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Water-soluble chiral monosulfonamide-cyclohexane-1,2-diamine-RhCp* complex and its application in the asymmetric transfer hydrogenation (ATH) of ketones

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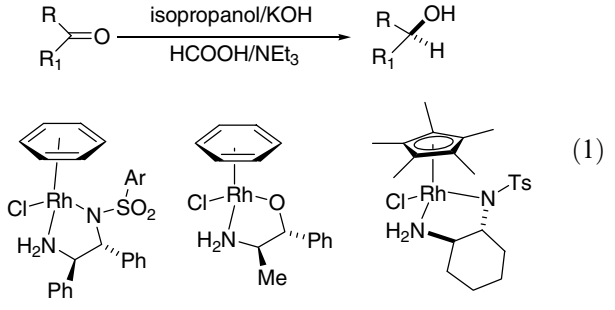
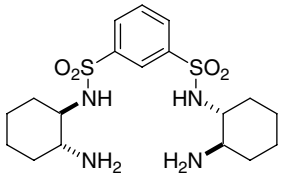
Abstract—Monosulfonamide ligands with heteroatom/heterocyclic systems were derived from *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine and complexed with $[Ru(benzene)Cl_2]_2$, $[Cp^*RhCl_2]_2$ in situ and used in the ATH of aromatic ketones with aqueous sodium formate as the hydrogen source. The chiral secondary alcohols were obtained with >93% enantioselectivity and >89% yield. Reduction in water was faster than in isopropanol/KOH. Addition of surfactants showed little or no effects.

Optically pure secondary alcohols are valuable intermediates in the synthesis of physiologically active molecules.[1] One direct approach to these molecules is by catalytic enantioselective reduction of the corresponding ketones, which has been extensively studied during the past decade.[2] A particularly useful method in the direct reduction of ketones is by asymmetric transfer hydrogenation (ATH). ATH is catalyzed by metal complexes associated with various chiral ligands using 2-propanol or $HCOOH/NEt_3$ as the hydrogen source. The metal complexes used are often derived from chiral 1,2-diamine, 1,2-amino alcohol and phosphorous-containing ligands, coordinated to Ru(II), Rh(III), and Ir(I) metals (Eq. 1).[3–6]



Although the catalytic ATH of ketones is operationally simple compared to hydrogenation using H_2 gas under pressure, the reaction is less appealing for the industrial applications, due to the use of 2-propanol/KOH or formic acid/NEt_3.[7] On an industrial scale the waste solvents generated by this process become an environmental issue. Because there is an increasing demand for environmentally friendly methods, the ATH performed in water is now of great interest, because water is safe, economical, and environmentally benign and is considered a 'greener' solvent than most organic solvents as a medium for conducting reactions.[8] Recently a number of reports have appeared on the use of water as a medium for ATH, using heterogenized or water-soluble metal complexes.[9] Addressing this we recently reported a C_2-symmetric bis(sulfonamide)-cyclohexane-1,2-diamine (**1**)-RhCp* complex which gave high enantioselectivities and conversion in the ATH of ketones in aqueous sodium formate.[9a]



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Xiao and co-workers have used Noyori's TsDPEN-Ru and Cp*Rh complexes in the ATH of ketones and obtained high enantioselectivity and conversion in

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water.[9b,m] This prompted us to explore new diamine ligands replacing the Tosyl group with a heteroatom containing molecule, which we expected to be more hydrophilic in nature and thus enhance the rate of reaction in water.

In this Letter, we disclose the facile synthesis of new chiral sulfonamide-based ligands **2a–g,** derived from readily available *trans*-cyclohexane-1,2-diamine and complexed to $[Cp^*RhCl_2]_2$ and $[RuCl_2(benzene)]_2$ (Fig. 1). These ligands contain pyridine, imidazole, isoxazole, benzoxadiazole and thiophene groups and were studied in the ATH of aromatic ketones in isopropanol, as well as in water with HCO_2Na as the hydrogen source. In order to evaluate the performance of our ligands in the ATH, we compared the catalysts in isopropanol and water with acetophenone as a model substrate. The pre-catalysts used for reduction in isopropanol were prepared by heating at 80 °C for 1 h ligands **2a**–**1g** with $[Cp^*RhCl_2]_2$ or $[RuCl_2(benzene)]_2$, while those in water were made by stirring the two species in water at 40 °C for 1 h. The results are summarized in Table 1.

The ATH of acetophenone in 2-propanol with $[RuCl_2(benzene)]_2$ and $[Cp^*RhCl_2]_2$ gave moderate enantioselectivity and yield. However, using $[Cp^*RhCl_2]_2$ with **2a**–**g** in aqueous sodium formate led to excellent enantioselectivty and yields, indicating that **2a**–**g**-RhCp* complexes are better catalysts in terms of the rate and enantioselectivity in comparison to the Ru complex with the same sulfonamide ligands. For instance, the reduction of acetophenone led to a 100% conversion with 93% ee in 30 min in water at 40 °C and higher S/C ratio of 100 (entry 6). In comparison, the reaction performed in 2-propanol using the same catalyst at 25 °C gave 82% ee and 75% conversion, but in 5 h at an S/C ratio of 33. These results showed that

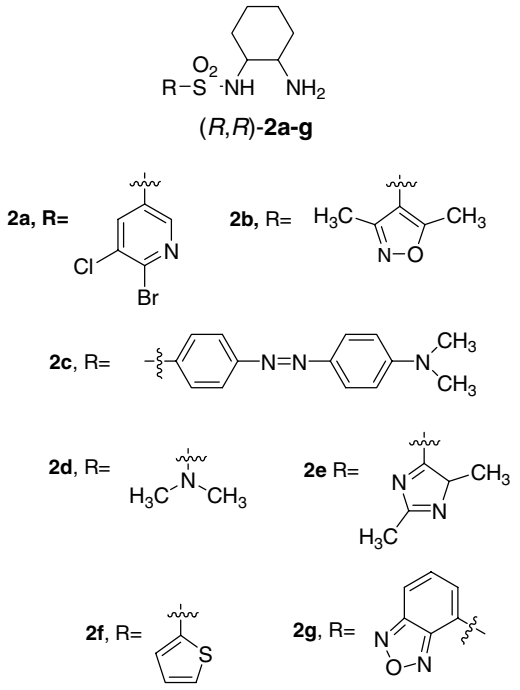


Figure 1. Monosulfonamide ligands.

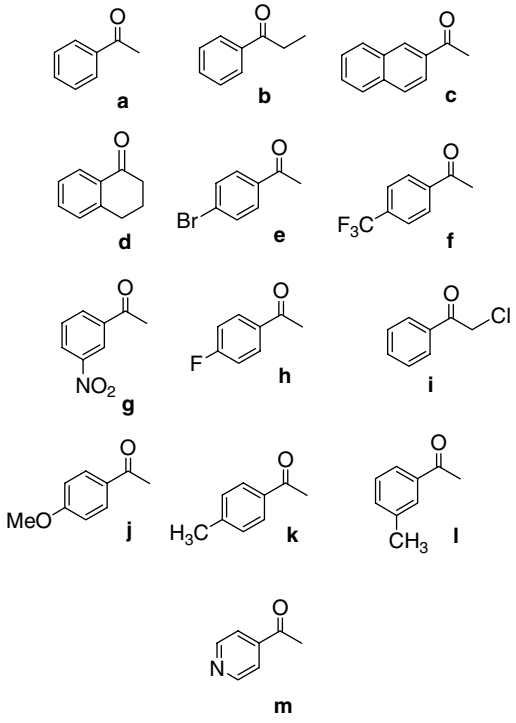


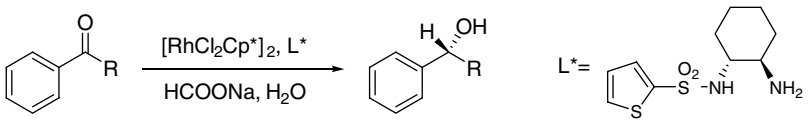
Figure 2. Ketones tested in the ATH.

Table 1. ATH of acetophenone catalyzed by ligands **2a**–**g** in isopropanol versus $HCOONa/H_2O$[a]

Entry	Ligand	[(Benzene)$RuCl_2]_2$/isopropanol/KOH[b]				[$Cp^*RhCl_2]_2$/isopropanol/KOH[b]				[$Cp^*RhCl_2]_2$/HCOONa/water[c]			
		t (h)	S/C	ee[d] (%)	Conv (%)	*t* (h)	S/C	ee (%)[d]	conv (%)	*t* (h)	S/C	ee[d] (%)	conv (%)
1	**2a**	5	33	77	26	5	33	92	96	0.5	100	90	>99
2	**2b**	5	33	84	11	5	33	89	91	0.5	100	94	100
3	**2c**	5	33	86	64	5	33	89	96	0.5	100	89	99
4	**2d**[9s]	5	33	80	88	5	33	87	67	0.5	100	89	100
5	**2e**	5	33	79	17	5	33	85	93	0.5	100	—	—
6	**2f**	5	33	79	56	5	33	82	75	0.5	100	93	100
7	**2g**	5	33	86	12	5	33	27	32	0.5	100	12	15

[a] Absolute configuration of the alcohol is *R*.
[b] 25 °C using a mixture of isopropanol/KOH.
[c] 40 °C using a mixture of water/sodium formate in air.
[d] Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.

Table 2. Aerobic ATH of ketones with Rh-**2f** in H_2O using S/C 100[a]



Entry	Ketone	t (h)	Without surfactant		CTAB[b]		SDS[c]		Conf. Abs.[e]
			ee[d] (%)	Conv. (%)	ee[d] (%)	Conv. (%)	ee[d] (%)	Conv. (%)	
1	a	0.5	93	100	94	100	94	100	*R*
2	b	6	92	94	90	80	78	87	*R*
3	c	2	99.8	100	100	98	99.4	100	*R*
4	d	4	>99	86	100	86	100	98	*R*
5	e	2	89	100	92	99	90.3	>99	*R*
6	f	2	94	98	73	100	68	100	*R*
7	g	6	82	96	80	13	93	100	*R*
8	h	2	91	>99	91	>99	93	>99	*R*
9	i	6	87	93	93	100	87	93	*R*
10	j	6	79	74	95	99	85	64	*R*
11	k	6	94	98	95	99	95	91	*R*
12	l	6	92	94	93	94	92	>99	*R*
13	m	6	82	96	70	95	80	16	*R*

[a] 40 °C using a mixture of water/sodium formate in air.
[b] CTAB, cetyltrimethylammonium bromide.
[c] SDS, sodium dodecyl sulfate.
[d] Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.
[e] Absolute configurations were assigned by comparing optical rotations with the literature values.

the ketone reduction was drastically accelerated in water. Ligands **2b** and **2f** (Table 1, entries 2 and 6) gave the best results, consequently, we extended the use of the (*R*,*R*)-**2f**-Rh-catalyst to a wide range of ketones (Fig. 2) under the same conditions with an S/C ratio of 100. Table 2 shows the results obtained.

The results indicated that a ketone with an electron-withdrawing substituent, such as $-CF_3$, $-NO_2$, –Br, –F, –Cl (Table 2, entries 5–9) gave a higher conversion owing to rapid hydride transfer and selectivity, while electron donating $-OCH_3$ led to a lower enantioselectivity and yield (entry 6). 4-Acetylpyridine (Table 2, entry 13) also gave low conversion, probably due to substrate interaction with the metal center. Increasing the alkyl chain from methyl to ethyl and cyclic form led to lower conversion with good enantioselectivity (Table 2, entries 1, 2 and 4). Interestingly, the rate of ATH with catalyst **2f**-RhCp* was much slower compared to C_2-symmetric ligand **1**-RhCp* and RhCp*–TsCYDN under identical conditions.[9a,b] It has been suggested that the rate enhancement in aqueous sodium formate may be due to the formation of formato species, which dissolves in hydrophobic ketone, and the reaction takes place in the substrate.[9d,e] In our case, with **2f**-RhCp*, the heteroatom probably competes with the formate anion intra- or intermolecularly for the metal center, slowing the formation of the catalytically active formato species. Thus, our system is kinetically slower than **1**-RhCp* and RhCp*–TsCYDN. Recently, several reports have shown that surfactants play an important role in the ATH of ketones in water.[9h,o,r,s] Although our ligand–RhCp* or Ligand–Ru complexes are water soluble, most ketone substrates are generally hydrophobic. This prompted us to investigate the effect of surfactants in our ATH reaction. Addition of cetyltrimethylammonium bromide (CTAB) or sodium dodecyl sulfate (SDS), showed a marginal effect on the enantioselectivity and yields and no rate enhancement was seen.

In conclusion we have synthesized a number of water-soluble monosulfonamide ligand–RhCp* complexes which gave good enantioselectivity and conversion in the ATH using aqueous sodium formate as the hydrogen source. The reaction requires neither organic solvents nor inert conditions or substrate solubility in water. The aqueous phase catalysis thus provides an attractive alternative for carrying out ATH in a safe, economical, and 'greener' manner.

Acknowledgments

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Supplementary data

Experimental procedures and spectroscopic and analytical data of compounds are supplied in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.116.

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