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Amino Alcohol Coordination in Ruthenium(II)-Catalysed Asymmetric Transfer Hydrogenation of Ketones

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The nature of ruthenium-amino alcohol precursors in the catalytic cycle of asymmetric hydrogen transfer reactions was studied using two C_2-symmetrical tetradentate ligands (**1** and **2**) that were synthesised from (nor)ephedrine. The structure of the catalyst precursor was examined through catalysis and NMR experiments. It was shown that the active catalyst contains one ligand per metal, which coordinates in a didentate N,O fashion (**9**). In addition, a $Ru^{II}Cl_2$ complex, in which *N*,*N*′-bis(2-hydroxy-1-methyl-2-phenylethyl)-1,2-diaminoethane (**1**) coordinates through two nitrogen atoms, was structurally characterised by X-ray diffraction (**8**). – Based on the results of this study a series of new amino alcohol ligands was synthesised from easily available starting materials. Optimisation of the amino alcohol ligand structure resulted in the most effective chiral amino alcohol ligand (**5**) so far that is capable of reducing acetophenone at 0 °C with up to 97% ee in the Ru^{II}-catalysed transfer hydrogenation.

Introduction

Transfer hydrogenation of ketones is a highly efficient method for the synthesis of chiral alcohols, owing to low fractional yields of side products and high product yields in high enantiomeric excess. The reaction conditions are relatively mild and the costs are low as a result of the operational simplicity of this method.

As a consequence, much effort has been devoted to the development of new chiral catalysts tailored to the transfer hydrogenation of prochiral ketones. Recently, rapid progress in this area has been made, mainly due to Noyori's work.[1−5] One of the highest catalyst activities so far was observed in ruthenium(II)-catalysed transfer hydrogenation with simple amino alcohols as ligands. Diamines and chiral phosphorus and nitrogen ligands gave rise to lower reaction rates.[5]

Despite these high activities obtained for Ru^{II} amino alcohol catalysts there are only a few reports on the use of simple amino alcohols as chiral ligands.[3,6,7] Amino alcohols are easily accessible and it would seem worthwhile optimising their performance in terms of activity and enantioselectivity by varying the structure. To this end we started to elucidate the nature of ruthenium amino alcohol catalysts. The chiral shielding around the metal centre is highly dependent on the ligand structure and the number of ligand donor atoms that coordinate to the metal.

From the work of Noyori and co-workers it is clear that for their Ru^{II}-TsDPEN [TsDPEN = *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine] system the active catalyst contains one ligand per metal.[4] However, for weakly coordinating amino alcohol ligands, which give rise to much higher reaction rates in the Ru^{II}-catalysed reduction of ketones using 2-propanol as an H-donor,[5] the ligand to ruthenium ratio has proven to be critical.[6] For these systems the ligand stoichiometry and the mechanism have not been elucidated as yet. In all cases reported so far two equivalents of amino alcohol ligand per ruthenium were used to maintain a high selectivity.

Other mechanistic studies concerning the ligand-to-metal ratio were limited to rhodium catalysts containing didentate nitrogen ligands. Gladiali's pioneering work resulted in a proposed catalytic cycle in which the active complex is a metal hydride complex containing two phenanthroline ligands.[8] In contrast to this, Bernard et al. postulated that the active catalyst is a rhodium complex having only one diamine ligand coordinated to the metal.[9]

In order to gain more insight into the mechanism of hydrogen transfer reactions and especially the influence of the ligand stoichiometry, two potentially tetradentate ligands (**1** and **2**) were synthesised and applied in enantioselective transfer hydrogenation. The preferred mode of coordination (i.e. either two, three or four donating atoms per metal) and the ligand stoichiometry were examined in catalysis. The catalytic results were compared with those of the didentate analogues **3** and **4**. ^{1}H-, ^{13}C-, and ^{15}N-NMR spectroscopy were used to study the catalyst in situ. The molecular structure of a ruthenium(II) catalyst precursor complex containing **1** was determined by X-ray diffraction.

Based on the results of the study towards the preferred mode of coordination of the ligands, a series of new amino alcohol ligands was synthesised to create higher selectivities in the transfer hydrogenation of ketones using ru-

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thenium(II) amino alcohol catalysts. Various substituents in the backbone and on the amine functionality were introduced to determine possible factors that influence the enantioselectivity of the reaction. We were able to develop the most effective chiral amino alcohol ligand to date for Ru^{II}-catalysed hydrogen transfer of acetophenone.

Results and Discussion

In order to elucidate the mode of coordination and the ligand stoichiometry in ruthenium(II) amino alcohol-catalysed transfer hydrogenations, ligands **1** and **2** were used (Figure 1). These ligands are suitable for this study as they can coordinate in a tetradentate manner, using two nitrogen and two oxygen donor atoms, in a tridentate manner or in a didentate manner, using either two nitrogen atoms or a nitrogen and an oxygen donor atom. In addition, these tetradentate ligands can possibly form a deeper chiral concave pocket around the metal centre compared to the corresponding didentate ligands, which might result in higher selectivities. Examples in which this effect was found are catalysts for hydrogen transfer reactions containing the chiral bis(oxazolinyl)pyridine ligand (pybox) and the bis(oxazolinyl)amine ligand (ambox).[10][11]

The synthesis of **1** {*N*,*N*′-bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminoethane} and **2** {*N*,*N*′-bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,3-dimethylaminopropane} is analogous to that described by Soai et al.[12]

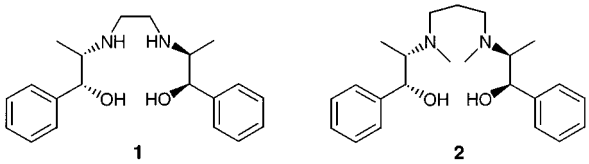


Figure 1. Tetradentate ligands **1** and **2**

The results of the use of catalysts generated in situ from ligands **1** and **2** (Figure 1) and various ruthenium(II) precursors in the reduction of acetophenone (Scheme 1) are depicted in Table 1. In a typical catalysis experiment a solution of ketone (0.1 M in dry 2-propanol), the ruthenium complex ($[RuCl_2(arene)]_2$, 0.5 mol-%), the chiral amino alcohol (1 mol-%) and *t*BuOK (2.5 mol-%) was stirred at room temperature under argon in dry 2-propanol. Conversions and enantioselectivities were monitored during the reaction. At lower conversions (i.e. < 60%) a zero order rate dependency in substrate concentration was found. The enantioselectivity proved to be constant in time for all catalytic reactions described here unless otherwise stated.

The use of **1** in combination with $[RuCl_2(p\text{-cymene})]_2$ and base in propan-2-ol resulted in reduction of acetophenone to (*S*)-phenethyl alcohol in 88% ee at 67% conversion after 44 hours (entry 1, Table 1). Under the same reaction conditions ligand **2** gave rise to 24% conversion and 82% ee after 44 hours (entry 2, Table 1). Both the lower reaction rate and asymmetric induction of **2** can be explained by the fact that at least one primary or secondary amine functionality is essential to obtain high yields and high enantiomeric excess. This has been observed before and Noyori et al. suggested that an NH-moiety in the ligand may promote a cyclic transition state through hydrogen bonding to a ketone substrate.[5]

Table 1. Hydrogen transfer reduction of acetophenone using ligands **1**−**7**[a]

Entry	Ligand	Ru/L	*t*[h]	Conv. [%] of ketone[b]	ee [%] alcohol[c]	Confign.
1	**1**	1/2	44	67	88	(*R*)
2	**2**	1/2	44	24	82	(*R*)
3	**3**	1/2	0.5	95	77	(*R*)
4	**4**	1/2	0.5	91	89	(*R*)
5	**1**	1/1.1	44	80	90	(*R*)
6	**1**	2/1.1	44	93	78	(*R*)
7	**5**	1/2	1	88	95	(*R*)
8[d]	**5**	1/2	4	75	97	(*R*)
9	**6**	1/2	2	64	91	(*R*)
10	**7**	1/2	20	25	20	(*R*)
11	**1**	1[e]/2	44	88	56	(*R*)
12	**1**	1[f]/2	44	2	nd	–
13	complex **8**	1/1	44	78	87	(*R*)

[a] The reaction was carried out at room temperature using a 0.1 M solution (5 mmol) in propan-2-ol. Substrate:$[RuCl_2(p\text{-cymene})]_2$/ligand/*t*BuOK = 200:1:1.1−4:10. − [b] Conversions were determined by GLC analysis. − [c] Determined by capillary GLC analysis using a chiral cycloSil-B column. − [d] The reaction was carried out at 0°C. − [e] Ru = $[RuCl_2(benzene)]_2$. − [f] Ru = $RuCl_2(PPh_3)_3$.

The use of another ruthenium arene complex, the (benzene)ruthenium(II) chloride dimer in combination with amino alcohol **1**, resulted in a large decrease of the enantiomeric excess and in a higher reaction rate (88% conversion and 56% ee, after 44 h; entry 11, Table 1). The increase in reactivity by decreasing steric bulk on the arene has been observed in other systems. As in our case, this is often accompanied by a decrease in enantioselectivity.[3][6] High selectivities have been observed using $RuCl_2(PPh_3)_3$ as a catalyst precursor in combination with tridentate nitrogen ligands.[10][11] This catalyst precursor does not contain an arene moiety and therefore offers additional coordination sites for amino alcohol coordination. Hardly any conversion was observed using this catalyst precursor in combination with ligand **1** (entry 12, Table 1).

In order to study the coordination fashion of ligand **1** during catalysis (i.e. either didentate, tridentate or tetradentate) it was compared to its corresponding didentate analogues (1*R*,2*S*)-(−)-norephedrine (**3**) and (1*R*,2*S*)-(−)-ephedrine (**4**) in the reduction of acetophenone (Figure 4) (see also Takehara et al.).[3] The use of **3** gave rise to a very fast reaction, but a lower selectivity compared to the use of **1** (95% conversion and 77% ee, after 0.5 h; entry 3, Table 1). On using amino alcohol **4**, however, a much higher reaction rate was found compared to the use of **1**, with similar enantioselectivity (91% conversion and 87% ee, after 0.5 h; entry 4, Table 1). These results show that no increase of enantioselectivity is observed on using the tetradentate ligand **1**, which contains additional donor atoms, compared to the use of **4**.

With the aim of resolving the mode of coordination for the tetradentate ligand **1** a series experiments was performed in which the ratio of ligand **1** to ruthenium was varied. When the ligand to ruthenium ratio was changed from two to one half, the initial selectivity of the reaction did not change. However, on using half an equivalent of ligand the enantioselectivity of the reaction dropped to 78% after 44 hours, probably due to catalyst deactivation (entry 6, Table 1). When 1 or 2 equivalents of ligand are in solution the excess of donating atoms of the amino alcohol must stabilise the complex, preventing the formation of black particles of ruthenium. The increasing reaction rate can be explained by the formation of a sterically less hindered bimetallic ruthenium complex containing only one tetradentate ligand that coordinates in a didentate fashion. From these results it is concluded that the active catalyst is most likely a ruthenium complex with one ligand coordinating to the metal in a didentate mode, because catalysis using a ligand stoichiometry of one half results in identical initial enantioselectivities and a higher reaction rate. Thus, half an equivalent of ligand suffices for the control of enantioselectivity, assuming a coordination mode similar to that of ligands **3** and **4** (i.e. coordination through one nitrogen and one oxygen donor atom). The remaining part of the C_2-symmetric molecule merely acts as a large substituent at the nitrogen atom which slows down the reaction and does not further increase the selectivity.

In order to confirm the conclusions we have drawn above, i.e. that ligand **1** prefers a didentate *N,O*-coordination fashion to ruthenium(II), we now describe our attempts to identify two different (1:1) ruthenium−amino alcohol complexes and establish their coordination mode.

When an equimolar mixture of $[\{RuCl_2(\eta^6\text{-}p\text{-cymene})\}_2]$ and **1** was stirred in dichloromethane for one hour at room temperature, the ruthenium(II) complex **8** was isolated and was crystallised from benzene.

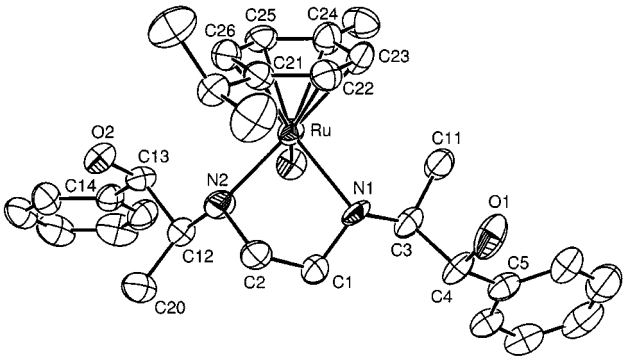


Figure 2. Crystal structure of **8**

The crystals were isolated and characterised by X-ray diffraction. A number of neutral complexes of the type [Ru(arene)Cl(amino−amido ligand)] have been crystallographically characterised.[10] The cationic complex **8** of the type [Ru(arene)Cl(neutral amino−amino ligand)]$^+$ described here contains a neutral amino−amino ligand. The single crystal X-ray analysis indicates that this cationic ruthenium(II) complex has a distorted octahedral coordination environment (see Figure 2). The metal centre is coordinated to two neutral nitrogen atoms, which are involved in a five-membered chelate ring displaying an envelope conformation with C1 and C2. A chloride anion and a *p*-cymene molecule, acting as a neutral six electron donor, complete the coordination sphere of the ruthenium atom. A second chloride anion is present as a noncoordinating counterion. Selected bond lengths and angles are collected in Table 2.

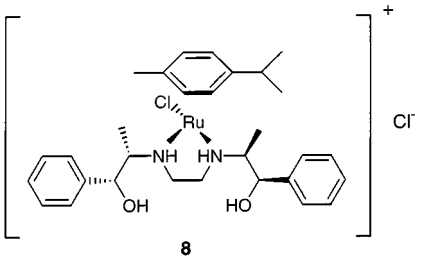
Table 2. Selected bond lengths [Å] and angles [°] for [Ru{*N,N′*-bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminoethane}{*p*-cymene}Cl]Cl (**8**) (with esd′s in parentheses)

Bond lengths			
Ru−N(1)	2.228(8)	C(2)−N(2)	1.50(1)
Ru−N(2)	2.182(8)	C(3)−C(4)	1.58(2)
Ru−Cl	2.387(3)	C(3)−C(11)	1.51(2)
Ru−C(21)	2.20(1)	C(3)−N(1)	1.50(2)
Ru−C(22)	2.19(1)	C(4)−C(5)	1.51(2)
Ru−C(23)	2.20(1)	C(4)−O(1)	1.41(2)
Ru−C(24)	2.25(1)	C(12)−C(13)	1.56(2)
Ru−C(25)	2.19(1)	C(12)−C(20)	1.54(2)
Ru−C(26)	2.18(1)	C(12)−N(2)	1.52(2)
C(1)−C(2)	1.50(2)	C(13)−C(14)	1.50(2)
C(1)−N(1)	1.48(2)	C(13)−O(2)	1.43(1)
Bond angles			
Cl−Ru−N(1)	84.8(2)	Ru−N(1)−C(1)	105.3(7)
Cl−Ru−N(2)	89.7(3)	Ru−N(1)−C(3)	121.4(7)
N(1)−Ru−N(2)	81.6(3)	Ru−N(2)−C(2)	103.1(6)
C(2)−C(1)−N(1)	109(1)	Ru−N(2)−C(12)	122.0(7)
C(1)−C(2)−N(2)	108(1)		

The ruthenium complex **8**, which catalyses the asymmetric transfer hydrogenation of acetophenone in 2-propanol containing *t*BuOK (entry 13, Table 1), is merely a catalyst precursor. Upon addition of base the most acidic protons are eliminated. Due to deprotonation of the OH group, N,O coordination will be preferred to didentate *N,N′* coordination. An unsymmetrical complex with a chiral metal centre is formed.

In order to elucidate the structure of this complex in solution, ^{1}H-NMR and ^{15}N-NMR experiments were performed on the in situ catalyst in CD_3OD. Upon mixing (*p*-cymene)ruthenium(II) chloride dimer and ligand **1**, complex **8** is formed as the major product. All the ^{1}H-NMR signals of the hydrogen atoms near the nitrogen atoms are shifted downfield in comparison to those of the free ligand. The two methyl signals become inequivalent. The NH protons in complex **8** show very slow H, D exchange in CD_3OD; the signal that is visible at $\delta = 6.45$, slowly decreases in size when the compound stands at room temperature in CD_3OD (i.e. to 50% of its original value after 7 days). After two hours at 60°C in CD_3OD the NH signal completely disappears. The ^{15}N-NMR spectrum shows two peaks at $\delta = -357$ and $\delta = -358$, while the free ligand shows a peak at $\delta = -336$. Upon addition of 2 equivalents of base a new complex (**9**) formed (see Figure 3). This complex showed two peaks in the ^{15}N-NMR spectrum at $\delta = -355$ and at $\delta = -343$. The ^{15}N-NMR spectrum did not change upon stepwise cooling to −40°C. In the ^{1}H-NMR spectrum, broadened signals were observed, which suggests fluxional behaviour. Under these basic conditions no NH

protons were observed for this compound in CD_3OD. It is concluded that in complex **9** one nitrogen atom coordinates to the ruthenium atom as in complex **8**; the chemical shift that is found at $\delta = -355$ is typical for a coordinated nitrogen atom.[13] The chemical shift of the second nitrogen atom is characteristic of a noncoordinated amine moiety; the position of the ^{15}N signal at $\delta = -343$ is comparable to the nitrogen resonance of $\delta = -336$ for the free ligand.[14] The presence of the hydride in **9** was proven by ^1H-NMR measurements in deuterated benzene, which showed a hydride signal at $\delta = -5.50$. In addition, the molecular formula of **9** was confirmed by electrospray mass spectrometry, which showed a signal for M^+ at 564.230 (calcd. 564.228).



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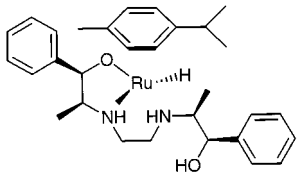

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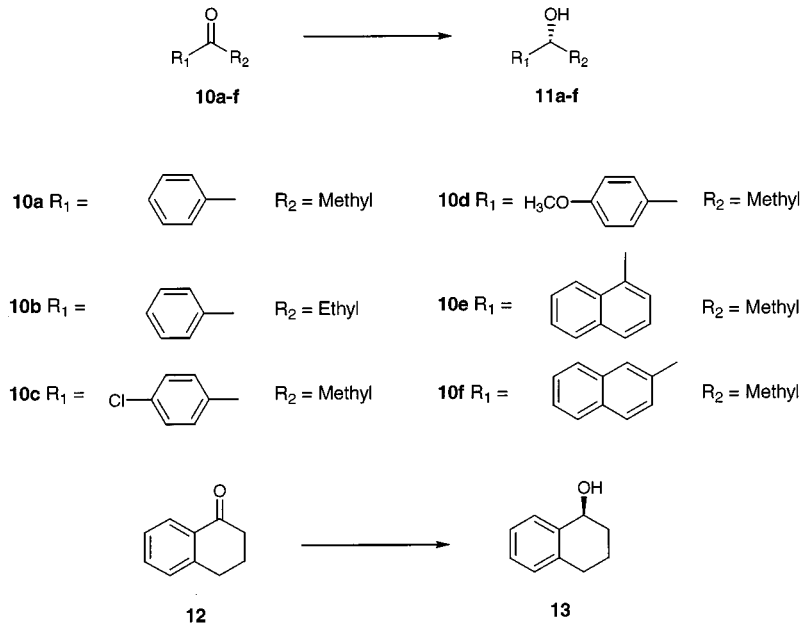
Figure 3. Ruthenium amino alcohol complexes **8** and **9**

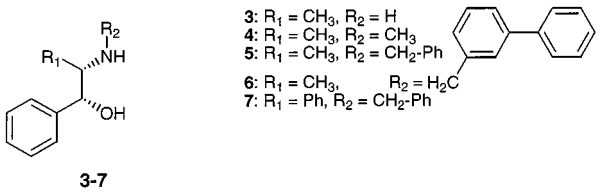
Since it now seems clear that a didentate coordination of amino alcohol ligands is preferred to either tridentate or tetradentate coordination, the design of new amino alcohols as ligands to create high selectivities should be directed towards didentate ligands. From Table 1 it can be seen that the selectivity of the reaction is influenced by the substitution pattern on the nitrogen (cf. **1**, **3**, and **4**). It is shown that the secondary amine gives rise to better selectivities than the corresponding primary amine or tertiary amine without decrease of reaction rate. In contrast, Palmer et al. reported that the substitution of the primary amine functionality with a methyl group resulted in a decrease of both the reaction rate and the enantioselectivity, when (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol was used as a ligand.[6]

In order to optimise the amino alcohol ligand structure both the substituents in the backbone and the substituents on the nitrogen atom were varied. Amino alcohols **5**, **6**, and **7** were synthesised in one step by reacting either (1*R*,2*S*)-(−)-2-aminodiphenyl ethanol or (1*R*,2*S*)-(−)-norephedrine with benzyl bromide and/or 3-phenylbenzyl bromide, respectively, under slightly basic conditions (see Figure 4). The effect of a bulky substituent on the nitrogen atom was assessed by using amino alcohols **5** and **6** as ligands in catalysis (Figure 4). The use of **5** in combination with $[\{RuCl_2(p\text{-cymene})\}]_2$ under the standard conditions gave an excellent result (95% ee at 88% conversion after 1 h; entry 7, Table 1). The selectivity could be further improved by lowering the reaction temperature to 0°C. The beneficial temperature effect resulted in the highest enantioselectivity observed so far in the Ru^{II} amino alcohol-catalysed reduction of acetophenone, i.e. 97% (entry 8, Table 1). A longer reaction time was required to reach high conversion. Changing the substituent from a benzyl to a 3-phenylbenzyl group did not improve the results any further. Both the conversion and the enantioselectivity decreased (91% ee at 64% conversion after 2 hours; entry 9, Table 1). Ligand **7** was synthesised to investigate the effect of an additional bulky



Scheme 1. Asymmetric transfer hydrogenation of ketones **10a**−**12**

substituent in the carbon backbone. Changing the substituent at the 1-position from a methyl to a phenyl group did not result in higher enantioselectivities (entry 10, Table 1). The phenyl substituent is clearly too bulky because the conversion dropped drastically.



3-7

Figure 4. Amino alcohol ligands **3**−**7**

A variety of other substrates could also be transformed to the corresponding secondary alcohols with high enantiomeric purity, using ligand **5** under optimised conditions (Table 3, Scheme 1). Changing the electronic and steric properties of the substrate did not clearly affect the enantioselective outcome of the reaction. In these catalytic experiments only one equivalent of ligand was required to obtain high enantioselectivities.

Table 3. Hydrogen transfer reduction of ketones **10a**−**12** using ligand **5**[a]

Entry	Ketone	*t*[h]	Conv. [%] of ketone[b]	ee [%] alcohol[c]	Confign.
1	**10a**	2	91	95[d]	(*R*)
2	**10b**	2	98	90	(*R*)
3	**10c**	2	96	86[d]	(*R*)
4	**10d**	3	68	93	(*R*)
5	**10e**	2	96	96	(*R*)
6	**10f**	2	94	93	(*R*)
9	**12**	2	68	96	(*R*)

[a] The reaction was carried out at room temperature using a 0.1 M solution (5 mmol) in propan-2-ol. Substrate/$[RuCl_2(p\text{-cymene})]_2$/ligand/*t*BuOK = 400:1:2.2:6. − [b] Conversions were determined by GLC and/or 300 MHz ^{1}H-NMR analysis. − [c] Determined using chiral HPLC with a Chiracel OD column unless otherwise specified. − [d] Determined by capillary GLC analysis using a chiral cycloSil-B column.

Conclusion

In the ruthenium-catalysed transfer hydrogenation of prochiral ketones using tetradentate ligand **1** the amino alcohol prefers a didentate coordination fashion, as was shown by catalysis experiments (see Table 1) and NMR experiments. The extra donor atoms in the ligand do not enhance the selectivity of the reaction but only give rise to lower reaction rates. In contrast to results in other reports, a ligand-to-metal ratio of one is sufficient to maintain selectivity.

The best amino alcohol ligand structure turned out to be NH-benzyl-(1*R*,2*S*)-(−)-norephedrine (**5**), which proved to be an excellent ligand for the control of asymmetric ruthenium-catalysed transfer hydrogenation of prochiral ketones.

Experimental Section

General Remarks: Reactions were performed under an atmosphere of argon in flame-dried Schlenk flasks and using anhydrous solvents. Propan-2-ol was freshly distilled from CaH_2 prior to use. − Column chromatography was performed with silica gel 60, 70−230 mesh ASTM (Merck). Thin layer chromatography was carried out on TLC aluminium foil, silica gel 60 G/UV_{254} and spots were detected with UV light or iodine vapour. − Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. − Optical rotations were measured on a Perkin−Elmer 241 automatic polarimeter. − IR spectra were recorded on a BioRad FT-IR (FTS-7) spectrophotometer. − ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AMX 300 spectrometer. Chemical shifts are on the δ scale (ppm) relative to TMS as internal standard. ^{15}N-NMR spectra were recorded on a Bruker DRX 300 instrument. Chemical shifts are relative to nitromethane as external standard. − Mass spectra were recorded on a JEOL JMS SX/SX102A four sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. − Microanalyses (C, H, N) were performed on an Elementar Vario EL apparatus (Foss Electric). − Gas chromatography was performed using a Carlo Erba GC 6000 Vega 2 instrument, 25 m column: CycloSil-B (chiral) and a Carlo Erba HRGC Mega 2 instrument, 25 m column: BPX 35 (SGE) (achiral). HPLC chromatography was performed using a Gilson HPLC apparatus and a Chiracel OD column.

***N*,*N*′-Bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminoethane (1):** Compound **1** was synthesised in analogy with the procedure of Soai et al.[12] 1,2-Dibromoethane (3.1 g, 16.5 mmol) was added to (1*R*,2*S*)-(−)-norephedrine (5.0 g, 33 mmol) and finely powdered Na_2CO_3 (7.0 g, 66 mmol) in ethanol (25 mL). The mixture was heated at reflux for 20 h. The salts that formed were filtered off and the solvent was evaporated in vacuo. The product was extracted with dichloromethane, the organic phases were dried with Na_2SO_4 and evaporated to dryness. After dissolving the residue in a minimal amount of ethanol and addition of HCl, a white precipitate formed, which was collected by filtration and recrystallised from water (40 mL) with a few drops of HCl. The HCl salt was dissolved in water and 0.1 M NaOH was added until pH = 12 was reached. The mixture was extracted three times with diethyl ether. The organic layers were combined and evaporated to dryness. Yield: 4.4 g (81%). M.p.: 108−110°C (free amine). − IR (neat): $\tilde{\nu}$ = 3387 cm^{-1}, 2976, 2927, 1452. − ^{1}H NMR (CD_3OD): δ = 0.94 (d, 6 H, *J* = 6.4 Hz, CH_3), 2.62 (m, 2 H, C*H*NH), 2.75 (m, 4 H, CH_2), 4.61 (d, 2 H, *J* = 4.8 Hz, C*H*OH), 7.21−7.34 (m, 10 H, C_6H_5). − ^{13}C NMR (CD_3OD): δ = 14.92 (*C*H$_3$), 59.85 (*C*HNH), 47.25 (*C*H$_2$), 76.17 (*C*HOH), 127.55 [*C*H$_{arom}$ (*o*)], 128.32 [CH$_{arom}$ (*p*)], 129.26 [*C*H$_{arom}$ (*m*)], 144.07 (*C*$_q$). − ^{1}H{^{15}N} NMR (CD_3OD): δ = −336. − HRMS (FAB$^+$): *m*/*z* calcd. for $C_{20}H_{29}N_2O_2$ [M + H]$^+$: 329.2229; found 329.2227. − $C_{20}H_{28}N_2O_2$ (328.458): calcd. C 73.14, H 8.59, N 8.53; found C 73.12, H 8.56, N 7.96. − $[\alpha]_D^{20}$ = +9.6 (*c* = 0.8, EtOH).

***N*,*N*′-Bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,3-dimethylaminopropane (2):** Compound **2** was prepared from (1*R*,2*S*)-(−)-ephedrine according to a literature procedure[12] and in an analogous way to **1**. Yield: 2.6 g (78%). IR (neat, HCl salt): $\tilde{\nu}$ = 3407 cm^{-1}, 2978, 2940, 2800, 1451, 754, 700. − ^{1}H NMR (CD_3OD): δ = 0.88 (d, 6 H, *J* = 6.8 Hz, CH_3), 1.69 (dt, 2 H, *J* = 6.7 Hz, *J* = 6.8 Hz, CH_2), 2.31 (s, 6 H, NCH_3), 2.41, 2.63 (each dt, 4 H, *J* = 6.4 Hz, *J* = 6.4 Hz, CH_2), 2.77 (dq, 2 H, *J* = 3.1 Hz, *J* = 6.8 Hz, C*H*N), 4.95 (d, 2 H, *J* = 3.6 Hz, C*H*OH), 7.20−7.32 (m, 10 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 8.08 (*C*H$_3$), 23.59 (N*C*H$_3$), 38.65 (*C*HNH), 52.05, 64.81 (*C*H$_2$), 73.15 (*C*HOH), 126.07 [*C*H$_{arom}$ (*o*)],

127.02 [CH_{arom} (*p*)], 128.07 [CH_{arom} (*m*)], 142.38 (C_q). − HRMS (FAB$^+$): *m*/*z* calcd. for $C_{23}H_{35}N_2O_2$ [M + H]$^+$: 371.2698; found 371.2699. − $C_{23}H_{37}Cl_3N_2O_2$ (479.923): calcd. C 57.56, H 7.77, N 5.84; found C 57.52, H 8.04, N 5.78. − $[\alpha]_D^{20}$ (HCl salt) = +5 (*c* = 0.6, EtOH).

NH-Benzyl-(1*R*,2*S*)-norephedrine (5): K_2CO_3 (234 mg, 1.70 mmol) was added to (1*R*,2*S*)-(−)-norephedrine (250 mg, 1.65 mmol) in acetonitrile at room temperature. At 0°C, benzyl bromide (171 mL, 1.65 mmol) was added and the resulting mixture was stirred for 16 h at 60°C. The reaction mixture was filtered through Celite and the filtrate evaporated to dryness. The crude compound was purified by column chromatography (silica gel 60, eluent: ethyl acetate, R_f value: 0.33). Yield: 200 mg (50%), colourless oil. − IR (neat): $\tilde{\nu}$ = 3334 cm^{-1}, 3062, 3028, 2973, 2871, 1603, 1494, 1452, 744, 700. − ^{1}H NMR ($CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.6 Hz, C*H*$_3$), 2.48 (s, 1 H, O*H*), 3.02 (dq, 1 H, *J* = 3.8 Hz, *J* = 6.6 Hz, C*H*NH), 3.90 (s, 2 H, CH_2), 4.82 (d, 1 H, *J* = 3.8 Hz, C*H*OH), 7.33 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 14.81 (*C*H$_3$), 51.44 (*C*H$_2$), 58.01, 73.57 (2 *C*H), 126.39, 127.27, 127.36, 128.31, 128.76 (10 CH_{arom}), 140.33, 141.77 (2 C_q). − HRMS (FAB$^+$): *m*/*z* calcd. for $C_{16}H_{20}NO$ [M + H]$^+$: 242.1545; found 242.1545. − $C_{16}H_{19}NO{\cdot}0.5H_2O$ (250.344): calcd. C 76.77, H 8.05, N 5.59; found C 76.80, H 7.94, N 5.58. − $[\alpha]_D^{20}$ = +16 (*c* = 0.70, EtOH).

NH-3-Phenylbenzyl-(1*R*,2*S*)-norephedrine (6): This compound was synthesised analogously to **5**. The crude compound was purified by column chromatography (silica gel 60, eluent: ethyl acetate, R_f value: 0.29). Yield: 620 mg (61%), yellow oil. − IR (neat): $\tilde{\nu}$ = 3397 cm^{-1}, 3059, 3031, 2974, 2872, 1601, 1480, 1453, 757, 738, 701. − ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, 3 H, *J* = 5.5 Hz, C*H*$_3$), 2.53 (s, 2 H, N*H*, O*H*), 3.05 (dq, 1 H, *J* = 3.9 Hz, *J* = 5.5 Hz, C*H*NH), 3.96 (s, 2 H, CH_2), 4.84 (d, 1 H, *J* = 3.9 Hz, C*H*OH), 7.33−7.69 (m, 9 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 14.48 (*C*H$_3$), 51.12 (*C*H$_2$), 57.71, 73.24 (2 *C*H), 125.85, 126.01, 126.76, 126.86, 126.93, 127.02, 127.21, 127.95, 128.68, 128.82 (*C*H_{arom}), 140.43, 140.87, 141.31, 141.35 (4 C_q). − HRMS (FAB$^+$): *m*/*z* calcd. for $C_{22}H_{24}NO$ [M + 1]$^+$: 318.1858; found 318.1850. − $[\alpha]_D^{20}$ = −17 (*c* = 1.75, $CHCl_3$).

(1*R*,2*S*)-2-(Benzylamino)-1,2-diphenylethanol (7): This compound was synthesised analogously to **5**. The crude compound was purified by crystallisation from ethyl acetate/hexane. Yield: 760 mg (59%), white solid. M.p.: 154−155°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 3020 cm^{-1}, 2977, 1524, 1424, 1453, 734, 670. − ^{1}H NMR ($CDCl_3$): δ = 3.13 (s, 2 H, N*H*, O*H*), 3.60 (d, 1 H, *J* = 13.4 Hz CH_2), 3.82 (d, 1 H, *J* = 13.4 Hz CH_2), 3.97 (d, 1 H, *J* = 5.3 Hz, C*H*OH), 5.03 (d, 1 H, *J* = 5.3 Hz, C*H*NH), 7.11−7.38 (m, 15 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 50.57 (*C*H$_2$), 67.57, 75.76 (2 *C*H), 126.56, 127.26, 127.48, 127.73, 127.80, 128.08, 128.30, 128.44 (*C*H_{arom}), 137.14, 137.95, 139.96 (3 C_q). − HRMS (FAB$^+$): *m*/*z* calcd. for $C_{21}H_{22}NO$ [M + 1]$^+$: 304.1701; found 304.1696. − $C_{21}H_{21}NO$ (303.408): calcd. C 83.13, H 6.98, N 4.62; found C 82.10, H 7.01, N 4.39. − $[\alpha]_D^{20}$ = −229 (*c* = 1.00, $CHCl_3$).

[Ru{*N*,*N*′-bis[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminoethane}{*p*-cymene}Cl]Cl (8): Complex **8** was prepared in analogy with a literature procedure.[15] To a solution of [{$RuCl_2(\eta^6$-*p*-cymene)}$_2$] (100 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added *N*,*N*′-bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminoethane (**1**) (108 mg, 0.33 mmol). After stirring the reaction mixture for 1 h at room temperature the solvent was removed in vacuo. The orange solid was washed twice with diethyl ether (10 mL) and dried in vacuo. Recrystallisation from chloroform/pentane afforded yellow needle-shaped crystals. − IR (neat): $\tilde{\nu}$ = 3287 cm^{-1}, 2959, 2927, 2855, 1452, 1216, 758. − ^{1}H NMR (CD_3OD): δ = 0.90 (d, 3 H, *J* = 6.6 Hz, C*H*$_3$), 1.06 (d, 3 H, *J* = 6.8 Hz, C*H*$_3$), 1.24, 1.25 [each d, 6 H, *J* = 6.9 Hz, CH(C*H*$_3$)$_2$], 2.02 (s, 3 H, C*H*$_3$ in *p*-cymene), 2.48 [m, 1 H, C*H*(CH$_3$)$_2$], 2.79 (m, 4 H, CH_2), 5.17 (d, 2 H, *J* = 2.5 Hz, C*H*), 5.41 (broad s, 2 H, C*H*), 5.56, 5.65, 5.75, 5.77 (each d, 4 H, *J* = 5.9 Hz, CH_{arom} in *p*-cymene), 6.45 (broad s, 2 H, N*H*), 7.13−7.46 (m, 10 H, C_6H_5). − ^{13}C NMR (CD_3OD): δ = 12.55, 18.61, 20.09, 25.11, 25.61 (5 *C*H$_3$), 53.57 (*C*H$_2$), 34.68, 60.83, 64.00, 72.96, 77.90 (5 *C*H), 118.34 (C_q), 129.26, 129.56, 129.60, 129.90, 130.74, 130.87 (8 *C*H_{arom}), 131.81, 132.00 (2 C_q). − ^{15}N{^{1}H} NMR (CD_3OD): δ = −357, −358. − HRMS (FAB$^+$): *m*/*z* calcd. for $C_{30}H_{42}ClN_2O_2Ru$ [M$^+$]: 599.1972; found 599.1979. − $C_{30}H_{43}Cl_3N_2O_2$ (570.048): calcd. C 53.69, H 6.46, N 4.17; found C 53.07, H 6.80, N 3.71.

Enantioselective Reduction of Ketones (General Procedure for [ketone]/[Ru] = 200): A solution of (*p*-cymene)ruthenium(II) chloride dimer (7.7 mg, 0.0125 mmol) and the amino alcohol as a ligand (0.030 mmol) in dry propan-2-ol (5 mL) was heated at 80°C for 1 h under argon. After cooling the mixture to room temperature, it was diluted with propan-2-ol (43.75 mL) and *t*BuOK (1.25 mL, 0.1M in propan-2-ol, 0.125 mmol) was added. The resulting solution was stirred for 30 min before the ketone (5 mmol) was added. The reaction was performed at room temperature under argon for the time indicated and monitored by GC and/or HPLC.

X-ray Structure Analysis of 8: A crystal with the approximate dimensions 0.05 × 0.08 × 0.80 mm was used for data collection on an Enraf−Nonius CAD-4 diffractometer with graphite-monochromated Cu-K_α radiation and ω-2θ scan. A total of 3449 unique reflections was measured within the range −13 < *h* < 12, 0 < *k* < 33, 0 < *l* < 17. Of these, 2964 were above significance level of 5σ(*F*) and were treated as observed. The range of (sinθ)/λ was 0.032−0.625 Å (2.9 < θ < 74.6°). Two reference reflections ([1 2 0], [0 0 10]) were measured hourly and showed no decrease during the 76 h collecting time. Unit-cell parameters were refined by a least square fitting

Table 4. Selected crystallographic data of [Ru{*N*,*N*′-bis[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminoethane}{*p*-cymene}Cl]Cl (**8**)

Crystal Data		Data Collection	
Formula	$[C_{30}H_{42}N_2O_2ClRu]^+$ Cl^-	Crystal size [mm]	0.050 × 0.08 × 0.80
M_r	1205.6	Temperature [°C]	−35
Crystal system	orthorhombic	Scan mode	ω−2θ
Space group	$P2_12_12_1$	θ_{min}, θ_{max} [°]	2.9, 74.6
a [Å]	9.378(1)	λ(Cu-K_α) [Å]	1.5418
b [Å]	10.233(5)	Total unique data	3449
c [Å]	30.91(2)	Observed data	2964
Z	4	Structure refinement	
V [Å^3]	2966(2)	Parameter/F_o	0.168
F(000) [e]	1320	*R*	0.057
D_x [g cm^{-3}]	1.42	R_w	0.063
μ(Cu-K_α) [cm^{-1}]	61.6	$(\Delta/\sigma)_{max}$	0.30

procedure using 23 reflections with $80 < 2\theta < 84$. Corrections for Lorentz and polarisation effects were applied. Absorption correction was performed with the program PLATON,[16] following the method of North et al. using Ψ-scans of three reflections, with coefficients in the range of 0.484−0.989.[17] The structure was solved by the PATTY option of the DIRDIF96 program system.[18] After isotopic refinement a ΔF synthesis revealed one peak, which was interpreted as a chloride ion. The hydrogen atoms were calculated. The hydrogen atoms on the alcohol and amine groups were located by Fourier synthesis. Full matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.0 Å, converged to $R = 0.057$, $R_w = 0.063$, $(\Delta/\sigma)\text{max} = 0.30$, $S = 0.93$. A weighting scheme $w = \{10 + 0.01 \times [\sigma(F\text{obs})]^2 + 0.0001/[\sigma(F\text{obs})]\}^{-1}$ was used. The secondary isotropic extinction coefficient refined to Ext = 0.015(6).[19][20] The absolute structure was determined by refining the inverse structure, which converged to $R = 0.068$, $R_w = 0.073$, thus confirming the correct enantiomer. A final difference Fourier map revealed a residual electron density between −1.7 and 1.9 eÅ^{-3} in the vicinity of the heavy atoms. Scattering factors were taken from Cromer and Mann; *International Tables for X-ray Crystallography*.[21] The anomalous scattering of Ru and Cl was taken into account.[22] All calculations were performed with XTAL, unless otherwise stated.[23]

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