Monatshefte für Chemie 135, 885–897 (2004)
DOI 10.1007/s00706-003-0162-6

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Enantioselective Catalysis. Part 156 [1]. Ruthenium Procatalysts and 2-Pyridinealdehyde/(*S*)-*NOBIN*-Derived Cocatalysts in the Transfer Hydrogenation of Acetophenone with 2-Propanol

Henri Brunner* and **Frauke Henning**

Institut für Anorganische Chemie, Universität Regensburg, D-93040 Regensburg, Germany

Received December 1, 2003; accepted December 5, 2003
Published online April 9, 2004

Summary. Several ruthenium procatalysts were tested in the transfer hydrogenation of acetophenone with 2-propanol using the chiral imine ligand (*S*)-2-(2-pyridinylmethyleneamino)-2′-hydroxy-1,1′-binaphthyl and the corresponding amine (*S*)-2-(2-pyridinylmethylamino)-2′-hydroxy-1,1′-binaphthyl. $Ru(PPh_3)_3Cl_2$ was the best procatalyst. Its triphenylphosphane ligands were crucial for the catalytic activity and take part in the chirality transfer. Triphenylphosphane removing reagents such as copper(I) chloride, *TEMPO*, or *TMAO* improved the catalytic performance to enantioselectivities up to 99% *ee*. The findings led to a mechanistic proposal including dissociation equilibria of triphenylphosphane and chelate ring opening of the tridentate chiral binaphthyl ligand. New ligands with an additional chiral center were synthesized and tested as cocatalysts. The nature of catalytically active intermediates was examined by MS and NMR spectroscopy.

Keywords. Binaphthyl ligands; Ruthenium complexes; Chirality; Enantioselective catalysis; Hydrogen transfer.

Introduction

The enantioselective transfer hydrogenation with 2-propanol or formic acid as hydrogen donors has received wide interest in the last ten years [2]. After the development of earlier successful catalysts [3, 4], *Noyori*'s complex [(*p*-cymene)-Ru(*TsDPEN*)Cl] led to increased research in this field [5]. Up to date a large number of active catalysts has been discovered. Among these *Andersson*'s azanorbornane ligands achieve *in situ* with $[(p\text{-cymene})RuCl_2]_2$ excellent results with turnover numbers of $8500\,s^{-1}$ and 96% *ee* [6]. Our tridentate imine and amine

* Corresponding author. E-mail: henri.brunner@chemie.uni-regensburg.de

ligands (*S*)-**1** and (*S*)-**2**, derived from (*S*)-*NOBIN* and 2-pyridinecarbaldehyde, yield equally high enantiomeric excesses of up to 97% [7]. Recently, an enantioselective aluminum catalyst was found for the *Meerwein-Schmidt-Ponndorf-Verley* reduction (*MPV* reduction) of prochiral ketones with up to 83% *ee* [8].

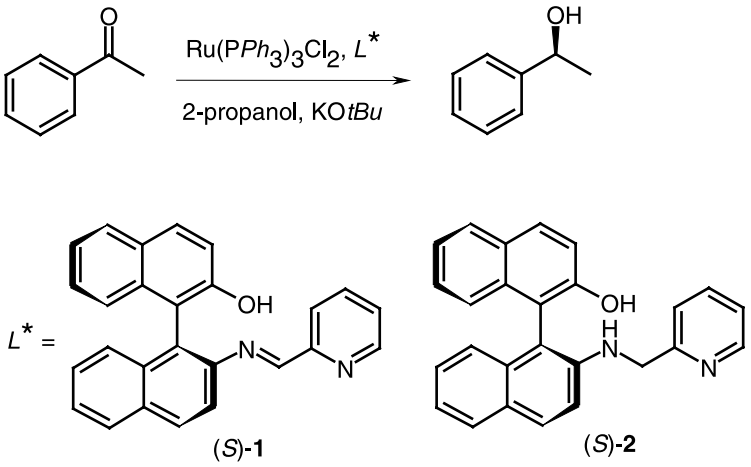
The difference between the transition metal catalysed transfer hydrogenation and the aluminum-catalysed *MPV* reduction lies in the mechanism. Oxophilic, *Lewis* acidic aluminum catalysts bind the substrate and the hydrogen donor by their oxygen atoms and thus enable an intramolecular hydride transfer between both organic molecules without metal contact. Transition metal catalysts favour the formation of hydride complexes, which are the catalytically active species and can transfer a hydride ligand to the substrate by two possible pathways, a stepwise hydridic route and a concerted metal-ligand bifunctional mechanism [2, 3c, 5b, 9–11].

The substrates of the enantioselective transfer hydrogenation can be olefins, ketones, and imines. Acetophenone is a common substrate for the testing of catalysts in standard reactions. Avoiding the handling of hydrogen gas and mild reaction conditions are the advantageous aspects of this reaction, when it is compared to conventional hydrogenation. It has been applied successfully to pharmaceutically relevant substrates and a growing number of patents shows the interest of the chemical industry [12]. In order to facilitate the separation and recycling some catalysts have been immobilised on solid phases [13] or attached to dendrimers [14]. Biphasic systems were explored as well as the use of ionic liquids or water as solvents [15]. Furthermore, biocatalysts were found for the enantioselective transfer hydrogenation [16].

So far the range of transition metal procatalysts that can be used with chiral ligands to generate the catalytically active species *in situ* is limited to ruthenium, rhodium, or iridium. Less common is the use of nickel, cobalt, and samarium complexes [17]. For halfsandwich complexes containing bidentate chiral ligands $[(p\text{-cymene})RuCl_2]_2$, $[Cp^*RhCl_2]_2$, and $[Cp^*IrCl_2]_2$ are appropriate procatalysts. For ligands with a higher coordination number $Ru(PPh_3)_3Cl_2$ or $Ru(DMSO)_4Cl_2$ are generally used. In this article we report new investigations into the catalytic properties of our transfer hydrogenation system with imine and amine ligands (*S*)-**1** and (*S*)-**2** [18]: (i) A series of ruthenium complexes was tested with (*S*)-**1** and (*S*)-**2** to elucidate the role of the procatalyst and to obtain information about the catalytically active species. (ii) We explored the effects of additives in order to further improve the catalytic performance. (iii) A yellow precipitate that formed during the catalytic experiments was analysed by spectroscopic methods. (iv) A methyl group was introduced into imine ligand (*S*)-**1** generating a chiral carbon atom in addition to the chiral axis with the aim of increasing the enantioselectivity by fine tuning.

Results and Discussion

In a preceeding paper we had published the imine ligand (*S*)-2-(2-pyridinylmethyleneamino)-2′-hydroxy-1,1′-binaphthyl ((*S*)-**1**), the corresponding amine (*S*)-2-(2-pyridinylmethylamino)-2′-hydroxy-1,1′-binaphthyl ((*S*)-**2**), and their use as cocatalysts *in situ* with $Ru(PPh_3)_3Cl_2$ in the transfer hydrogenation of acetophenone with 2-propanol, yielding (*S*)-1-phenylethanol with 94% conversion and 97%



Scheme 1

ee in 15 h reaction time at 28°C reaction temperature and with a substrate/catalyst ratio of 100/1 (Scheme 1) [7]. In the present study the standard substrate/catalyst ratio was 200/1.

Both ligands were tested in the catalytic standard reaction employing the following procatalysts: $Ru(PPh_3)_3Cl_2$, $Ru(DMSO)_4Cl_2$, $Ru_2((R,R)\text{-}DIOP)_2Cl_4$, and $[(p\text{-cymene})RuCl_2]_2$ (Fig. 1, bars 2 and 3). These ruthenium complexes were also tested without the addition of the chiral ligands (*S*)-**1** and (*S*)-**2** (bars 1). In the case of the standard procatalyst $Ru(PPh_3)_3Cl_2$ the ligand accelerating effect is clearly visible. The complex $Ru(DMSO)_4Cl_2$ with *DMSO* instead of triphenylphosphane hardly displayed any catalytic activity of its own and the reaction rates could not be improved much by adding the chiral ligands. However, a significant enantiomeric excess was observed. The procatalyst $Ru_2((R,R)\text{-}DIOP)_2Cl_4$

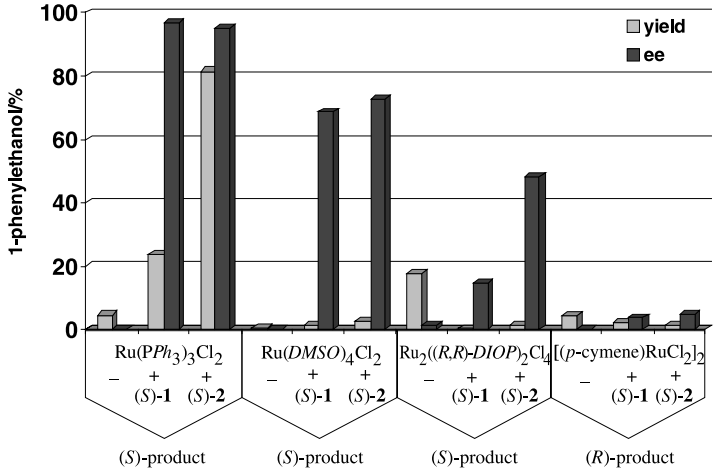


Fig. 1. Enantioselective transfer hydrogenation of acetophenone in the presence of different ruthenium procatalysts and the ligands (*S*)-**1** and (*S*)-**2** (standard reaction conditions)

contained (*R*,*R*)-*DIOP* as a chiral bisphosphane. It showed some catalytic activity and low enantioselectivity with 1.3% *ee* (*S*). Upon addition of the chiral ligands the enantiomeric excess increased, but the conversion was reduced to less than 1%. As for the procatalyst $[(p\text{-cymene})RuCl_2]_2$ we refer to published results, that were obtained with the preformed complex [19]. Conversions and enantiomeric excesses were below 5% in either case. Thus, phosphane ligands in the procatalyst led to good catalytic activity, whereas *DMSO* did not. It must be assumed that many of the species formed *in situ* from the procatalysts and cocatalysts in Fig. 1 do not provide enough empty coordination sites to bind the reactants. Obviously, in the case of $Ru(PPh_3)_3Cl_2$ and its reaction products with (*S*)-**1** and (*S*)-**2** these open sites can be generated by dissociation of the monodentate phosphane, whereas chelation of the bisphosphane ligand in $Ru_2((R,R)\text{-}DIOP)_2Cl_4$ and its derivatives prevents ligand dissociation. Thus, out of four easily accessible ruthenium procatalysts only $Ru(PPh_3)_3Cl_2$ is suitable for good catalytic results.

To further elucidate the crucial role of the triphenylphosphane ligand we performed cross experiments with $Ru(PPh_3)_3Cl_2/(S)$-**1** and $Ru(DMSO)_4Cl_2/(S)$-**1** by adding the missing monodentate ligand, *DMSO* or PPh_3 (Table 1).

The results show that an addition of *DMSO* to the complex formed from $Ru(PPh_3)_3Cl_2$ and (*S*)-**1** does not change the enantioselectivity of the reaction. The catalytically active species remains unaltered (entries 1–3). The diminishing conversion may be attributed to a competition between *DMSO* and the substrate acetophenone, with *DMSO* partially blocking the active coordination sites of the catalyst (see below). On the contrary, upon addition of two or six equivalents of PPh_3 to the complex derived from $Ru(DMSO)_4Cl_2$ and (*S*)-**1** the enantiomeric excess of the product increases from an average of 68% to values close to those obtained with the catalyst $Ru(PPh_3)_3Cl_2/(S)$-**1** (entries 4–6). These findings indicate an exchange of the *DMSO* ligand by PPh_3 and the formation of the catalytically active triphenylphosphane-containing species.

Given that one or two equivalents of triphenylphosphane are required for good catalytic results, we investigated the effect of an excess amount of PPh_3 (Table 1). The addition of three or ten equivalents of additional PPh_3 to $Ru(PPh_3)_3Cl_2/(S)$-**1**

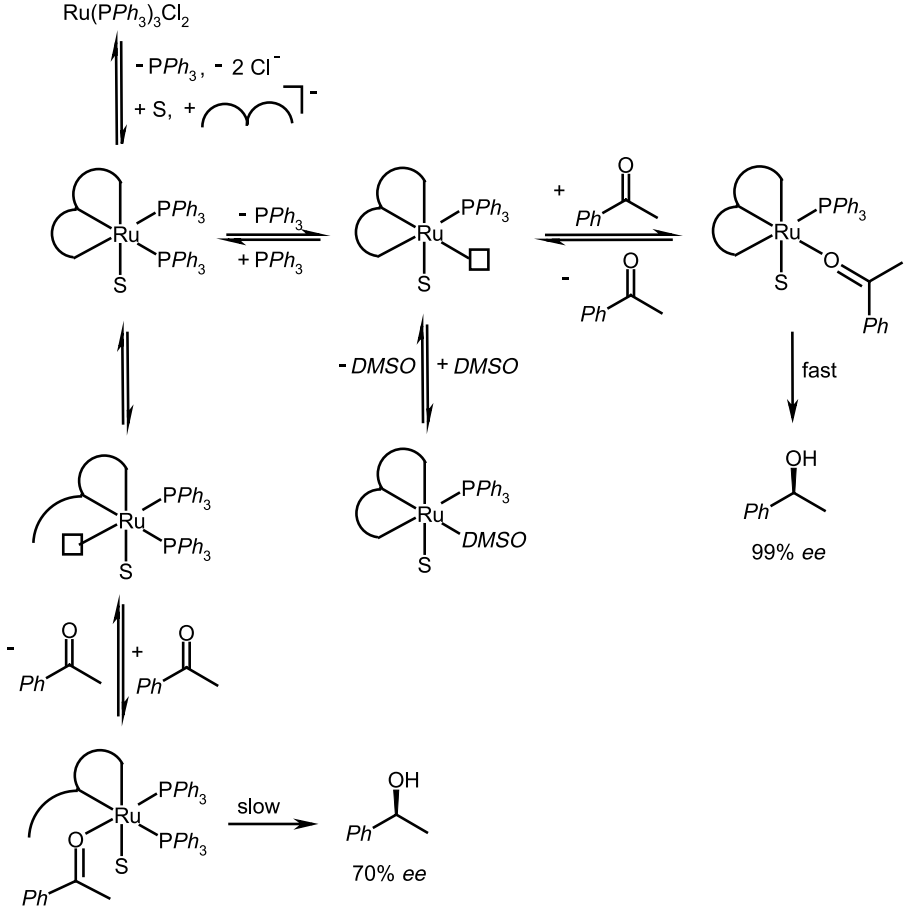
Table 1. Ligand exchange and excess experiments of the transfer hydrogenation catalysts $Ru(PPh_3)_3Cl_2/(S)$-**1** and $Ru(DMSO)_4Cl_2/(S)$-**1** with *DMSO* and PPh_3 (standard conditions)

Entry	Ligand	Procatalyst	Additive	Yield/%	*ee*/% (*S*)
1	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	–	22.8, 22.6, 25.1	97.1, 97.2, 96.6
2	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	20 eq *DMSO*	14.4	97.2
3	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	40 eq *DMSO*	7.5	97.9
4	(*S*)-**1**	$Ru(DMSO)_4Cl_2$	–	0.6, 2.5	64.7, 72.1
5	(*S*)-**1**	$Ru(DMSO)_4Cl_2$	2 eq PPh_3	3.8, 2.9	98.0, 92.7
6	(*S*)-**1**	$Ru(DMSO)_4Cl_2$	6 eq PPh_3	4.4	98.3
7	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	3 eq PPh_3	48.9, 49.8	84.4, 90.5
8	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	10 eq PPh_3	21.1, 27.2	70.4, 78.5
9	(*S*)-**2**	$Ru(PPh_3)_3Cl_2$	3 eq PPh_3	53.4, 54.7	90.4, 95.0
10	(*S*)-**2**	$Ru(PPh_3)_3Cl_2$	10 eq PPh_3	20.6, 23.6	92.8, 87.9

leads to a decreasing catalytic activity and enantioselectivity (entries 7–8). The same trend can be observed for the catalyst $Ru(PPh_3)_3Cl_2/(S)$-**2** (entries 9–10). Therefore, the amount of triphenylphosphane is not only contributing to the activity of the catalyst, but also plays a role in the chirality transfer.

The procatalyst $Ru(PPh_3)_3Cl_2$ contains three phosphane ligands, whereas the experimentally determined optimum quantity lies in the range of one or two equivalents. Taking into account that the chiral binaphthyl ligand may bind in a bidentate or tridentate way and that two further coordination sites are needed for binding the substrates, a dissociation of triphenylphosphane from $Ru(PPh_3)_3Cl_2$ must occur in order to enable the complex to enter the catalytic cycle (first step in Scheme 2).

S in Scheme 2 may stand for a hydride or a hydrogen donor, such as 2-propanol, resulting in a neutral species in the first case or a cationic species in the latter case. The position of the open site (□) is chosen arbitrarily as well as the arrangement of the various ligands around the metal center. Chelate ring opening of the chiral tridentate ligand may occur at the pyridine or at the phenolate side. Whether the rate limiting step, designated fast for the horizontal branch and slow



Scheme 2

Table 2. Effects of additives on the transfer hydrogenation with the catalysts $Ru(PPh_3)_3Cl_2$/(*S*)-**1** and $Ru(PPh_3)_3Cl_2$/(*S*)-**2** (standard conditions)

Entry	Ligand	Procatalyst	Additive	Yield/%	*ee*/% (*S*)
1	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	30 eq CuCl	73.7, 70.6	99.1, 99.0
2	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	2 eq *TEMPO*	91.1, 94.8	98.5, 97.6
3	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	2 eq *TMAO*	90.2, 92.0	97.8, 97.7
4	(*S*)-**2**	$Ru(PPh_3)_3Cl_2$	30 eq CuCl	58.1, 59.2	96.1, 98.5
5	(*S*)-**2**	$Ru(PPh_3)_3Cl_2$	2 eq *TEMPO*	95.5, 95.0	96.4, 97.3
6	(*S*)-**2**	$Ru(PPh_3)_3Cl_2$	2 eq *TMAO*	60.1, 48.7	96.5, 94.8

for the perpendicular branch, are at the positions indicated in Scheme 2 remains an open question.

The horizontal branch of Scheme 2 shows how an open site is formed by dissociation of triphenylphosphane. Either *DMSO* (decreasing the conversion) or the substrate can subsequently bind to the metal center reacting rapidly with high enantiomeric excess. In the perpendicular branch an open site is generated by chelate ring opening, the consequence of which is a change in the chiral environment of the metal center lowering the enantiomeric excess in a slower reaction.

Copper(I) chloride was not soluble in 2-propanol, but it is known to be able to absorb free phosphane ligands [20]. An excess of 30 equivalents of copper(I) chloride increased the yield of the standard reaction with the catalyst $Ru(PPh_3)_3Cl_2$/(*S*)-**1** from 25% to 70% and the enantiomeric excess from 97% to 99% (Table 2, entry 1), obviously favouring the horizontal branch in Scheme 2. Reactions employing copper(I) chloride alone or with (*S*)-**1** did not show any product formation. The salts $Cu(OTf)_2$, $NiBr_2$, and $CoCl_2$ were soluble in 2-propanol but did not show any sign of catalytic activity.

2,2,6,6-Tetramethylpiperidin-1-oxyl (*TEMPO*) and trimethylamineoxide (*TMAO*) oxidize free triphenylphosphane in solution and thus shift the dissociation equilibria of Scheme 2 to the desired side of the mono-PPh_3 species. Using these two additives in the standard transfer hydrogenation of acetophenone with 2-propanol more than 90% conversion and 98% *ee* were obtained with the imine ligand (*S*)-**1** (Table 2, entries 2–3). The catalytic activity observed with 2 equivalents of *TEMPO* added was equivalent to that with twice the catalyst concentration [7], while the enantiomeric excess maintained on a higher level with 98% rather than 94%. The favourable effect of the phosphane removing additives *TEMPO* and *TMAO* was less clear in the case of the amine ligand (*S*)-**2** only *TEMPO* giving a measurable improvement (entries 4–6). The addition of *TEMPO* stabilizes the catalytically active species in the $Ru(PPh_3)_3Cl_2$/(*S*)-**1** system resulting in an increased and highly selective product formation (Fig. 2).

During the catalysis experiments with the ligands (*S*)-**1** and (*S*)-**2** and $Ru(PPh_3)_3Cl_2$ the formation of a yellow precipitate was observed. In the case of the imine ligand (*S*)-**1** it occurred at the end of the reaction, whereas with the amine ligand (*S*)-**2** the precipitate formed while the catalyst was generated *in situ*. The isolated precipitate showed catalytic activity in the transfer hydrogenation of acetophenone yielding 67% (*S*)-1-phenylethanol in 70% *ee* (standard conditions). Thus, the isolated intermediate is an active and selective catalyst but not the highly

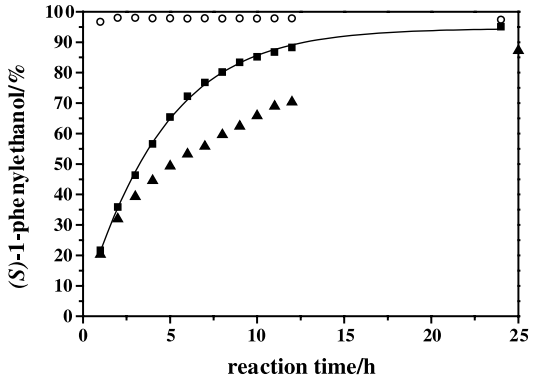


Fig. 2. Reaction profile of the transfer hydrogenation of acetophenone with 2-propanol (standard conditions) employing the *in situ* catalyst $Ru(PPh_3)_3Cl_2/(S)$-**1**: ▲ conversion without any additive, ■ conversion with 2 eq of *TEMPO* added, ○ enantiomeric excess with 2 eq of *TEMPO* added

enantioselective catalyst in the $Ru(PPh_3)_3Cl_2/(S)$-**1** and $Ru(PPh_3)_3Cl_2/(S)$-**2** systems. Since the precipitate occurred at the end of the reaction with catalyst $Ru(PPh_3)_3Cl_2/(S)$-**1** it may be a reduction product (imine → amine) of the initial catalyst. In accord with this assumption an ESI-MS of the isolated yellow powder displayed the fragments of mononuclear complexes containing the tridentate amine ligand (*S*)-**2** and one or two PPh_3 ligands (Fig. 3).

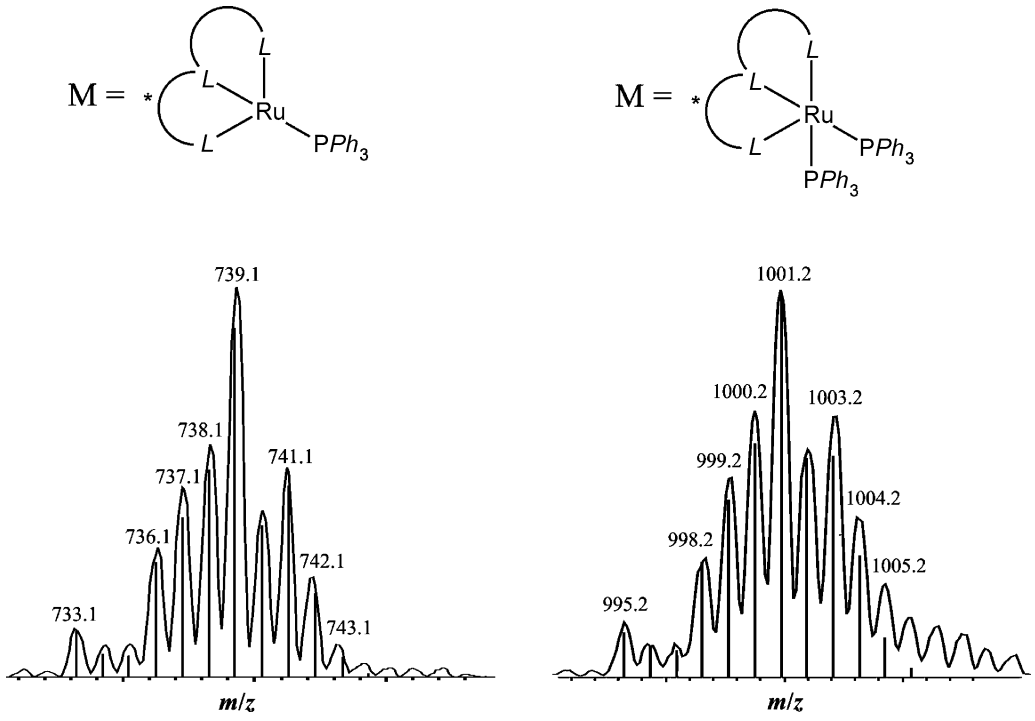


Fig. 3. ESI-MS fragments of the isolated catalytically active intermediate; detected were MH^+ ions; enclosing line = measurement; single line pattern = simulation

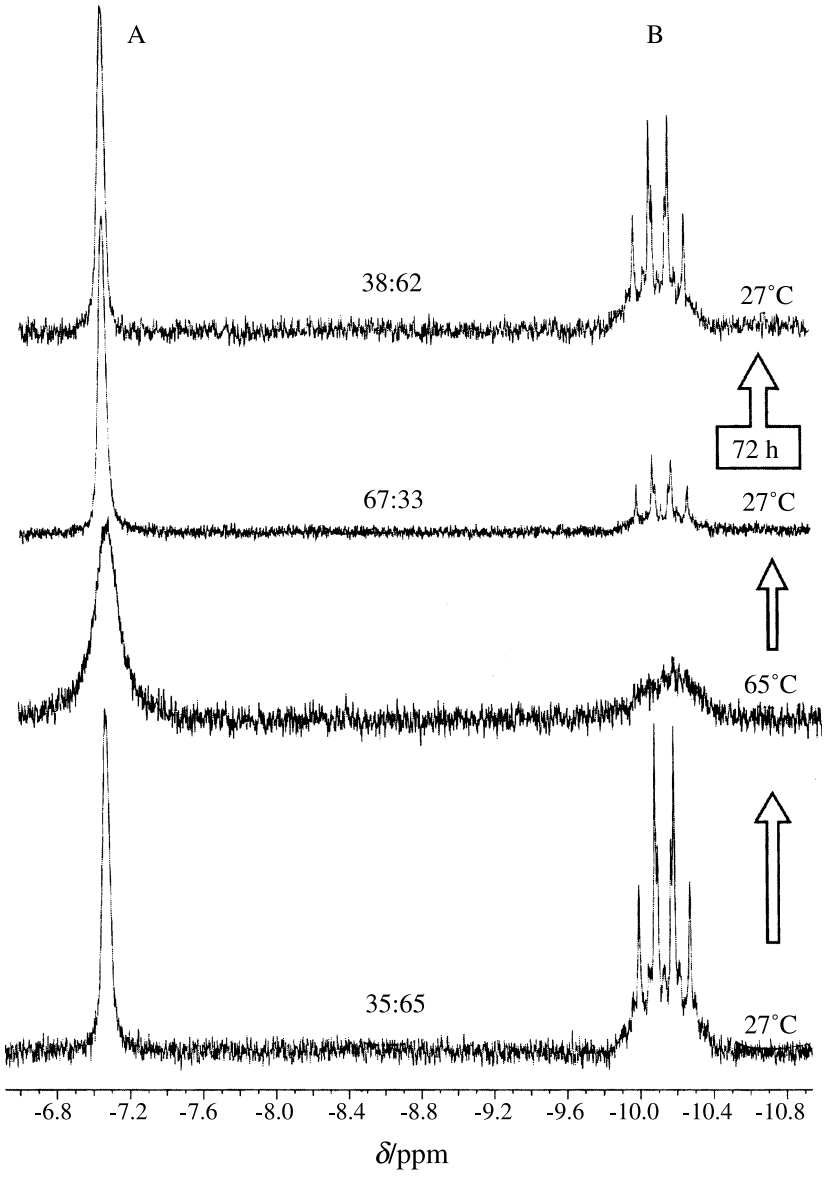
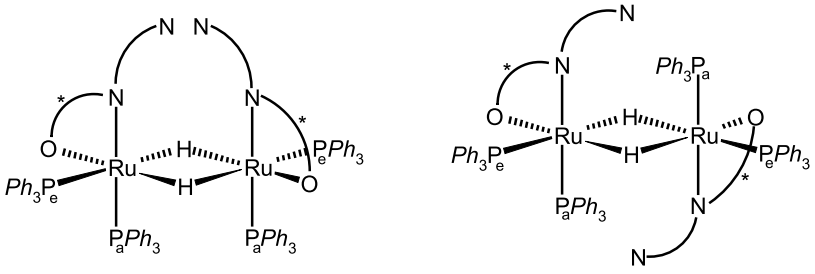


Fig. 4. Hydride region of the ^{1}H NMR spectrum (400 MHz, C_6D_6) of the yellow precipitate at different temperatures and time intervals

The ^{1}H NMR spectrum of the yellow precipitate showed two signals in the hydride region at −7.1 (A) and −10.2 ppm (B) indicating the presence of two hydride species in solution. Upon heating to 65°C these peaks broadened due to an exchange reaction. After cooling down the same sharp signals were obtained, but the ratio of the integrals had changed in favour of complex A (Fig. 4). After 72 h the initial ratio had reestablished.

In the 400 MHz ^{31}P NMR spectrum a singlet was observed at 58.36 ppm for complex A and two pseudo triplets for complex B at 49.91 and 41.74 ppm. The ^{31}P NMR spectrum also showed temperature dependence of the signals due to an



Scheme 3

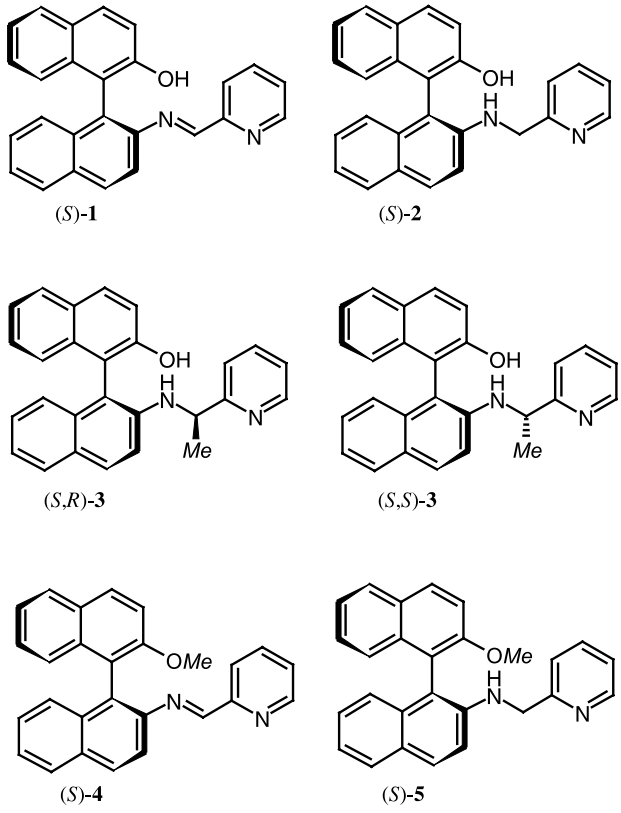
exchange reaction. A $^{1}H/^{31}P$-HMQC spectrum confirmed the coupling of the two phosphorus groups in B with the hydrides in B [18].

Furthermore, the complex multiplet of the hydride signal B is highly symmetric, which is typical for AA'BB' systems, and it has identical peak distances at 400 and 600 MHz. Signal B is not an accidental overlap of two hydride signals, but it represents a genuine spin system, which can be described as AA'MM'X_2. Keeping in mind that a possibly tridentate chiral ligand is bound to the metal center one can exclude monomeric species. Since Ru(P*Ph*$_3$)$_3$Cl$_2$ is known to dimerize in solution [21], we suggest that dimerization occurs also with the chiral ligand present in the complex. Since the hydride ligands are inequivalent, two structure proposals can be made that have the corresponding symmetry (Scheme 3). The ^{1}H and ^{31}P NMR peaks of complex A support a monomeric structure in accord with the MS spectrum. We suggest that the chemical exchange observed in solution is a dimerization reaction accompanied by a phosphane dissociation and/or a chelate ring opening.

We introduced a further chiral center into the binaphthyl ligand by reacting the imine (*S*)-**1** with methyllithium (Scheme 4). The diastereomer ratio of the crude product was 62:38 in favour of (+)-**3**. The diastereomers were seperated by repeated column chromatography. Since no suitable crystals were obtained, the assignment of the absolute configuration remains open. Both diastereomers were tested *in situ* with Ru(P*Ph*$_3$)$_3$Cl$_2$ in the transfer hydrogenation of acetophenone with 2-propanol (Table 3).

Ligand (+)-**3** achieved up to 93% conversion and 92% *ee* (*S*), whereas (−)-**3** resulted in up to 83% conversion and 85% *ee* (*S*). Thus, derivatives (+)-**3** and (−)-**3** with an additional chiral center are *matched* and *mismatched* combinations. However, they did not improve the enantioselectivity of the parent ligand (*S*)-**2**.

Comparing the catalytic performance of all four ligands (*S*)-**1**, (*S*)-**2**, (+)-**3**, (−)-**3** we did not observe any NH effect indicating a bifunctional mechanism [22]. Instead, inclusion of the O*Me* derivatives (*S*)-**4** and (*S*)-**5** showed that the phenolic OH function is crucial for the catalytic activity and enantioselectivity (Table 3). Two reasons may account for this OH effect. Upon addition of base the hydroxy group is deprotonated and then binds the chiral part of the ligand to the ruthenium center. Methylation of the hydroxy group does not allow this bond to form and thus the enantiomeric excess drops [8]. On the other hand the ligand could bind in a bidentate way via both nitrogen atoms leaving the hydroxy group in a fixed position. The hydrogen atom of the hydroxy group then could participate in a bifunctional mechanism strongly favouring one substrate orientation.



Scheme 4

Table 3. Enantioselective transfer hydrogenation of acetophenone with 2-propanol (standard conditions) in the presence of different (*S*)-*NOBIN*-derived ligands

Entry	Ligand	Procatalyst	Yield/%	*ee*/% (*S*)
1	(*S*)-**1**	$Ru(PPh_3)_3Cl_2$	22.8, 22.6, 25.1	97.1, 97.2, 96.6
2	(*S*)-**2**	$Ru(PPh_3)_3Cl_2$	85.7, 77.2	96.3, 94.1
3	(+)-**3**	$Ru(PPh_3)_3Cl_2$	89.1, 93.1	92.8, 91.8
4	(−)-**3**	$Ru(PPh_3)_3Cl_2$	83.0, 42.9	85.9, 84.5
5	(*S*)-**4**	$Ru(PPh_3)_3Cl_2$	2.3, 3.7	rac.
6	(*S*)-**5**	$Ru(PPh_3)_3Cl_2$	38.2, 11.1	2.4, 2.6

Experimental

^{1}H NMR spectra: Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz) with *TMS* or solvent as internal standard. ^{31}P NMR spectra: Bruker Avance 400 (162 MHz) and Bruker Avance 600 (243 MHz) with H_3PO_4 as external reference. MS spectra: ThermoQuest Finnigan TSQ 7000. (*S*)-**1**, (*S*)-**2**, (*S*)-**4**, and (*S*)-**5** were prepared as described in previous communications [7, 19]. $Ru(PPh_3)_3Cl_2$ was purchased from Merck. $Ru(DMSO)_4Cl_2$ [23], $Ru_2((R,R)\text{-}DIOP)_2Cl_4$ [24], and $[(p\text{-cymene})RuCl_2]_2$ [25] were synthesised according to literature procedures. The catalytic experiments and the synthesis of (*S*)-**3** were conducted in an inert atmosphere using standard *Schlenk* techniques. Solvents were dried

and distilled under inert gas according to standard procedures. Acetophenone was dried with Siccapent® and distilled under nitrogen prior to use.

(S)-2-[1-(2-Pyridinyl)ethylamino]-2′-hydroxy-1,1′-binaphthyl ((±)-**3**, $C_{27}H_{22}N_2O$)

Ligand (*S*)-**1** (374.0 mg, 1.0 mmol) was dissolved in 80 cm^3 of toluene and cooled to −78°C. $BF_3 \times OEt_2$ (0.2 cm^3, 1.6 mmol) and 1.9 cm^3 (3.0 mmol) of a 1.6 *M MeLi* solution in ether were added with a syringe. After stirring for 5 h at −78°C the reaction mixture was warmed to room temperature and hydrolysed with 20 cm^3 of a saturated $NaHCO_3$ solution. The *pH* was adjusted to 10 with KOH and the mixture was extracted with 5×20 cm^3 of ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and the solvent was evaporated. Thus, 315.0 mg (81%) of the crude product, a colourless residue, were obtained. It was purified by column chromatography on silica with ethyl acetate/petroleum ether 40–60 (1/1). The second fraction ($R_f = 0.68$, (−)-**3**) and the third fraction ($R_f = 0.52$, (+)-**3**) were collected and subjected to repeated chromatography for purification (2×). Dissolving the residues in a minimum of CH_2Cl_2 and stirring with an excess of *n*-hexane yielded colourless powders.

(+)-**3**: Yield 190 mg (49%); mp 180°C; ESI MS (CH_2Cl_2): $m/z = 390.0$ (M, 100), 375.0 (M–CH_3, 70); ^{1}H NMR (400 MHz, $CDCl_3$, *TMS*): $\delta = 1.34$ (d, $J = 6.7$ Hz, CH_3), 4.24 (b, NH), 4.79 (bq, $J = 6.7$ Hz, CH), 5.25 (b, OH), 6.81–8.00 (m, Ar–H), 8.43 (ddd, $J = 5.0$, 1.7, 0.9 Hz, o–Py–H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 23.17$ (CH_3), 55.12 (CH), 108.58 (C_q), 114.07 (C_q), 114.95 (CH), 117.79 (CH), 119.58 (CH), 121.93 (CH), 122.36 (CH), 123.64 (CH), 124.72 (CH), 125.09 (CH), 126.72 (CH), 127.15 (CH), 127.61 (C_q), 128.14 (CH), 128.36 (CH), 129.63 (C_q), 130.51 (CH), 130.55 (CH), 133.53 (C_q), 134.08 (C_q), 136.80 (CH), 144.22 (C_q), 149.06 (CH), 152.16 (C_q), 164.12 (C_q) ppm; IR (KBr): $\bar{\nu} = 3350$ (b), 3060 (w), 3040 (m), 3020 (w), 2960 (w), 1610 (s), 1590 (s), 1555 (m), 1510 (m), 1480 (s), 1460 (m), 1430 (m), 1340 (s), 1275 (m), 1210 (m), 1150 (m), 820 (s), 755 (s) cm^{-1}; $[\alpha]_D^{26} = +217° cm^2 g^{-1}$ ($c = 0.4$, $CHCl_3$).

(−)-**3**: Yield 100 mg (26%); mp 70°C; ESI MS (CH_2Cl_2): $m/z = 390.0$ (M, 100), 375.0 (M–CH_3, 67); ^{1}H NMR (400 MHz, $CDCl_3$, *TMS*): $\delta = 1.35$ (d, $J = 6.7$ Hz, CH_3), 4.29 (b, NH), 4.96 (bq, $J = 6.7$ Hz, CH), 6.81–8.00 (m, Ar–H), 8.37 (ddd, $J = 5.0$, 1.7, 0.9 Hz, o–Py–H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 23.56$ (CH_3), 54.48 (CH), 112.12 (C_q), 115.32 (CH), 118.16 (C_q), 119.77 (CH), 121.73 (CH), 122.05 (CH), 122.32 (CH), 123.49 (CH), 123.72 (CH), 124.35 (CH), 125.09 (CH), 126.71 (CH), 127.30 (C_q), 127.68 (C_q), 127.90 (CH), 128.06 (CH), 129.75 (CH), 130.22 (CH), 130.34 (C_q), 134.38 (C_q), 137.30 (CH), 144.10 (C_q), 148.61 (CH), 152.77 (C_q), 163.47 (C_q) ppm; IR (KBr): $\bar{\nu} = 3480$ (b), 3400 (b), 3060 (w), 2970 (w), 2930 (w), 2870 (w), 1620 (s), 1590 (s), 1570 (m), 1510 (s), 1490 (s), 1440 (m), 1430 (m), 1350 (m), 1270 (m), 1225 (m), 1155 (m), 825 (s), 760 (s) cm^{-1}; $[\alpha]_D^{26} = -265° cm^2 g^{-1}$ ($c = 0.4$, $CHCl_3$).

General Procedure for the Catalytic Transfer Hydrogenation

Ligand (*S*)-**1** (3.53 mg, 9.43 µmol) was dissolved in 15.3 cm^3 (14.4 cm^3 for amine ligands) of 2-propanol. 0.94 cm^3 (9.40 µmol) of 0.01 *M* KO*tBu* in 2-propanol were added (1.88 cm^3 (18.80 µmol) for amine ligands). After 5 min 8.57 µmol of the ruthenium procatalyst were added (8.22 mg $Ru(PPh_3)_3Cl_2$, 4.15 mg $Ru(DMSO)_4Cl_2$, 5.75 mg (4.29 µmol) $Ru_2((R,R)\text{-}DIOP)_2Cl_4$). The solution was stirred for 1 h at 28°C. Acetophenone (0.20 cm^3, 1.72 mmol) was added and the reaction was started with 0.86 cm^3 (8.60 µmol) of the 0.01 *M* KO*tBu* solution. When necessary additional reagents, such as PPh_3, *DMSO*, CuCl, *TEMPO*, or *TMAO*, were added before starting the catalysis. After stirring for 15 h at 28°C the reaction was stopped with 0.30 cm^3 (0.03 mmol) of 0.1 *M* acetic acid in 2-propanol. The solvent was removed under reduced pressure and the products were isolated by bulb-to-bulb distillation. Conversion and enantiomeric excess were analysed by quantitative GC with biphenyl as internal standard (Fisons 8130, CP-Chirasil-Dex-CB-column (25 m×0.25 mm), 113°C, 123 kPa, He 2.56 cm^3/min).

References

[1] Part 155: Brunner H, Henning F, Zabel M (2004) Z Anorg Allg Chem **630**: 91

[2] For reviews see: a) Zassinovich G, Mestroni G, Gladiali S (1992) Chem Rev **92**: 1051; b) Palmer MJ, Wills M (1999) Tetrahedron: Asymmetry **10**: 2045

[3] a) Brunner H, Leitner W (1988) Angew Chem **100**: 1231, Angew Chem Int Ed Engl **27**: 1180; b) Brunner H, Graf E, Leitner W, Wutz K (1989) Synthesis 743; c) Leitner W, Brown JM, Brunner H (1993) J Am Chem Soc **115**: 152

[4] Müller D, Umbricht G, Weber B, Pfaltz A (1991) Helv Chim Acta **74**: 232

[5] a) Hashiguchi S, Fuji A, Takehara J, Ikariya T, Noyori R (1995) J Am Chem Soc **117**: 7562; b) Haack KJ, Hashiguchi S, Fuji A, Ikariya T, Noyori R (1997) Angew Chem **109**: 297, Angew Chem Int Ed Engl **36**: 285

[6] Nordin SJ, Roth P, Tarnai T, Alonso DA, Brandt P, Andersson PG (2001) Chem Eur J **7**: 1431

[7] Brunner H, Henning F, Weber M (2002) Tetrahedron: Asymmetry **13**: 37

[8] Campbell EJ, Zhou H, Nguyen ST (2002) Angew Chem **114**: 1062, Angew Chem Int Ed **41**: 1020

[9] a) Laxmi YR, Bäckvall JE (2000) Chem Commun 611; b) Bäckvall JE (2002) J Organomet Chem **652**: 105

[10] Noyori R, Yamakawa M, Hashiguchi S (2001) J Org Chem **66**: 7931

[11] a) Yamakawa M, Ito H, Noyori R (2000) J Am Chem Soc **122**: 1466; b) Alonso DA, Brandt P, Nordin SJ, Andersson PG (1999) J Am Chem Soc **121**: 9580

[12] a) Yamano Y, Wanatabe Y, Wanatabe N, Ito M (2002) J Chem Soc Perkin Trans 1 2833; b) Everaere K, Scheffler JL, Mortreux A, Carpentier JF (2001) Tetrahedron Lett **42**: 1899; c) Yamashita H, Ohtani T, Morita S, Otsubo K, Kan K, Matsubara J, Kitano K, Yoshikazu U, Uchida M, Tabusa F (2002) Heterocycles **56**: 123; d) Mohar B, Valleix A, Desmurs JR, Felemez M, Wagner A, Mioskowski C (2001) Chem Commun 2572; e) Kawamoto A, Wills M (2000) Tetrahedron: Asymmetry **11**: 3257; f) Meuzelaar GJ, Van Vliet MC, Maat L, Sheldon RA (1999) Eur J Org Chem: 2315; g) Vedejs E, Trapencieris P, Suna E (1999) J Org Chem **64**: 6724; h) Alcock NJ, Mann I, Peach P, Wills M (2002) Tetrahedron: Asymmetry **13**: 2485

[13] a) Sandee AJ, Petra DG, Reek JN, Kramer PC, Van Leeuwen PWNM (2001) Chem Eur J **7**: 1202; b) Laue S, Greiner L, Wöltinger J, Liese A (2001) Adv Synth Catal **343**: 711; c) Leadbeater NE (2001) J Org Chem **66**: 2168; d) Rolland A, Hérault D, Touchard F, Saluzzo C, Duval R, Lemaire M (2001) Tetrahedron: Asymmetry **12**: 811; e) Gao JX, Yi XD, Tang CL, Xu PP, Wan HL (2001) Polym Adv Technol **12**: 716; f) Breysse E, Pinel C, Lemaire M (1998) Tetrahedron: Asymmetry **9**: 897; g) Touchard F, Fache F, Lemaire M (2000) Eur J Org Chem: 3787; h) Saluzzo C, Ter Halle R, Touchard F, Fache F, Schulz E, Lemaire M (2000) J Organomet Chem **603**: 30; i) Polborn K, Severin K (2000) Chem Eur J **6**: 4604

[14] a) Chen YC, Wu TF, Deng JG, Liu H, Jiang YZ, Choi MC, Chan AS (2001) Chem Commun 1488; b) Chen YC, Wu TF, Deng JG, Liu H, Cui X, Zhu J, Jiang YZ, Choi MC, Chan AS (2002) J Org Chem **67**: 5301; c) Liu PN, Chen YC, Li XQ, Tu YQ, Deng JG (2003) Tetrahedron: Asymmetry **14**: 2481

[15] a) Maillard D, Nguefack C, Pozzi G, Quici S, Valadé B, Sinou D (2000) Tetrahedron: Asymmetry **11**: 2881; b) Comyns C, Karodia N, Zeler S, Andersen JA (2000) Catal Lett **67**: 113; c) Bubert C, Blacker J, Brown SM, Crosby J, Fitzjohn S, Muxworthy JP, Thorpe T, Williams JM (2001) Tetrahedron Lett **42**: 4037; d) Rhyoo HY, Park HJ, Suh WH, Chung YK (2002) Tetrahedron Lett **43**: 269; e) Rhyoo HY, Park HJ, Chung YK (2001) Chem Commun 2064

[16] a) Stampfer W, Kosjek B, Moitzi C, Kroutil W, Faber K (2002) Angew Chem **114**: 1056, Angew Chem Int Ed **41**: 1014; b) Yasohara Y, Kizaki N, Hasegawa J, Wada M, Kataoka M, Shimizu S (2001) Tetrahedron: Asymmetry **12**: 1713; c) Hage A, Petra DG, Field JA, Schipper D, Wijnberg JP, Kramer PC, Reek JN, Van Leeuwen PWNM, Wever R, Schoemaker HE (2001) Tetrahedron: Asymmetry **12**: 1025; d) Matsuda T, Watanabe K, Kamitanaka T, Harada T, Nakamura K (2003) Chem Commun 1198

[17] a) Le Page MD, James BR (2000) Chem Commun 1647; b) Ter Halle R, Bréhéret A, Schulz E, Pinel C, Lemaire M (1997) Tetrahedron: Asymmetry **8**: 2101; c) Evans DA, Nelson SG, Gagné MR, Muci AR (1993) J Am Chem Soc **115**: 9800; d) Kuhl S, Schneider R, Fort Y (2003) Organometallics **22**: 4184
[18] Henning F (2003) Dissertation, University of Regensburg
[19] Brunner H, Henning F, Weber M, Zabel M, Carmona D, Lahoz FJ (2003) Synthesis 1091
[20] a) Louie J, Grubbs RH (2001) Angew Chem **113**: 253, Angew Chem Int Ed **40**: 247; b) Wilkinson G (1987) Comprehensive Coordination Chemistry, vol 5. Pergamon, Oxford, p 583
[21] Hoffmann PR, Caulton KG (1975) J Am Chem Soc **97**: 4221
[22] a) Gao JX, Ikariya T, Noyori R (1996) Organometallics **15**: 1087; b) Gao JX, Xu PP, Yi XD, Yang CB, Zhang H, Cheng SH, Wan HL, Tsai KR, Ikariya T (1999) J Mol Catal A **147**: 105; c) Jiang Y, Jiang Q, Zhang X (1998) J Am Chem Soc **120**: 3817; d) Gamez P, Fache F, Lemaire M (1995) Tetrahedron: Asymmetry **6**: 705; e) Petra DG, Kramer PC, Van Leeuwen PWNM, Goubitz K, Van Loon AM, De Vries JG, Schoemaker HE (1999) Eur J Inorg Chem 2335; f) Frost CG, Mendonça P (2000) Tetrahedron: Asymmetry **11**: 1845; g) Zhou YB, Tang FY, Xu HD, Wu XY, Ma JA, Zhou QL (2002) Tetrahedron: Asymmetry **13**: 469
[23] Evans IP, Spencer A, Wilkinson G (1973) J Chem Soc Dalton Trans 204
[24] Joshi AM, Thorburn IS, Rettig SJ, James BR (1992) Inorg Chim Acta **198**–**200**: 283
[25] a) Bennett MA, Smith AK (1974) J Chem Soc Dalton Trans 233; b) Bennett MA, Huang TN, Matheson TW, Smith AK (1982) Inorg Chem **21**: 74