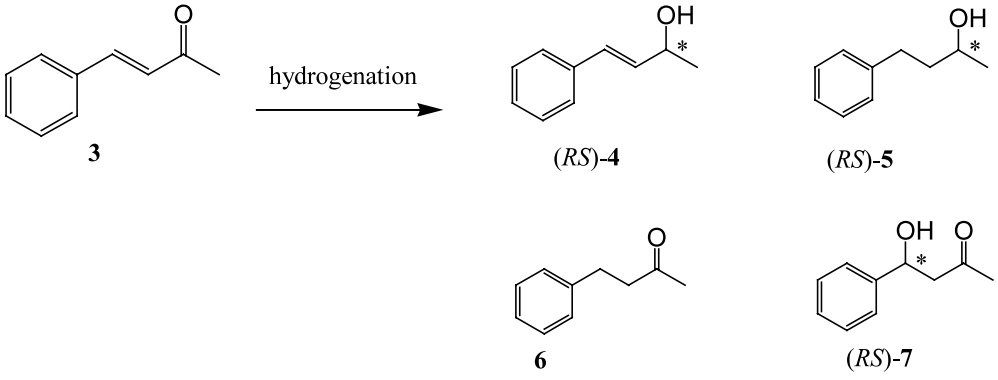
Table 1. Ruthenium-catalyzed hydrogenation of **3**[a]

Run	Catalyst	Conversion (%)[b]	H_2 (bar)	TOF[c]
1	$\mathbf{2L_1}$	90	3	1120
2	$\mathbf{2L_2}$	80	3	960
3	$\mathbf{2L_3}$	67	3	670
4	$\mathbf{2L_4}$	100	2	1010
5	$\mathbf{2L_5}$	100	2	1690
6	$\mathbf{2L_4}$[d]	100	2	1030
7	$\mathbf{2L_5}$[d]	100	2	1460
8	$\mathbf{2L_4}$[e]	100	2.5	480
9	$\mathbf{2L_5}$[e]	100	2.5	520
10	$\mathbf{2L_4}$[f]	100	2.5	1880
11	$\mathbf{2L_5}$[f]	100	2.5	1990
12	$\mathbf{2L_4}$[g]	100	2.5	1090
13	$\mathbf{2L_5}$[g]	100	2.5	1500

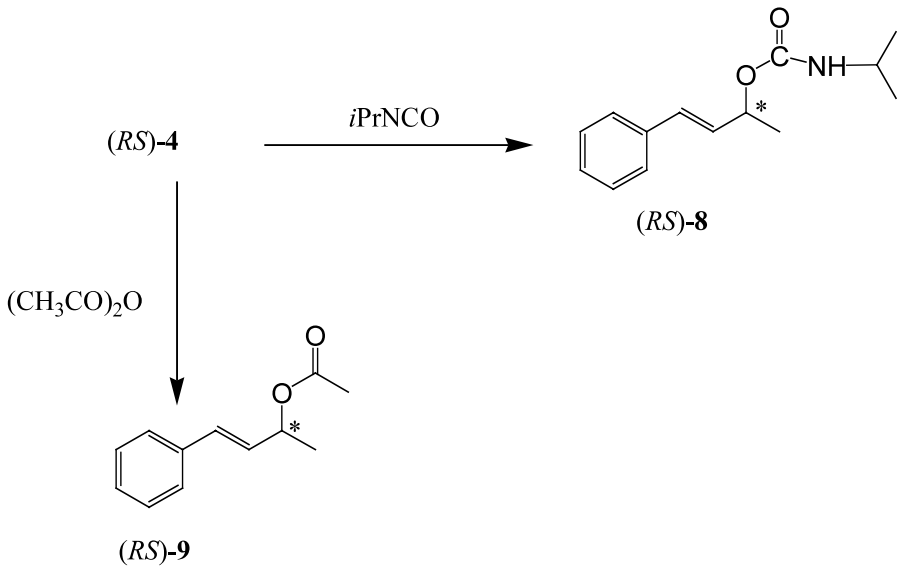
[a] Reaction was conducted at 35°C using substrate (S/C = 1000, 3–10 g) in 2-propanol (50 ml) [Ru:KOH:substrate] [1:10:1000].
[b] Yields and selectivities were determined by GC and GCMS analyses.
[c] TOF: turnover requency (mol_{sub} $mol^{-1}{}_{cat}$ h^{-1}).
[d] [Ru:*t*KOBu:**3**] [1:10:1000].
[e] [Ru:KOH:AgOTf:**3**] [1:10:5:1000].
[f] [Ru:KOH:**3**] [1:40:1000].
[g] [Ru:KOH:**3**] [1:10:4000].

All hydrogenations were carried out under mild conditions (2–3 bar hydrogen pressure and 35°C) using several cocatalysts (KOH, *t*BuOK, AgOTf). The results are summarized in Table 1.

The excellent regioselectivity in the hydrogenation of only the carbonyl group is reminiscent to a stoichiometric reduction with $NaBH_4$. Turnover frequencies and conversions decreased when methyl groups were introduced at one carbon atom of the diamine in the complexes $\mathbf{2L_1}$–$\mathbf{2L_3}$. This is clearly due to steric effects (Table 1, runs 1–3). In the case of $\mathbf{2L_4}$ and $\mathbf{2L_5}$ containing chiral ligands and the substrate **3** the formation of the enantiomerically enriched alcohol **4** was formed which was detected as **9** (Scheme 3 and Fig. 2).



Scheme 2. Different possibilities for the hydrogenation of **3**.



Scheme 3. Derivatization of (*RS*)-**4** with *i*PrNCO (carbamate) and $(CH_3CO)_2O$ (acetate) to achieve a base-line separation in GC.

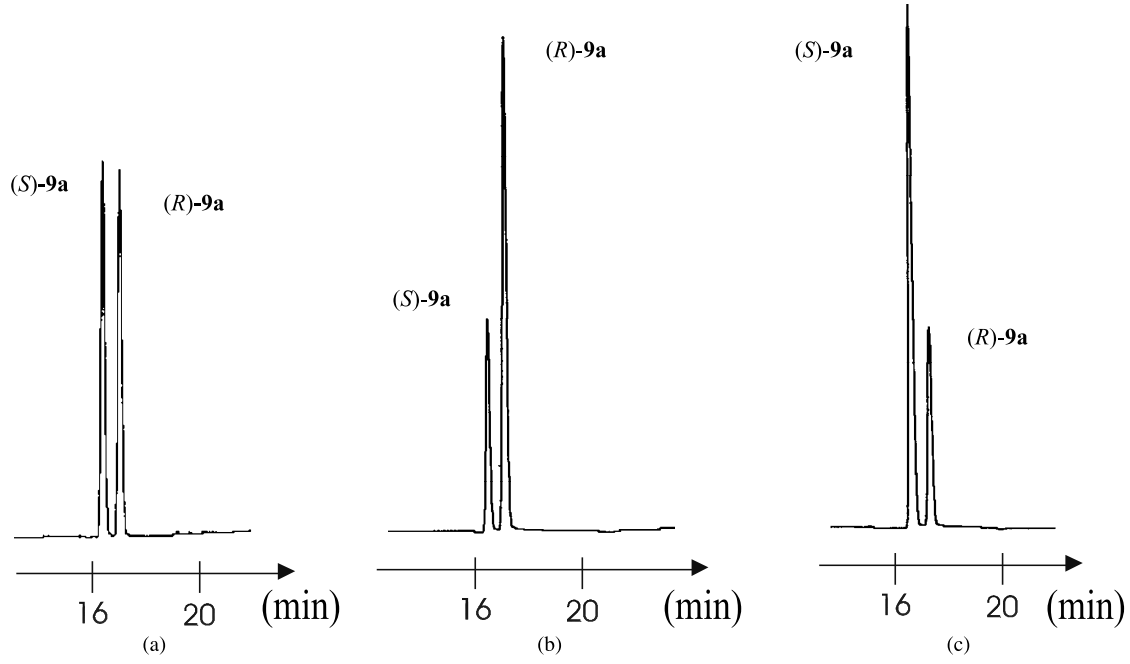


Figure 2. Gas-chromatographic separation of (*RS*)-**4** derivatized as the acetate (*RS*)-**9** (a), enantiomerically enriched (*R*)-**4** (45% ee) resulting from the $\mathbf{2L_5}$ catalyst and derivatized as acetate (*R*)-**9** (b), enantiomerically enriched (*S*)-**4** (45% ee) resulting from the $\mathbf{2L_4}$ catalyst derivatized as acetate (*S*)-**9** (c). Heptakis-(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin was used as chiral stationary phase. Oven temperature was 130 isothermal for 20 min.

In runs 6 and 7, *t*KOBu was applied as cocatalyst. Similar conversions, turnover frequencies and enantioselectivities as in the case of KOH were observed. To enhance the enantioselectivity of the hydrogenation of the carbonyl group AgOTf was used (runs 8 and 9). However, only the turnover frequencies decreased markedly, while the enantioselectivity was not affected. The saturated alcohol (*RS*)-**5** was detected only in small amounts, when the concentration of the cocatalyst (KOH) was increased ($\geq$40 mol) (Table 1, runs 10 and 11).

2.3. Enantioselectivity of the ruthenium(II) complexes $\mathbf{2L_1}$–$\mathbf{2L_5}$

The product resulting from the hydrogenation of **3** in the presence of catalysts $\mathbf{2L_4}$ and $\mathbf{2L_5}$ with (*R*,*R*)- and (*S*,*S*)-diamines $\mathbf{L_4}$, $\mathbf{L_5}$, afforded the alcohols (*S*)-**4** and

(*R*)-**4**, respectively, with ee values of 45% ($[\alpha]_D^{20}$ −6.0/+6.0) (Figs. 2 and 3)

2.4. Lipase-catalyzed kinetic resolution of the enantiomerically enriched alcohol 4

The use of an enantiomerically enriched alcohol rather than a racemic one should reduce the time needed to effect complete resolution.[22–25] The kinetic resolution of **4** was performed starting from the enantiomerically enriched alcohol (*R*)- or (*S*)-**4** (45% ee) obtained by the ruthenium-catalyzed asymmetric reduction of **3** with the aim to reach ~100% ee in a consecutive approach. Four lipases from *Pseudomonas cepacia* (PSL), *Pseudomonas cepacia* immobilized on diatomaceous earth (PSL-D), Novozyme 435 (CAL-B) and Lipozyme RM IM (RML) were screened in resolving the enantiomerically enriched **4** either in the enantioselective transesterification of (*S*)-**4** (45% ee) using isopropenyl acetate as an acyl donor in toluene in non-aqueous medium or in the enantioselective hydrolysis of the corresponding acetate (*R*)-**9**, (45% ee) using a phosphate buffer (pH 6) in aqueous medium. The transesterification of **4** (45% ee *S*) was carried out at 40°C in toluene at a molar ratio of isopropenyl acetate:**4** of 2:1 to ensure the reaction was irreversible (Scheme 4).

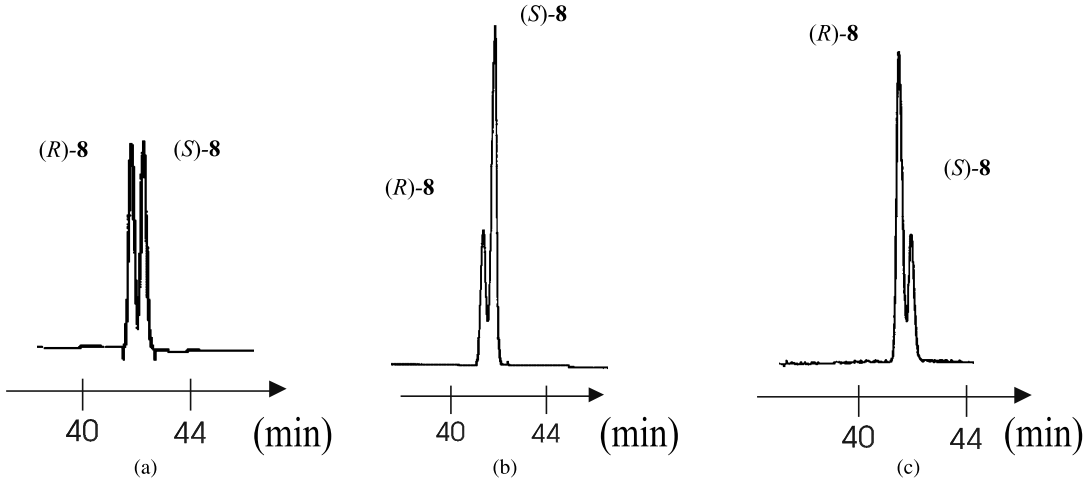
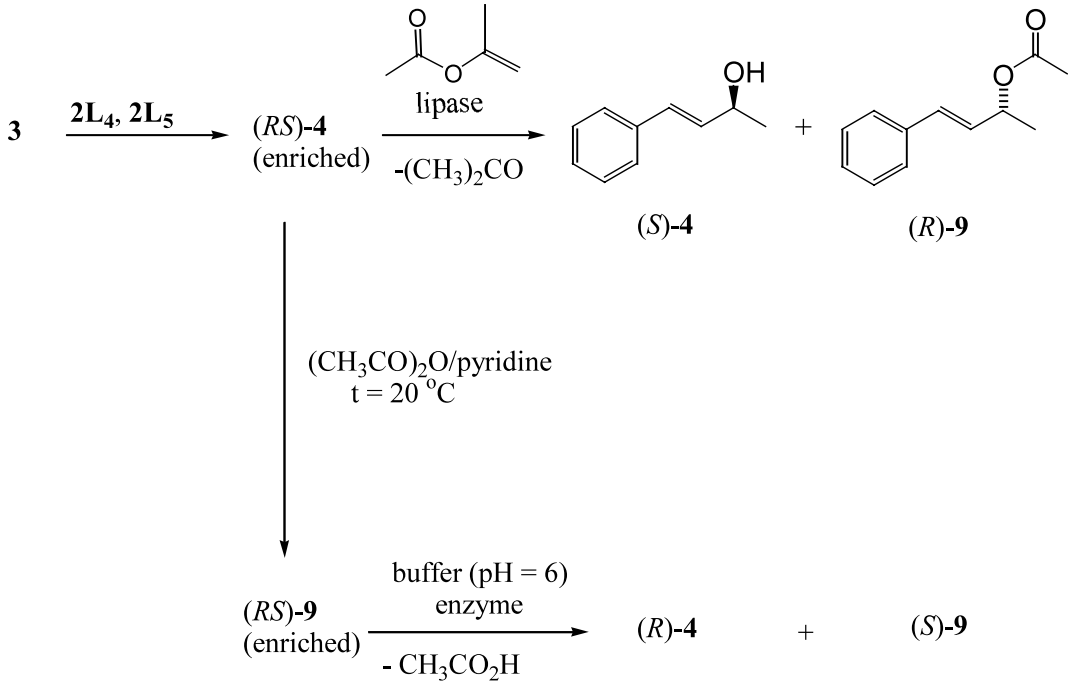


Figure 3. Gas-chromatographic separation of the racemic mixture (*RS*)-**4** derivatized as carbamate (*RS*)-**8** (a), enantiomerically enriched (*S*)-**4** (45% ee) resulting from the $\mathbf{2L_4}$ catalyst and derivatized as carbamate (*S*)-**8** (b), enantiomerically enriched (*R*)-**4** (45% ee) resulting from the $\mathbf{2L_5}$ catalyst and derivatized as carbamate (*R*)-**8** (c). Heptakis-(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin was used as chiral stationary phase. Oven temperature was 130 isothermal for 20 min, 30°C/min until 160 for 25 min.



Scheme 4. $\mathbf{2L_4}$, $\mathbf{2L_5}$/lipase-catalyzed separation of enriched (*RS*)-**4**.

The results of the lipase-catalyzed transesterification of enriched (*RS*)-**4** are summarized in Table 2.

In the transesterification reaction of enantiomerically enriched **4**, (*R*)-**4** was the faster reacting enantiomer yielding (*R*)-**9** in high ee and leaving (*S*)-**4** unreacted in enantiomerically pure form. Both lipases from *Pseudomonas cepacia* immobilized on diatomaceous earth (PSL-D) and CAL-B displayed high enantioselectivity towards (*RS*)-**4** (Table 2). In regard to the ee of the remaining substrate (*S*)-**4** and that of the product (*R*)-**9** as well as the rate of conversion (52.1% in 2 h) and enantiomeric ratio E >200, PSL-D was the best lipase employed in the transesterification of (*RS*)-**4**. PSL-D was the enzyme of choice applied in the transesterification of (*RS*)-**4** using isopropenyl acetate in toluene on a preparative scale. An E value of 300 was observed and the reaction was terminated after 3 h yielding (*S*)-**4** with >99% ee and the ester (*R*)-**9** (cf. Scheme 4), which was recovered with 86% ee determined by capillary GC after 50% conversion. 4 Å molecular sieves were added in order to scavenge the liberated acetone formed as a by-product from the lipase-catalyzed reaction using isopropenyl acetate as an acyl donor. The beneficial effect of molecular sieves was reported previously in the lipase-catalyzed transesterification of 1-(2-furyl)ethanol using isopropenyl acetate in organic solvents.[7]

Compared to the transesterification experiments in non-aqueous medium described above, the enzymatic hydrolysis of *R*-enriched **9** proceeded slowly. Only moderate conversion (45%) but enantioselectivity (up to 99% for the alcohol (*R*)-**4** and 80.8% for the remaining unreacted ester (*S*)-**9** (Table 3) was achieved after 24 h using Novozyme IM (CAL-B). In all cases, the hydrolysis reaction was still rapid until 9 h, afterwards, the reaction proceeded very slowly. This is probably due to product inhibition resulting from the accumulation of products when the conversion is increased in the enzymatic hydrolysis of *R* enriched **9**, thus competing with the active site of the enzyme. Adding to that, the acid released from the enzymatic hydrolysis (Scheme 4) might be involved in the acylation of the resulting unreacted enantiomerically pure alcohol (*R*)-**4**, thus, increasing the amount of the racemic ester **9** leading to a decrease in the conversion and enantiomeric excess.

CAL-B (Novozyme) not only showed the best performance in the analytical runs, but also gave an excellent result for the hydrolysis of (*RS*)-**9** enriched at a multigram scale (in 24 h, ee_s 74.5%, ee_p >99, conv. 43 and E >300).

3. Conclusion

A set of diamine(ether–phosphine)ruthenium(II) complexes $\mathbf{2L_1}$–$\mathbf{2L_5}$ with different diamines $\mathbf{L_1}$–$\mathbf{L_5}$ were prepared and used as highly active and selective catalysts in the hydrogenation of **3** under mild conditions. The complexes $\mathbf{2L_4}$ and $\mathbf{2L_5}$ containing chiral diamine ligands afforded enantiomerically enriched unsaturated alcohols **4** with 45% ee. Several cocatalysts, e.g. KOH, *t*BuOK, AgOTf, were tested in the hydrogenation process in the presence of $\mathbf{2L_4}$ and $\mathbf{2L_5}$ at different conditions. A consecutive approach using the ruthenium(II) complexes $\mathbf{2L_4}$, $\mathbf{2L_5}$ for the enantioselective reduction and lipase-catalyzed kinetic resolution of the *R* or *S* enriched *trans*-4-phenyl-3-butene-2-ol **4** (45% ee) was applied. Four lipases were screened for the transesterification/hydrolysis reactions in order to obtain both *R* and *S* enantiomers of the alcohol with >99% ee.

Table 2. Lipase-catalyzed transesterification of scalemic **4** using isopropenyl acetate in toluene (analytical scale)

Lipase	Time (h)	ee_s (%)[a] (*S*)-**4**	ee_p (%)[b] (*R*)-**9**	Conversion (%)	E[c]
PSL	2	97.2	86.9	52.8	60
PSL-D	2	>99	91.8	52.1	230
CAL-B	4	>99	80.3	55.4	95
RML	4	49.2	>99	33.0	3800

[a] ee_s: enantiomeric excess of substrate (*S*)-**4**.
[b] ee_p: enantiomeric excess of product (*R*)-**9**.
[c] E: ratio ee_s:ee_p.

Table 3. Lipase-catalyzed enantioselective hydrolysis of scalemic **9** using phosphate buffer, pH 6 (analytical scale)

Lipase	Time (days)	ee_s (%)[a] (*S*)-**9**	ee_p (%)[b] (*R*)-**4**	Conversion (%)	E[c]
PSL	2	57.5	>99	36.5	5000
PSL-D	4	30.2	>99	23.2	4000
CAL-B	1	80.8	>99	45.0	7500
RML	4	39.9	>99	28.6	1500

[a] ee_s: enantiomeric excess of substrate (*S*)-**9**.
[b] ee_p: enantiomeric excess of product (*R*)-**4**.
[c] E: ratio ee_s:ee_p.

4. Experimental

4.1. General remarks, chemicals and instrumentation

The synthesis of the ruthenium(II) complexes was carried out in an inert atmosphere (argon) by using standard high vacuum and Schlenk-line techniques unless otherwise noted. Prior to use CH_2Cl_2, *n*-hexane, and Et_2O were distilled from CaH_2, $LiAlH_4$, and from sodium/benzophenone, respectively.

The ether–phosphine ligand $Ph_2PCH_2CH_2OCH_3$ was prepared according to the literature method.[26] The diamines were purchased from Acros, Fluka, and Merck and were purified by distillation and recrystallization, respectively. Ph_3P and $RuCl_3 \cdot 3H_2O$ were available from Merck and ChemPur respectively, and were used without further purification. Lipases from *Pseudomonas cepacia* (PSL), *Pseudomonas cepacia* immobilized on diatomaceous earth (PSL-D) were gifts from Amano (Nagoya, Japan), Novozyme 435 (an immobilized non-specific lipase, Candida antarctica B, CAL-B, produced by submerged fermentation of a genetically modified *Aspergillus oryzae* microorganism and adsorbed on a macroporous resin) and Lipozyme RM IM (RML, an immobilized 1,3-specific lipase from *Rhizomucor miehei* produced by submerged fermentation of a genetically modified *Aspergillus oryzae* microorganism) were gifts from Novo Nordisck *A*/*S* Denmark. The racemic alcohol **3** was synthesized according to a literature procedure.[24] Elemental analyses were carried out on an Elementar Vario EL analyzer. High-resolution ^1H, $^{13}C\{^1H\}$, DEPT 135, and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker DRX 250 spectrometer at 298 K. Frequencies are as follows: ^1H NMR 250.12 MHz, $^{13}C\{^1H\}$ NMR 62.9 MHz, and $^{31}P\{^1H\}$ NMR 101.25 MHz. Chemical shifts in the ^1H and $^{13}C\{^1H\}$ NMR spectra were measured relative to partially deuterated solvent peaks which are reported relative to TMS. ^{31}P chemical shifts in the $^{31}P\{^1H\}$ NMR spectra were measured relative to 85% H_3PO_4 ($\delta = 0$). Mass spectra: EI-MS; Finnigan TSQ70 (200°C). FAB-MS; Finnigan 711A (8 kV), modified by AMD and reported as mass/charge (m/z).

4.2. General procedure for the catalytic studies

The diamine–bis(ether–phosphine)ruthenium(II) complexes **2L$_1$**–**2L$_5$**, (0.026 mmol) were placed into a 150 ml Schlenk tube and solid KOH (0.26 mmol) was added as a cocatalyst. The solid mixture was stirred and warmed during the evacuation process to remove oxygen and water. Subsequently the Schlenk tube was filled with argon and 2-propanol (20 ml) was added. The mixture was vigorously stirred, degassed by two freeze–thaw cycles, and then sonicated for 20–40 min. A solution of **3** (26 mmol) in 2-propanol (60 ml) was subjected to a freeze–thaw cycle in a different 150 ml Schlenk tube and was added to the catalyst solution. Finally the reaction mixture was transferred to a pressure Schlenk tube which was pressurized with dihydrogen of 2–3 bar. The reaction mixture was vigorously stirred at 35°C for 1 h. During the hydrogenation process samples were taken from the reaction mixture and analyzed by GC.

4.3. General procedure for the gram-scale ruthenium-catalyzed production of enantiomerically enriched 4

Complexes **2L$_4$** and **2L$_5$** (0.018 mmol), respectively, were placed in a 150 ml Schlenk tube and solid KOH (0.36 mmol) was added as a cocatalyst. The solid mixture was stirred and warmed during the evacuation process to remove oxygen and water. Subsequently the Schlenk tube was filled with argon and 2-propanol (20 ml) was added. The mixture was vigorously stirred, degassed by two freeze–thaw cycles, and then sonicated for 20–40 min (this is important to complete the dissolving of the catalyst and cocatalyst). A solution **3** (72.0 mmol) in 2-propanol (60 ml) [Ru:KOH:sub] [1:20:4000], was subjected to a freeze–thaw cycle in a different 150 ml Schlenk tube and was added to the catalyst solution. Finally the reaction mixture was transferred to a pressure Schlenk tube which was pressurized with dihydrogen of 2.5 bar. The reaction mixture was vigorously stirred at 40°C for 3 h. During the hydrogenation process samples were taken from the reaction mixture to control the conversion and turnover frequency. The samples were inserted by a special glass syringe into a gas chromatograph and the kind of the reaction products was compared with authentic samples.

4.4. General procedure for the lipase-catalyzed asymmetric transesterification of enriched (*S*)-4

All reactants (alcohols, esters) were stored over activated molecular sieves (4 Å) the enantiomerically enriched alcohol ((*S*)-**4**; 45% ee—74 mg 0.5 mmol, analytical scale or 8.8 g, 0.06 mol, gram-scale resulting from the **2L$_4$**-catalyzed asymmetric hydrogenation of *trans*-4-phenyl-3-butene-2-one **3**) and isopropenyl acetate (108.8 mg, 1.0 mmol, analytical scale or 24 g, 0.24 mol, gram-scale) were dissolved in toluene (3 ml analytical scale or 500 ml gram-scale) in a 5 ml reaction vial (analytical scale) or 1 L round-bottomed flask (gram-scale). The reaction mixture was thermostated in an oil bath to 40°C. A 100 μl sample of the reaction mixture was withdrawn and derivatized with isopropyl isocyanate (10 μl) at 100°C for 30 min, diluted with toluene (100 μl) and analyzed by GC ($t = 0$ of sample). Afterwards, lipase (100 mg, analytical scale or 3.08 g gram-scale) was added, followed by the addition of molecular sieves 4 Å (100 mg analytical scale or 5 g gram-scale). 100 μl samples were taken after several time intervals. The samples were centrifuged to separate lipase. The organic layer was treated with isopropyl isocyanate heated to 100°C for 30 min, then diluted with toluene (100 μl) and analyzed by GC. The reaction progress was monitored qualitatively by thin layer chromatography using *n*-hexane/ethyl acetate (9:1 v/v) as eluent. An aliquot of the supernatant was used for GC analysis. When maximum conversion was reached (50% after 2 h), the reaction was terminated by filtration. The enzyme was washed with acetone and then dried in air

for further use. Substrate (*S*)-**4** and product (*R*)-**9** were separated by flash chromatography over silica gel (*n*-hexane/ethyl acetate 9:1) affording 4.1 g ((*S*)-**4**) (>99% ee by GC) $[\alpha]_D^{20}$ −19.9 (*c* 1, CH_2Cl_2) [lit. $[\alpha]_D^{20}$ −24.5 (*c* 5.16, $CHCl_3$), 98% ee], yield: 47% and 4.3 g ((*R*)-**9**) (87% ee by GC) $[\alpha]_D^{20}$ +74.2 (*c* 1, CH_2Cl_2), yield: 49%.

4.5. General procedure for the lipase-catalyzed asymmetric hydrolysis of enriched (*R*)-9

Enzyme (100 mg, analytical scale or 3.15 g of Novozyme 435, gram-scale) was dissolved in phosphate buffer (pH 6, 2.8 ml, analytical scale or 250 ml, gram-scale) and added to the enantiomerically enriched acetate (*R*)-**9** (45% ee *R*, 0.5 mmol, analytical scale or 7.8 g, 40 mmol, gram-scale resulting from the **2L$_5$**-catalyzed asymmetric reduction of *trans*-4-phenyl-3-butene-2-one **3**) dissolved in toluene (1 ml, analytical scale or 20 ml, gram-scale) in a 5 ml reaction vial (analytical scale) or 1 L round-bottomed flask (gram-scale). The reaction mixture was thermostated in an oil bath at 40°C. Then, 100 μl of the reaction mixture (organic layer) was withdrawn at several time intervals, derivatized with isopropyl isocyanate, heated to 100°C for 30 min, then diluted with toluene (100 μl) and analyzed by GC. The reaction progress was monitored qualitatively by thin layer chromatography (*n*-hexane/ethyl acetate 9:1). When maximum conversion was reached (44% after 24 h), the reaction was terminated by filtration. Substrate (*S*)-**9** and product (*R*)-**4** were separated by column chromatography (*n*-hexane/ethyl acetate 9:1) affording the 3.3 g (*R*)-**4** (>99% ee by GC) $[\alpha]_D^{20}$ +19.9 (*c* 1, CH_2Cl_2), yield: 43% and 3.5 g (*S*)-**9** (74.5% ee by GC) $[\alpha]_D^{20}$ −71.2 (*c* 1, CH_2Cl_2), yield: 46%.

4.6. Enantioselective gas-chromatographic analysis

The enantiomers of the underivatized alcohol (*RS*)-**4** could not be separated on heptakis-(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin used as chiral stationary phase in GC, however, upon derivatization with acetic anhydride (the acetate (*RS*)-**9**) or isopropyl isocyanate (the carbamate (*RS*)-**8**, cf. Scheme 3) a base-line separation has been achieved (Figs. 2 and 3). Thus, the enantioselective analysis of racemic (*RS*)-**4** as the carbamate (*RS*)-**8** and acetate (*RS*)-**9** were performed simultaneously using a gas chromatograph (Hewlett–Packard 580, Waldbronn, Germany) equipped with a flame ionization detector (FID). The chiral stationary phase heptakis-(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin, 20% (w/w) was dissolved in PS 86 (Gelest, ABCR GmbH & Co., Karlsruhe, Germany) and coated on a 25 m×0.25 mm fused silica capillary column (0.25 μm film thickness) according to the literature.[27] The analytical conditions were: injector temperature, 200°C; FID temperature, 250°C; oven temperature 130°C for 18 min then 30°C/min until 160 for 25 min. Hydrogen was used as the carrier gas (40 KPa column head pressure). The retention time of (*S*)-**9**, (*R*)-**9**, (*R*)-**4**, (*S*)-**4**, were 16.4, 17.0, 40.8, 41.2 min, respectively. Upon derivatization of the racemic alcohol (*RS*)-**4** with acetic anhydride, the elution of the acetate (*RS*)-**9** was in the order (*S*)<(*R*) with 16.4 and 17.0 min, respectively and a separation factor $\alpha = 1.08$ and resolution $R_s = 2.83$. Upon derivatization of the racemic alcohol (*RS*)-**4** with isopropyl isocyanate, the elution of the carbamate (*RS*)-**8** was in the reverse order (*R*)<(*S*) with 40.8 and 41.2 min, respectively and a separation factor $\alpha = 1.01$ and resolution $R_s = 1.07$.

The substrates **4**, **5**, **6**, and the product **9** were identified by using a GC/MSD-system HP 6890/5973 (Hewlett–Packard, Waldbronn, Germany) equipped with an HP 7683 autosampler.

The enantiomeric excess ee of both substrate (ee_s) and product (ee_p) as well as conversion (conv.) and enantiomeric ratio (*E*) were determined by the computer program available on the internet http://www.orgc.TUGraz.at/orgc/programs/selectiv/selectiv.htm.

5. X-Ray structural analysis of complex 2L$_4$

Crystals of **2L$_4$** were obtained by slow diffusion of diethyl ether into a dichloromethane solution of **2L$_4$**. A selected crystal was mounted on a Siemens P4 four-circle diffractometer by using a perfluorinated polyether (Riedel de Haen) as protecting agent. Graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) was used for the measurement of intensity data in the ω-scan mode at a temperature of 173(2) K. Cell parameters were determined from 50 automatically centered reflections. The intensity data were corrected for polarization and Lorentz effects. The structure was solved by direct methods with SHELXS-86.[28a] Refinement was carried out by full-matrix least-squares methods based on F^2 in SHELXL-97,[28b] with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included at calculated positions using a riding model with isotropic temperature factors equal to 1.2 times the U_{eq} value of the corresponding parent atom.

Crystallographic details of the structure determination of **2L$_4$** are summarized below:

Empirical formula $C_{44}H_{50}Cl_2N_2O_2P_2Ru$; Formula weight 872.77; Crystal system: monoclinic; Space group $P2_1$, *a* (Å) 12.136(3), *b* (Å) 29.307(3), *c* (Å) 12.898(3); α (°) 90, β (°) 114.194(17), γ (°) 90; Volume (Å^3) 4184.7(13) *Z* 4; Calculated density (g cm^{-3}) 1.385; Absorption coefficient (mm^{-1}) 0.617; Reflections collected/unique 20134/18465 [R(int) = 0.0356]; Data/restraints/parameters 18465/1/959; Goodness-of-fit on F_o^2 1.009; Final *R* indices [$I > 2\sigma(I)$];[a] $R_1 = 0.0443$, $R_w(F_o^2) = 0.0861$; *R* indices (all data).[a] $R_1 = 0.0704$, $R_w(F_o^2) = 0.0958$; Absolute structure parameter 0.01(3); Largest diff. peak and hole (e Å^{-3}) 0.334 and −0.596.

[a] $R_1 = \sum(||F_o| - |F_c||)/\sum|F_o|$; $R_w(F_o^2) = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{0.5}$.

The crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 190369. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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