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Evaluation of Ligands for Ketone Reduction by Asymmetric Hydride Transfer in Water by Multi-Substrate Screening

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Abstract: Various ligands for the ruthenium-catalyzed enantioselective reduction of ketones in water have been investigated. Multi-substrate reactions have been carried out for the comparison of various proline amides and aminoalcohol ligands. Two sets of six aromatic ketones have been selected in order to evaluate the enantiomeric excesses of all the resulting alcohols by a single chromatographic analysis. The proline amide derivative prepared from (1*R*,2*S*)-*cis*-aminoindanol revealed as the best ligand for most of the ketones used in the multi-substrate reductions. This ligand has been employed for the enantioselective reduction of a variety of other aromatic ketones and in all cases the enantiomeric excesses were improved compared to those obtained with phenylprolineamide used in our previous work.

Keywords: asymmetric catalysis; hydride transfer; multi-substrate screening; reduction; ruthenium

Introduction

Nowadays a major concern for chemists is the design of new, low-cost and highly sustainable methodologies following green chemistry principles which require atom economy, use of environmental friendly methods, safe reagents and solvents, recyclability of catalysts and easy separation of reaction products.[1] The use of water as solvent allows one to fulfill most of these requirements and catalysis in water represents a major area.[2] Asymmetric transfer hydrogenation offers many advantages for the easy preparation of enantiomerically enriched alcohols avoiding the use of hydrogen gas under high pressures and has been the subject of numerous studies.[3] Ruthenium associated to the chiral ligand, mono-*N*-tosylated diphenylethylenediamine (Ts-DPEN) as described by Noyori et al., is a highly efficient and attractive catalyst,[3a,b] although other systems based on metals such as rhodium, iridium or lanthanides have been reported.[4,5] The development of asymmetric transfer hydride catalysts in water is also challenging and has been developed in the last years.[6] The first system described by Chung involves ruthenium catalysts coordinated by amides derived from (*S*)-proline.[7] Ruthenium, rhodium and iridium catalysts coordinated by sulfonated analogues of Noyori's ligand are also efficient for the enantioselective reduction of ketones in water.[8] Amino alcohols and their ammonium salts have been recently employed as ligands for ruthenium for the enantioselective reduction of ketones in water.[9] Previously, we have studied the enantioselective reduction of aromatic ketones with a catalyst prepared by addition of *N*-phenyl-L-proline amide ligand **1a** to $[RuCl_2(p\text{-cymene})]_2$ in water.[10] We found that this catalyst can be easily reused. In a multi-substrate recycling it afforded successively seven alcohols with similar enantiomeric excesses as the one recorded in a single run. However, high enantiomeric excesses have been found only for *ortho*-substituted acetophenones.

We now report the use of a multi-substrate screening method for evaluating ligands for ruthenium-catalyzed asymmetric hydrogen transfer in water. We have investigated various proline amides and amino alcohols and selected an L-proline amide ligand affording higher asymmetric inductions than those obtained with *N*-phenyl-L-proline amide for aromatic ketones with various structures.

Results and Discussion

In 1998 Kagan reported a new method for the rapid screening of enantioselective catalysts, which consisted of the evaluation of the catalysts on several sub-

strates in a one-pot procedure that was studied for the reduction of ketones.[11] Some applications of this methodology for enantioselective catalysis of various reactions such as the addition of diethylzinc on aldehydes, cycloalkenones or nitroalkenes, hydroformylation of olefins or hetero-Diels–Alder reactions were later described and summarized in a review.[12] The enantioselective reduction of ketones by hydride transfer in water is well-adapted to multi-substrate screening. Reactions are performed in water and after total conversion the catalyst remains in water while alcohols are extracted by hexane. This allows one to measure the enantiomeric excesses directly on the crude products. The one-pot multi-substrate screening was first studied for the enantioselective reduction of ketones by an oxazaborolidine and the enantiomeric excesses of the mixtures of alcohols have been measured by HPLC.[11] In some cases the separation of the reaction mixtures in several fractions was necessary to perform the analyses. Thus we decided to use chiral GC as an appropriate analytical tool for multi-substrate asymmetric hydride transfer. We had previously studied the reduction of a variety of aromatic ketones using a catalyst obtained by addition of *N*-phenyl-L-proline amide ligand **1a** to $[RuCl_2(p\text{-cymene})]_2$ in water under nitrogen. Amongst these different substrates we selected five ketones (acetophenone **4a**, *o*-methylacetophenone **4b**, *o*-methoxyacetophenone **4c**, *o*-chloroacetophenone **4d**, 2-chloroacetophenone **4e**) leading to five pairs of enantiomeric alcohols which could be separated by chiral gas chromatography on a Chiraldex column in a single analysis without overlap of the peaks. With the aim to test a mixture of ketones with different structures we checked whether enantiomeric excess of the alcohol **5f** obtained by the reduction of 2-acetonaphthone **4f** could be determined in the same analysis as the five alcohols indicated above. The chromatogram of an equimolecular mixture of the six alcohols is represented in Figure 1.

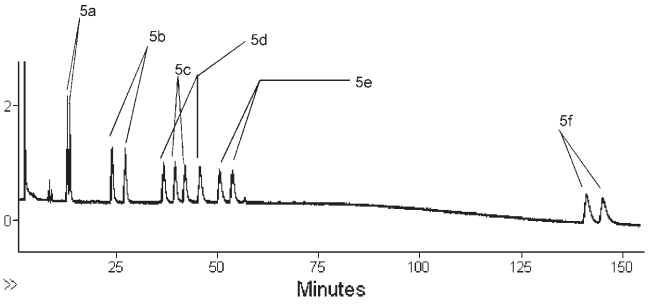


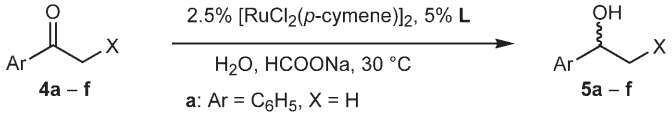
Figure 1. Analysis of the mixture of enantiomers of alcohols **5a–f** by chiral GC [Chiraldex β-PM column (50 m × 0.25 mm), hydrogen as carrier gas (1.0 mL min^{-1}); oven temperature: 130 °C during 65 min, heated to 150 °C (10 °C min^{-1}) and maintained at 150 °C during 100 min].

Before studying the multi-substrate reduction of the ketones, we examined the reduction of 2-acetonaphthone **4f** catalyzed by $[RuCl_2(p\text{-cymene})]_2$ coordinated by *N*-phenyl-L-proline amide **1a** and obtained alcohol **5f** with 55% enantiomeric excess after a 5 h reaction time. The reduction of the mixture of the six ketones **4a–4f** in water using 5 mol% $[RuCl_2(p\text{-cymene})]_2$ and *N*-phenyl-L-proline amide **1a** (ratio ruthenium/total amount of ketones) was performed. We thus checked that under these conditions there was no decrease of the enantiomeric excesses compared to those observed with each single ketone.[10] The results are collected in Table 1 (entry 1). Surprisingly we observed a small increase in the asymmetric inductions when the mixture of ketones was reduced.

To improve the enantiomeric excesses of the alcohols obtained by hydride transfer catalyzed by ruthenium in water we investigated a variety of proline amides and amino alcohols as easily available ligands which are represented in Figure 2. The influence of the amide group in the proline amide ligand was first examined and especially the role of an electron-attracting group, a chelating group or the bulkiness of the arylamine. The use of ligand **1b** containing a *para*-trifluoromethylphenylamino group resulted in a slight decrease of the enantiomeric excesses of the three alcohols **5b**, **5c**, **5d** resulting from *ortho*-substituted acetophenones and a more important decrease for the other alcohols compared to that observed with the *N*-phenyl-L-proline amide **1a** (Table 1, entries 1 and 2). A very similar effect was observed using ligand **1c** in which the phenyl group is replaced by the more bulky 1-naphthyl group (entries 1 and 3). The *N*-2-pyridyl-L-proline amide ligand **1d** yielded similar or higher enantiomeric excesses than **1b** or **1c** (entry 4), but still lower than *N*-phenyl-L-proline amide **1a**. These first results indicated that chelation could have a better influence than steric or electronic factors on the asymmetric inductions.

Amino alcohols which are efficient ligands for enantioselective reduction of ketones by hydride transfer have been next evaluated.[13] We selected (1*S*,2*R*)-ephedrine and (1*R*,2*S*)-*cis*-aminoindanol which have been already employed to perform asymmetric hydride transfer to compare with the proline amide ligands. (1*S*,2*R*)-Ephedrine **2a** was first examined and afforded the alcohols with an increased reaction time and low enantiomeric excesses for the three alcohols **5b**, **5c**, **5d** resulting from *ortho*-substituted acetophenone reduction. Yet for alcohols **5a**, **5e** and **5f** the enantiomeric excesses were very close to those given by *N*-phenyl-L-proline amide **1a** (entry 5). The use the ammonium salt of ephedrine **2b** as ligand allowed us to reduce the reaction time compared to **2a**, but improved only slightly the enantiomeric excesses of alcohols **5a**, **5e** and **5f** (entries 5 and 6). This effect has been already noticed for the reduction of several

Table 1. One-pot enantioselective reduction of ketones **4a–4f** catalyzed by $[RuCl_2(p\text{-cymene})]_2$ coordinated by various ligands in water.



a: Ar = C_6H_5, X = H
b: Ar = *o*-MeC_6H_4, X = H
c: Ar = *o*-$OMeC_6H_4$, X = H
d: Ar = *o*-ClC_6H_4, X = H
e: Ar = C_6H_5, X = Cl
f: Ar = 2'-$C_{10}H_7$, X = H

Entry	Ligand **L**	*t* [h]	*ee* Products [%][a,b]					
			5a	**5b**	**5c**	**5**d	**5e**	**5f**
1	**1a**	12	63 (*R*)	>99[c] (*R*)	>99[c] (*R*)	>99[c] (*R*)	65 (*S*)	68 (*R*)
2	**1b**	18	44 (*R*)	87 (*R*)	94 (*R*)	90 (*R*)	52 (*S*)	51 (*R*)
3	**1c**	18	48 (*R*)	86 (*R*)	90 (*R*)	88 (*R*)	37 (*S*)	54 (*R*)
4	**1d**	24	58 (*R*)	93 (*R*)	87 (*R*)	90 (*R*)	51 (*S*)	73 (*R*)
5	(1*S*,2*R*)-**2a**	72	67 (*S*)	43 (*S*)	31 (*S*)	26 (*S*)	68 (*R*)	67 (*S*)
6	(1*S*,2*R*)-**2b**	48	73 (*S*)	40 (*S*)	34 (*S*)	20 (*S*)	74 (*R*)	78.5 (*S*)
7	(1*R*,2*S*)-**2c**	24	74 (*S*)	66.5 (*S*)	55 (*S*)	63.5 (*S*)	69 (*R*)	74.5 (*S*)
8	**3a**	40	84 (*R*)	97 (*R*)	92.5(*R*)	95.5 (*R*)	83 (*S*)	97 (*R*)

[a] Reactions were performed with 2.5% $[RuCl_2(p\text{-cymene})]_2$ and 5% ligand **1** in water at 30 °C, for total conversion.
[b] Absolute configuration of the major enantiomer was assigned by comparison with our precedent results and experiments performed with single substrates.
[c] Only one peak was observed in GC analysis.

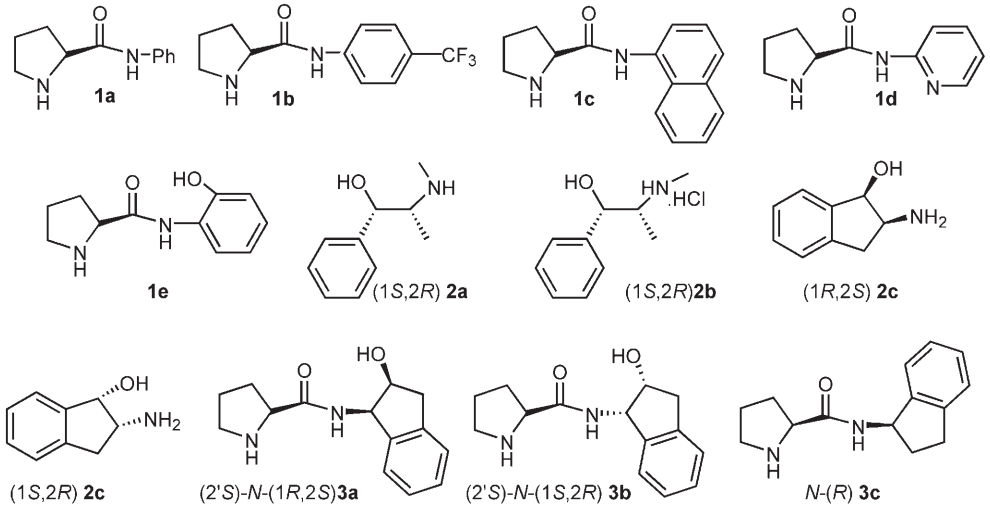


Figure 2. Ligands **L*** tested in enantioselective ruthenium-catalyzed multi-substrate reduction of ketones.

aromatic ketones.[9b] With (1*R*,2*S*)-*cis*-aminoindanol **2c** the reaction time is shorter than with amino alcohol **2a** and the asymmetric induction higher for the reduction of all the ketones except **4e** (entries 5 and 7). Comparison of ligands **2c** and **1a** shows that enantiomeric excesses of alcohols **5a**, **5e** and **5f** are increased with the former. The configurations of all alcohols **5a–f** obtained by reduction with (1*R*,2*S*)-*cis*-aminoindanol **2c** are opposite to the configurations of alcohols formed in reactions involving *N*-phenyl-L-proline amide **1a**.

Peptide ligands have been developed by Adolfsson as efficient ligands for asymmetric hydride transfer reactions and we planned to study a ligand combining the chirality of L-proline and that of (1*R*,2*S*)-*cis*-aminoindanol.[14] Thus the proline amide **3a** already prepared by Najera for enantioselective organocatalysis of nitro-Michael reactions has been tested for the

one-pot reduction of mixture of ketones.[15] The reaction time was longer than with *N*-phenyl-l-proline amide **1a** or (1*R*,2*S*)-*cis*-aminoindanol **2c**. To our delight, the enantiomeric excesses of the three alcohols **5a**, **5e** and **5f** were highly increased compared to all other ligands while those of alcohols **5b**, **5c**, **5d** resulting from *ortho*-substituted acetophenones remained close to that obtained with ligand **1a** (entry 8). The configurations of all alcohols are the same than the ones displayed by *N*-phenyl-L-proline amide **1a**. Thus the proline amide **3a** prepared from (1*R*,2*S*)-aminoindanol was found to be the best ligand for the reduction of acetophenone (84% *ee*), 2-chloroacetophenone (83% *ee*) and 2-acetonaphtone (97% *ee*) while enantiomeric excesses over 90% were recorded for *ortho*-substituted acetophenones.

The results of the multi-ketone reduction by the different ligands gathered in Table 1 indicate that the *ortho*-substituted acetophenones **4b**, **4c** and **4d** are reduced with similar asymmetric inductions whatever ligand is employed. With the aim to obtain a better evaluation of the ligands we decided to use a different set of ketones including *meta*- and *para*-substituted acetophenone derivatives. We checked that the pairs of enantiomers of alcohols **5g** and **5h** corresponding to *meta*-methylacetophenone **4g** and *para*-chloroacetophenone **4h** can be separated by chiral chromatography in the presence of alcohols **4a**, **4c**, **4e** and **4f** without peak overlap. The chromatogram of an equimolecular mixture of the six racemic alcohols is presented in Figure 3.

The reduction of *meta*-methylacetophenone **4g** and *para*-chloroacetophenone **4h** as single substrates catalyzed by $[RuCl_2(p\text{-cymene})]_2$ and *N*-phenyl-L-proline amide **1a** afforded respectively **5g** (65% *ee*) and **5h** (60% *ee*) after 4 h reaction time. The reduction of the mixture of the six ketones **4a**, **4c**, **4e**–**4h** in water using 5% mol $[RuCl_2(p\text{-cymene})]_2$ and *N*-phenyl-L-proline amide **1a** (ratio ruthenium/total amount of ketones) has been first performed. Various ligands were then evaluated for the catalytic reduction in water of this set of ketones. The results are indicated in Table 2.

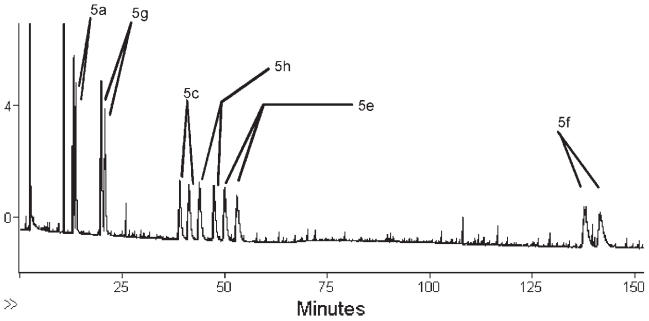


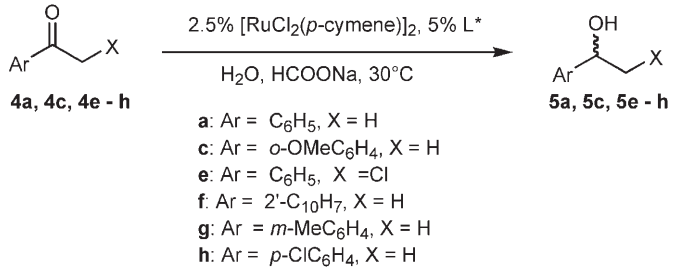
Figure 3. Analysis of the mixture of enantiomers of alcohols **5a**, **5c**, **5e**–**h** by chiral GC [Chiraldex β-PM column (50 m × 0.25 mm), hydrogen as carrier gas (1.0 mL min^{-1}); oven temperature : 130 °C during 65 min, heated to 150 °C (10 °C min^{-1}) and maintained at 150 °C during 100 min].

As observed for the first set of ketones, the presence of an electron-attracting group on the proline amide (ligand **1b**, entry 2) or of a bulky amino group (ligand **1c**, entry 3) led to a decrease in the enantiomeric excesses of the six alcohols compared to the values given by *N*-phenyl-L-proline amide **1a** (entry 1). The ligand *N*-2-pyridyl-L-proline amide **1d** afforded interesting results for the reduction of ketones **4f** and **4h** with respectively similar or slightly higher values for enantiomeric excesses than with ligand **1a** (compare entries 4 and 1). We previously observed high asymmetric inductions with the proline amide ligand **3a** prepared from (1*R*,2*S*)-aminoindanol **2c** containing a hydroxy group. We thus decided to test the proline amide ligand **1e** prepared from 2-aminophenol which has also a chelating hydroxy group. Ligand **1e** provided the mixture of alcohols with higher enantiomeric excesses than *N*-phenyl-L-proline amide **1a** for alcohols **5a**, **5f**, **5g** and **5h** and only slightly lower for **5c**, and **5e** (entry 5). The presence of a hydroxy group on the proline amide ligand has a positive influence on the enantioselective reduction of ketones in water. The reaction catalyzed by ruthenium coordinated by (1*S*,2*R*)-ephedrine **2a** was very slow but asymmetric induction was higher than with ligand **1a** for all alcohols except **5c** (entry 6). As for the first set of ketones the change of ligand **2a** for its ammonium salt **2b** allowed the reaction time to be reduced without significant change in the enantiomeric excesses except for **5e** (a diminution is noticed, entry 7). For the alcohols already prepared by ruthenium-catalyzed reactions in water with ephedrine as ligand,[9a] or with ephedrine ammonium salt,[9b] the multi-substrate reductions provided very close values for the enantiomeric excesses.

(1*R*,2*S*)-*cis*-Aminoindanol **2c** afforded shorter reaction time than **2a** without a noticeable change in the enantiomeric excesses excepted for alcohol **5c** (entry 8). Gratifyingly proline amide **3a** prepared from (1*R*,2*S*)-*cis*-aminoindanol furnished high asymmetric inductions for all the ketones and proved to be a better ligand than those described above (entry 10). The alcohols were obtained with enantiomeric excesses in the range 84–94%, all values but one being increased in comparison with **1a** and **1e** and all in comparison with **2c**. The alcohols formed in the reaction catalyzed with proline amide **3a** have a configuration similar to that given by *N*-phenyl-L-proline amide **1a** and opposite to that given by (1*R*,2*S*)-*cis*-aminoindanol **2c**.

With the aim to evaluate the influence of the chirality of the amino alcohol part, the proline amide ligand **3b** has been prepared from the other enantiomer of *cis*-aminoindanol (1*S*,2*R*)-**2c**. Unfortunately this ligand gave lower enantiomeric excesses than **3a**

Table 2. One-pot enantioselective reduction of ketones **4a**, **4c**, **4e**–**4g** catalyzed by $[RuCl_2(p\text{-cymene})]_2$ coordinated by various ligands in water.



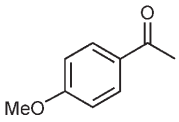
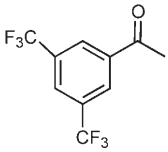
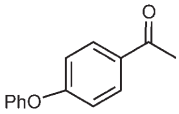
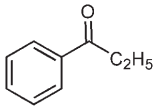
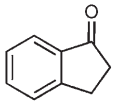
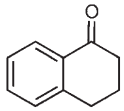
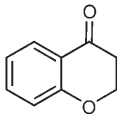
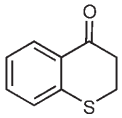
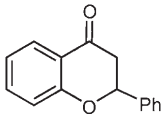
Entry	Ligand	*t* [h]	*ee* Products [%][a,b]					
			5a	**5c**	**5e**	**5f**	**5g**	**5h**
1	**1a**	12	67 (*R*)	>99[c] (*R*)	61 (*S*)	76 (*R*)	66 (*R*)	60 (*R*)
2	**1b**	18	60 (*R*)	95.5 (*R*)	57 (*S*)	71 (*R*)	61 (*R*)	61 (*R*)
3	**1c**	18	54.5 (*R*)	92 (*R*)	43 (*S*)	66 (*R*)	55.5 (*R*)	52 (*R*)
4	**1d**	24	60.5 (*R*)	83 (*R*)	47 (*S*)	73 (*R*)	63 (*R*)	67 (*R*)
5	**1e**	40	77 (*R*)	97.5(*R*)	58.5 (*S*)	94.5 (*R*)	78 (*R*)	74 (*R*)
6	(1*S*,2*R*)-**2a**	72	74 (*S*)	29 (*S*)	78.5 (*R*)	82 (*S*)	73 (*S*)	74 (*S*
7	(1*S*,2*R*)-**2b**	48	70 (*S*)	32 (S)	56 (*R*)	77 (*S*)	76 (*S*)	72(*S*)
8	(1*R*,2*S*)-**2c**	24	76 (*S*)	56 (*S*)	81 (*R*)	78 (*S*)	76 (*S*)	71 (*S*)
9	(1*S*, 2*R*)-**2c**	24	74 (*R*)	58 (*R*)	81 (*S*)	75 (*R*)	76.5 (*R*)	73 (*R*)
10	**3a**	40	84 (*R*)	89 (*R*)	84 (*S*)	94 (*R*)	83.5 (*R*)	87 (*R*)
11	**3b**	40	67 (*R*)	28 (*R*)	56 (*S*)	61.5 (*R*)	60 (*R*)	50.5 (*R*)
12	**3c**	20	40 (*R*)	69 (*R*)	40 (*S*)	52 (*R*)	43 (*R*)	47 (*R*)

[a] Reactions were performed with 2.5% $[RuCl_2(p\text{-cymene})]_2$ and 5% ligand **1** in water at 30°C, for total conversion.
[b] Absolute configuration of the major enantiomer was assigned by comparison with our precedent results and experiments performed with single substrates.
[c] Only one peak was observed in GC analysis.

for all the alcohols and even lower than with *N*-phenyl-L-proline amide **1a** (entry 11). The role of the hydroxy group in ligand **3a** was further investigated by performing the multi-ketones reduction under the same conditions with a proline amide ligand **3c** prepared from (*R*)-1-aminoindane. With the latter an important decrease in the enantiomeric excesses compared to those given by ligand **3a** is observed (entry 12). The presence of a hydroxy group on the L-proline amide ligands provides an improvement in the asymmetric inductions for asymmetric hydride transfer reactions for all aromatic ketones except the *ortho*-substituted acetophenones, as shown by the comparison of enantiomeric excesses given by **1a** and **1e**, or by **3a** and **3c**. A similar effect was evidenced by Wills in the asymmetric hydride transfer hydrogenation of aromatic ketones in non-aqueous conditions.[16] The configuration of the chiral center bearing the nitrogen of the amino alcohol has also a dramatic influence on the enantioselectivity of the reductions as revealed by the comparison of results furnished by the diastereomeric ligands **3a** and **3b** in which chiralities of L-proline and *cis*-aminoindanol are respectively matched and mismatched.

The ruthenium-catalyzed multi-substrate reductions in water studied so far have shown that the proline amide **3a** provides the highest enantiomeric excesses for all alcohols except those resulting from *ortho*-substituted acetophenones compared to other ligands. To determine if such an improvement is really occurring on other substrates we performed the reduction of various aromatic ketones in water in the presence of ruthenium coordinated with proline amide **3a** and compared the enantiomeric excesses to those given by ligand **1a**. The results are gathered in Table 3. With proline amide **3a** prepared from (1*R*,2*S*)-*cis*-aminoindanol as ligand reactions were slower than with **1a**, but all the ketones examined were reduced with higher asymmetric inductions. All the alcohols have been isolated with enantiomeric excesses over 80% except chromanol (67%). The alcohols resulting from the reduction of acetophenone derivatives with *meta*- and *para*-substituents have enantiomeric excesses in the range 80–86% (entries 1–3). Enantiomerically pure benzylic alcohols such as 2-phenylchroman-4-ol, chromanol or thiochromanol have interesting properties as antioxidants, or building blocks.[17] Interestingly the reduction of tetralone (entry 6) and thiochromanone (entry 8) afforded the corresponding alcohols with respectively 94% and 98% *ee*. These results truly validate the method of evaluation of asymmetric hydride transfer described above.

Table 3. Enantioselective reduction of ketones catalyzed by $[RuCl_2(p\text{-cymene})]_2$ coordinated by ligands **1a** and **3a** in water.

Entry	Ketone	Ligand **1a**			Ligand **3a**			Configuration[c]
		t [h]	Yield [%]	*ee* [%]	*t* [h]	Yield [%]	*ee* [%]	
1		24	58	68	40	90	80.5	(*R*)
2		2	76	62	20	79	85	(*S*)
3		3	77	71	40	73	86	(*R*)
4		4	85	53.5	20	83	78.5	(*R*)
5		4	79	46	20	85	88	(*R*)
6		4	68	77	20	82	94	(*S*)
7		3	67	55	20	76	67	(*R*)
8		4	72	61	20	69	98	(*R*)
9		120	50[a]	62	144	46[b]	83	(−)

[a] 55% conversion.
[b] 51% conversion.
[c] Absolute configuration of the major enantiomer was assigned by comparison of the rotation values in the literature or by analogy.

Conclusions

Ruthenium-catalyzed asymmetric hydride transfer reductions of ketones in water have been studied by a multi-substrate screening method. Proline amides and amino alcohols have been compared for one-pot reductions of two sets of six ketones. Substitution of the phenylamino group of the proline amides by electron-attracting, bulky group or chelating groups have minor effects on the asymmetric induction while substitution by a hydroxy group increases the enantiomeric excesses. The proline amide **3a** prepared from (1*R*,2*S*)-*cis*-aminoindanol has provided the highest enantiomeric excesses for all but one of the ketones involved in the multi-substrate reactions. This ligand provides an improvement to the enantioselectivity of the reduction of various aromatic ketones compared to *N*-phenyl-L-proline amide **1a** formerly employed. Several alcohols have been isolated with high enantiomeric excesses up to 98%. This really demonstrates the power of our method for optimizing ligands for asymmetric hydride transfer. The search for more active and enantioselective ligands is ongoing in our laboratories.

Experimental Section

General Remarks

All asymmetric reactions were carried out under a nitrogen atmosphere. L-Proline-derived catalysts **1a–e** and **3a–c** were prepared from Cbz-L-proline and the corresponding commercially available amines and chiral β-amino alcohols, as described in the literature.[17] Other reagents are commercially available. Reactions were monitored by TLC analysis and products were purified by preparative thin layer chromatography using plates prepared from silica gel 60 F_{254}. A Bruker AM 250 spectrometer, operating at 250 MHz for ^1H, and at 62.5 MHz for ^{13}C, was used for the NMR spectra which are referenced to the solvent as internal standard. Infrared spectra were recorded in $CHCl_3$ solution using CaF_2 cells on a Perkin–Elmer 1000 FT-IR spectrometer. HR-MS were measured with a Thermo-Finnigan-Mat 95 spectrometer. Optical rotations were determined using a Perkin–Elmer 241 Polarimeter at room temperature using a cell of 1 dm length and $\lambda = 589$ nm. Data are reported as follows: $[\alpha]_D^{20}$(concentration in g/100 mL, solvent). Enantiomeric excesses of alcohols were determined by gas chromatograph (GC) analysis on Fisons 9000 apparatus equipped with Chiraldex β-PM column (50 m × 0.25 mm), hydrogen as carrier gas (1.0 mL min^{-1}) or HPLC on Chiralcel OD-H column. For the separation of the enantiomers of the mixtures of alcohols **5a**, **5b**, **5c**, **5d**, **5e** and **5f**, or of alcohols **5a**, **5c**, **5e**, **5f**, **5g** and **5h**, the program was as follows: oven temperature was maintained at 130 °C during 65 min, then heated to 150 °C (10 °C min^{-1}) and maintained at 150 °C during 100 min.

Synthesis of the Ligand 4-(Trifluoromethyl)phenyl-L-proline Amide (1b)

N-Carbobenzyloxy-L-proline (1.625 g, 6.5 mmol) and triethylamine (0.658 g, 6.5 mmol) were dissolved in 30 mL of THF and cooled to 0 °C. To the resulting solution was added dropwise ethyl chloroformate (0.715 g, 6.5 mmol) for 15 min. After 30 min stirring 4-(trifluoromethyl)phenylamine (1.046 g, 6.5 mmol) was added over 15 min. The resulting solution was stirred at 0 °C for 1 h and at room temperature for 16 h, and heated at reflux for 3 h. Then the solution was washed with ethyl acetate, filtered, evaporated to dryness, and purified by column chromatography on silica gel (heptane/ethyl acetate, 2:1). Removal of the solvent afforded Cbz-L-proline amide; yield: 2.05 g (82 %). This compound was reduced with 10 % Pd/C (0.2 g) in ethanol under hydrogen (1 atm). The solution was washed with ethanol, filtered on celite, and evaporated to dryness. The residue was recrystallized in hexane/CH_2Cl_2 to give pure **1b**; yield: (1.25 g (75 %). $[\alpha]_D^{20}$: −56 (*c* 0.5, EtOH); ^1H NMR ($CDCl_3$): $\delta = 9.97$ (s, 1H), 7.56–7.52 (m, 2H), 7.72–7.68 (m, 2H), 3.92–3.85 (m, 1H), 2.99–2.93 (m, 2H), 2.39 (bs, 1H), 2.26–2.15 (m, 2H), 2.05–2.00 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 173.7$, 141.0, 128.9, 126.2, 123.9, 118.9, 61.0, 47.3, 30.7, 26.3; IR: $\nu = 1681$ cm^{-1} (s); HR-MS: $m/z = 259.1056$ (calcd. for $C_{12}H_{14}F_3N_2O^+$: 259.1053), anal. calcd. for $C_{12}H_{13}F_3N_2O$: C 55.81 %, H, 5.07 %, N 10.85 %; found: C 56.01 %, H, 5.17 %, N 10.49 %.

General Procedure for One-Pot Multi-Substrate Reactions

In a Schlenk tube, $[RuCl_2(p\text{-cymene})]_2$ (0.075 mmol, 46.5 mg) and ligand (0.15 mmol) were dissolved in water (4 mL). After one hour stirring at 30 °C, sodium formate (0.68 g, 10 mmol) and 0.5 mmol of each ketone were added to the solution. The reaction mixture was maintained at 30 °C until total reduction of all ketones was monitored by TLC. The mixture of alcohols was extracted with hexane (3 × 8 mL) and the solution dried over $MgSO_4$ and analyzed by chiral GC.

General Procedure for Catalytic Reactions

In a Schlenk tube, a solution of $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 0.025 mmol) and *N*-phenyl-L-proline amide (9.5 mg, 0.05 mmol) in 4 mL of water was stirred at 30 °C during 1 h. Sodium formate (0.68 g, 10 mmol) and substrate (1 mmol) were then added and the solution was maintained at 30 °C until total reduction of the ketone as monitored by TLC (reaction times reported in Table 3). Organic products were then extracted with hexane (2 × 8 mL) and dried over $MgSO_4$. After concentration the product was purified by thin layer chromatography with hexane/ethyl acetate mixtures and spectral data compared with literature. Enantiomeric excesses were determined as precedently described,[10] or as indicated below.

***R*-(+)-1-(Naphthalen-2-yl) ethanol (5f):** GC (ChiralDex β-PM): $t_R = 138.0$, $t_S = 141.6$ min ($T_{column} = 150$ °C), $[\alpha]_D^{20}$: + 21 (*c* 0.25, MeOH) for 55 % *ee* {Lit $[\alpha]_D$: −31 (*c* 3.5, MeOH) for 97 % *ee*}.[19]

***R*-(+)-1-(3-Methylphenyl)-1-ethanol (5g):** GC (ChiralDex β-PM): $t_R = 19.9$, $t_S = 20.8$ min ($T_{column} = 130$ °C), $[\alpha]_D^{20}$: +23.9 (*c* 2.15, EtOH) for 65 % *ee*, {Lit $[\alpha]_D$: −36.5 (*c* 1.97, EtOH) for 97 % *ee* (*S*)}.[20]

***R*-(+)-1-(4-chlorophenyl)-1-ethanol (5h):** GC (ChiralDex β-PM): $t_R = 43.9$, $t_S = 47.4$ min ($T_{column} = 130$ °C), $[\alpha]_D^{20}$: 28 (*c* 2.67, $CHCl_3$) for 60 % *ee*, {Lit $[\alpha]_D$: 45 (*c* 0.9, $CHCl_3$) for 96 % *ee* (*S*)].[21]

***(S)*-(−)-1-[3,5 Bis(trifluoromethyl)phenyl]ethanol:** GC (ChiralDex β-PM): $t_S = 22.6$, $t_R = 24.2$ min ($T_{column} = 120$ °C), $[\alpha]_D^{20}$: 9 (*c* 0.3,$CHCl_3$), for 62 % *ee*, {Lit $[\alpha]_D$: +16 (*c* 1.2, $CHCl_3$), for > 99 % *ee* (*S*)}.[22]

***R*-(+)-1-phenyl-1-propanol:** GC (ChiralDex β-PM): $t_R =$ 49.0, $t_S = 51.8$ min ($T_{column} = 120$ °C), $[\alpha]_D^{20}$: 22.8 (*c* 1.14, $CHCl_3$) for 78 % *ee*, {Lit $[\alpha]_D$: 10 (*c* 2.02, $CHCl_3$) for 41 % *ee*}.[23]

***R*-(−)-1-indanol:** HPLC (Chiralcel OD-H): $t_S = 20.8$, $t_R =$ 23.4 min (hexane/*i*-PrOH: 98/2, flow 0.8 mL min^{-1}), $[\alpha]_D^{20}$: −26.4 (*c* 1.0, $CHCl_3$) for 88 % *ee*, {Lit $[\alpha]_D$: 29 (*c* 2.11, $CHCl_3$) for 98 % *ee*, *S*}.[19]

***R*-(+)-thiochroman-4-ol:** HPLC (Chiralcel OD-H): $t_S =$ 20.5, $t_R = 25.8$ min (hexane/*i*-PrOH: 85/15, flow 0.5 mL min^{-1}, $[\alpha]_D^{20}$: 143 (*c* 1.0, $CHCl_3$) for 98 % *ee*, {Lit $[\alpha]_D$: 141 (*c* 2.11, $CHCl_3$) for > 97 % *ee*}.[23]

(−)-3,4-dihydro-2-phenyl-2*H*-chromen-4-ol: HPLC (Chiralcel OD-H): t = 20.1, t = 29.4 min (hexane/*i*PrOH: 90/10, flow 0.5 mL min^{-1}), $[\alpha]_D^{20}$: −4.3 (*c* 1.0, $CHCl_3$) for 83 % *ee*.

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