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A recyclable multi-substrates catalytic system for enantioselective reduction of ketones in water

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Abstract

Enantioselective reductions of a variety of aromatic ketones catalyzed by $[RuCl_2(p\text{-cymene})]_2$ coordinated by *N*-phenyl-(L)-proline amide in water have been performed with high asymmetric inductions in several cases. The reusability of catalyst has been studied. A multi-substrate recycling of the catalyst afforded successively seven alcohols each with similar enantiomeric excess than the one recorded in a single run.

Keywords: Ruthenium; Enantioselective catalysis; Alcohols; Reduction; Catalyst recycling

1. Introduction

One of the most important goals nowadays is the development of new methods for green chemistry and environmental friendly processes. Considering criteria of atom economy enantioselective catalysis is by definition the best route to prepare enantiopure molecules. However, it is still important to improve enantioselective catalysts by minimizing amounts of catalysts and solvents. This requires methods involving low catalyst loadings and easy separation of products. Different solutions can be proposed to fulfill these requirements such as the heterogenization of catalysts [1], the use of biphasic sytems [2], or the use of water as solvent [3]. Most of the studies carried out on the recovery and recycling of catalyst are performed on the same substrate. The use of recovered catalyst to react with other substrates is more challenging since it constitutes a realistic problem. We thus wished to look for the possibility to employ the same enantioselective catalyst to carry out successive reactions with various substrates to get insight into a new method for preparing libraries of enantioenriched compounds.

Catalytic enantioselective reductions of ketones by hydrogen transfer reactions are of fundamental synthetic importance [4]. Numerous enzymatic reactions have also been reported [5], as well as catalytic systems based on the use of various metals such as rhodium, iridium [6], or lanthanide-based catalysts [7]. The highly efficient ruthenium catalysts described by Noyori involve the mono-*N*-tosylated diphenylethylenediamine (DPEN-NTs) as chiral ligand [4a,b]. Recently several teams were successful in carrying out enantioselective hydride transfer reductions of ketones in aqueous solutions using ruthenium complexes with different ligands such as aminoamide ligands [8], or sulfonated analogues of Noyori ligand [9]. Chung described the first water-soluble ruthenium (II) catalyst coordinated by amides derived from (*S*)-proline [8]. Optimization of the system led to high enantioselectivities for the reduction of *o*-substituted acetophenones with sodium formiate as hydrogen source. In the case of the asymmetric reduction of *o*-methoxyacetophenone the catalyst was reused six times without loss of enantioselectivity. We thus selected this system to test the possibility to perform multi-subtrates recycling reactions.

2. Results and discussion

We wished first to determine the maximum number of reuses that can be carried out without loss of activity and enantioselectivity of the catalytic system under Chung's reaction conditions. We synthesized the *N*-phenyl-(L)-proline amide ligand **1** according to the reported method [10]. The catalyst was prepared as

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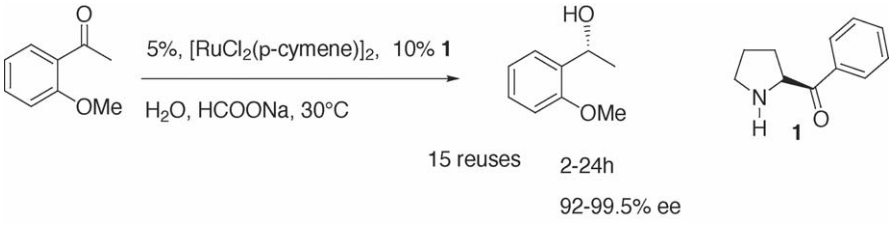

Scheme 1.

described [8], by addition of ligand **1** to $[RuCl_2(p\text{-cymene})]_2$ in water under nitrogen, and after 1 h stirring *o*-methoxy acetophenone **2** and sodium formiate were added (Scheme 1). After each catalytic cycle the produced alcohol was extracted by hexane and the aqueous phase was carefully separated. Equimolar amounts of formic acid and of substrate were successively added to the reaction mixture to perform the next reduction. The catalyst has been recycled 15 times. An increase in enantiomeric excess was observed after the two first reuses (from 92 to 99.5% ee). Such an increase of enantiomeric excess after the first reuses of catalysts has been already observed in similar reactions [11]. The six experiments from reuse 2 to reuse 7 afforded enantiomeric excesses over 99%. In further reductions a slight decrease in asymmetric inductions with enantiomeric excesses over 90% until run 14 was obtained. The next reuse showed a decrease in enantiomeric excess and, moreover, in the rate of the reaction. The 15 uses of the catalyst without loss of activity and enantioselectivity allow to envisage multi-substrates recycling. Substrate/catalyst ratio was decreased (s/c = 100). Similar enantioselectivities with an increase of enantiomeric excess for the second reuse (99.6% ee) were found although a longer reaction time (72 h) was needed to achieve complete conversion. A 10% catalyst to substrate ratio was thus employed for the following of the work.

Before studying the recycling of catalyst with various substrates we tried to widen the scope of substrates compared to that previously reported. Results are indicated in Table 1. Since aryl methyl ketones with *ortho* substituents were found to be reduced with good asymmetric inductions by ruthenium coordinated by several proline amide ligands [8], we studied first *o*-substituted aromatic ketones. Excellent results were obtained for *o*-nitro and *o*-amino substituted ketones **3** and **4** since only one enantiomer could be detected (entries 1–2). Enantiomeric excess was lower for substrate **5** with *o*-trifluoromethyl substituent (entry 3). *p*-Phenoxy substituted acetophenone **9** afforded the corresponding alcohol with 77% ee (entry 4). 2-Chloroacetophenone **11** was reduced with low asymmetric inductions (entry 5). Noteworthy was the reduction of 1-acetonaphtone **12** which gave, with the proline amide ligand **1**, the alcohol with 94.5% enantiomeric excess (entry 7), whereas 89.4% ee were reported with the *p*-fluorophenyl proline amide ligand [8]. Recycling the catalyst four times did not result in a decrease of enantiomeric excess (entry 8). Aromatic cyclic ketones **13** and **14** afforded the corresponding alcohols with 77% ee (entry 9) and 54% ee (entry 11), respectively (Chart 1).

The possibility to reuse the same catalyst for successive reductions was studied on a variety of substrates, which have been previously described in the literature or in this work. Two different sequences for recycling have been realized (Tables 2 and 3). In both cases six consecutive uses of the same catalyst with different substrates allowed to recover the alcohols in good yields and with enantiomeric excesses close to those obtained when catalyst was employed in a single run. Tetralone **13** was reduced with lower enantiomeric excess than in the first run using the same catalyst. A decrease of enantiomeric excess after two uses of the catalyst for the reduction of tetralone has been already noticed (Table 1, entry 10). Reaction times were difficult to compare since most reactions were

Table 1
Ketone reductions catalyzed by $[RuCl_2(p\text{-cymene})]_2$ coordinated by ligand **1** in water

Entry	Recycle no.	Substrate	*t* (h)	Conversion (%)	Yield (%)[a]	ee (%)	Configuration[c]
1	0	**3**	6	100	73	>99.5[b]	(+)[d]
2	0	**4**	5	100	61	>99.5[b]	(−)[d]
3	0	**5**	2	100	62	86	(+)-*R* [13]
4	0	**9**	3	100	71	77	(+)-*R* [14]
5	0	**11**[e]	3	100	65	45	(+)-*R* [15]
6	1–3	**11**[e]	3	100	60	45–39	
7	0	**12**	5	100	59	94.5	(*R*)[16]
8	1–4	**12**	18–24	100	53	95–93	
9	0	**13**	4	100	68	77	(+)-*S* [13]
10	1–3	**13**	24	100	55	76–69	
11	0	**14**[e]	3	100	67	54	(+)-*R* [17]

[a] Reactions were performed with 5% $[RuCl_2(p\text{-cymene})]_2$ and 10% ligand **1** in water at 30 °C.
[b] Only one peak was observed in GC analysis.
[c] Absolute configuration was determined by the sign of rotation of the isolated product (reference).
[d] Absolute configuration was not determined.
[e] In CH_2Cl_2 solution.

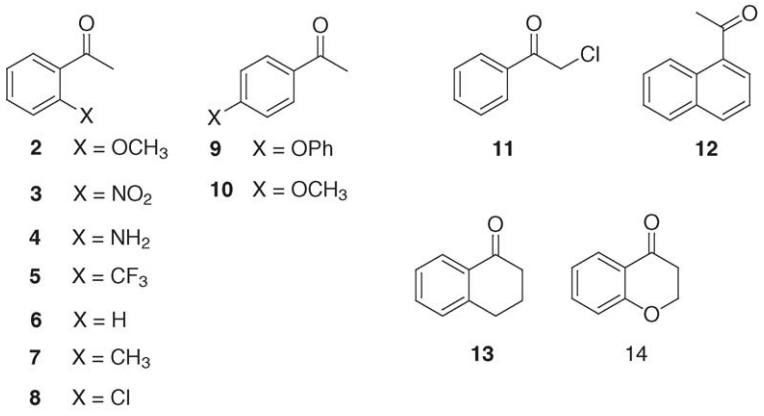

Chart 1.

Table 2
Multi-substrates catalyst recycling: ketones reductions catalyzed by [$RuCl_2$(*p*-cymene)]$_2$ coordinated by ligand **1** in water

Recycle no.	Substrate	*t* (h)	Yield (%)[a]	ee	ee lit	Configuration[f]
0	**2**	2	50	95	94.5[c]	(+)-*R* [12]
1	**8**	14	65	>99	91[c]	(+)-*R* [12]
2	**7**	4	57	>99	91[c]	(+)-*R* [12]
3	**12**	6	55	92.5	89[d], 94[e]	(+)-*R*
4	**13**	20	48	71	77[e]	(+)-*S*
5	**6**	20	51	63	61[c]	(+)-*R* [12]
6	**10**	24[b]	49	68	58[c]	(+)-*R* [13]

[a] Reactions were performed with 5% [$RuCl_2$(*p*-cymene)]$_2$ and 10% ligand **1** in water at 30 °C.
[b] In CH_2Cl_2 solution.
[c] Ee reported in ref. [8] with ligand **1**.
[d] Ee reported in ref. [8] with *p*-fluorophenyl proline amide as ligand.
[e] Ee determined in this work (Table 1).
[f] Absolute configuration was determined by the sign of rotation of the isolated product (reference).

performed overnight without checking the end of the reaction. To improve the efficiency of our process we tried to decrease the initial amount of catalyst using 5% for the first cycle (Table 4). We did succeed in performing the same number of cycles, changing of substrate in each reduction. The seven alcohols were obtained

Table 3
Multi-substrates catalyst recycling: ketones reductions catalyzed by [$RuCl_2$(*p*-cymene)] $_2$ coordinated by ligand **1** in water

Recycle no.	Substrate	*t* (h)	Yield[a]	ee	ee lit	Configuration[d]
0	**7**	4	82	99	91[b]	(+)-*R*
1	**8**	2	67	99	91[b]	(+)-*R*
2	**4**	14	49	99	>99.5[c]	(+)-*R*
3	**5**	4	61	82	86[c]	(+)-*R*
4	**14**	6	64	55	54[c]	(+)-*R*
5	**13**	13	59	54	77[c]	(+)-*S*
6	**9**	18	68	66	77[c]	(+)-*R*

[a] Reactions were performed with 5% [$RuCl_2$(*p*-cymene)$_2$]$_2$ and 10% ligand **1** in water at 30 °C.
[b] Ee reported in ref. [8] with ligand **1**.
[c] Ee determined in this work (Table 1).
[d] Absolute configuration was determined by the sign of rotation of the isolated product.

Table 4
Multi-substrates catalyst recycling: ketones reductions catalyzed by 5% [$RuCl_2$(*p*-cymene)] $_2$ coordinated by ligand **1** in water

Recycle no.	Substrate	*t* (h)	Yield[a]	ee
0	**2**	3	60	92
1	**11**	14	55	48[b]
2	**8**	7	73	93.5
3	**7**	18	76	97
4	**5**	40	69	82.5
5	**12**	40	88	92.5
6	**13**	40	60	67

[a] Reactions were performed with 2.5% [$RuCl_2$(*p*-cymene)$_2$]$_2$ and 5% ligand **1** in water at 30 °C.
[b] 45% ee was obtained for the simple reduction of **11** with 10% catalyst.

in good yields without loss of enantioselectivity albeit with an increase in reaction times for the three last recyclings. For every recycling sequence all alcohols were isolated in high purity without any trace of neither the ketone substrate involved nor of the alcohol produced in the preceeding reaction.

3. Conclusion

We have shown that the catalyst obtained by in situ addition of *N*-phenyl-(L)-proline amide **1** on [$RuCl_2$(*p*-cymene)]$_2$ in water is a reusable catalyst for consecutive reductions of the same substrate as well as for multi-substrates reductions. The catalyst is easily prepared since no modification of ligand is needed, and is easily recycled by simple liquid extraction of the reaction products from the catalyst. We have succeeded to perform successive reductions of a variety of substrates without loss of purity or enantioselectivity of the isolated products compared to reactions carried out in similar conditions with each individual substrate.

4. Experimental

4.1. General

All asymmetric reactions were carried out under a nitrogen atmosphere. *N*-Phenyl-(L)-proline amide **1** was prepared

as described in literature [10]. 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}. Bruker AM 250 spectrometer, operating at 250 MHz for ^{1}H, 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. 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).

4.2. General procedure for catalytic reactions

A solution of $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 0.05 mmol) and *N*-phenyl-(L)-proline amide (19 mg, 0.1 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 ketone monitored by TLC (reaction times reported in Table 2). 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 the literature. Yields and ee are included in Table 1. Enantiomeric excesses were determined as described below.

4.3. General procedure for recycling catalyst and reuse in a following reaction

Catalytic reaction was performed as described above at 30 °C with 1 mmol ketone. After total disappearance of the ketone, alcohol was extracted with hexane (4 × 8 ml) by using a syringe, the aqueous phase was left in the reaction vessel under nitrogen atmosphere and the organic phase was treated as described above. Substrate (1 mmol) was then added to the aqueous phase (same or different ketone than in the preceeding run), followed by the addition of 1 eq. HCOOH (0.1 ml, 10 M). The reaction mixture was maintained at 30 °C until the end of reaction and treated as indicated above. Yields and ee are included in Tables 1, 3 and 4. Enantiomeric excesses were determined as described below.

(*R*)-(+)-1-(2-methoxyphenyl)-1-ethanol: HPLC (Chiralcel® OD-H), $t_S = 16.2$; $t_R = 17.2$ (hexane/iPrOH 90:10, flow 0.4 ml/min) [12].

(+)-1-(2-nitrophenyl)-1-ethanol: GC Chiraldex β-PM, $t_+ = 58.5$; $t_- = 60.0$ ($T_{column} = 140$ °C) $[\alpha]_D^{20} = +20$ (c 0.23, $CHCl_3$) for 99.5% ee.

(−)-1-(2-aminophenyl)-1-ethanol: GC Chiraldex β-PM, $t_+ = 59.1$; $t_- = 60.5$ ($T_{column} = 140$ °C) $[\alpha]_D^{20} = -51.5$ (c 0.175, $CHCl_3$) for 99.5% ee.

(*R*)-(+)-1-(2,2,2-trifluoromethylphenyl)-1-ethanol: GC Chiraldex β-PM, $t_R = 21.2$; $t_S = 23.0$ ($T_{column} = 140$ °C) [13].

(*R*)-(+)-1-phenyl-1-ethanol: HPLC (Chiralcel® OD-H), $t_R = 14.2$; $t_S = 16.5$ (hexane/iPrOH 90:10, flow 0.4 ml/min) [13].

(*R*)-(+)-1-(2-methylphenyl)-1-ethanol: HPLC (Chiralcel® OD-H), $t_S = 14.0$; $t_R = 14.5$ (hexane/iPrOH 90:10, flow 0.4 ml/min) [12].

(*R*)-(+)-1-(2-chlorophenyl)-1-ethanol: GC Chiraldex β-PM: $t_R = 25.6$; $t_S = 28.3$ ($T_{column} = 140$ °C) [13].

(*R*)-(+)-1-(4-phenoxyphenyl)-1-ethanol: HPLC (Chiralcel® OD-H), $t_S = 42.7$; $t_R = 45.7$ (hexane/iPrOH 98:2, flow 0.5 ml/min) [14].

(*R*)-(+)-1-(4-methoxyphenyl)-1-ethanol: HPLC (Chiralcel® OD-H), $t_R = 17.9$; $t_S = 19.6$ (hexane/iPrOH 90:10, flow 0.4 ml/min) [13].

(*S*)-(+)-2-chloro-1-phenylethanol: GC Chiraldex β-PM, $t_S = 34.8$; $t_R = 36.2$ ($T_{column} = 140$ °C) [15].

(*R*)-(+)-1-(1-naphthyl)-1-ethanol: HPLC (Chiralcel® OD-H), $t_S = 15.5$; $t_R = 24.6$ (hexane/iPrOH 90:10, flow 0.6 ml/min) [16].

(*S*)-(+)-1,2,3,4-tetrahydronaphtalen-1-ol: HPLC (Chiralcel® OD-H), $t_R = 31.0$; $t_S = 34.6$ (hexane/EtOH 99:1, flow 0.5 ml/min) [13].

(*R*)-(+)-chroman-4-ol: HPLC (Chiralcel® OD-H), $t_S = 11.6$; $t_R = 12.9$ (hexane/iPrOH 90:10, flow 0.5 ml/min) [6].

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