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New C_2-symmetric bis(sulfonamide)-cyclohexane-1,2-diamine-RhCp* complex and its application in the asymmetric transfer hydrogenation (ATH) of ketones in water

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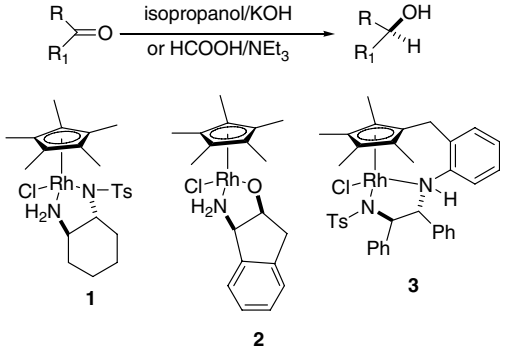
Abstract—C_2-symmetric bis(sulfonamide) ligands derived from *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine were synthesized and complexed with $[Cp^*RhCl_2]_2$ in situ and used in the ATH of aromatic ketones with aqueous sodium formate as the hydrogen source. The chiral secondary alcohols were obtained with 90–99% enantioselectivity and in 50–100% yield. Reductions in water were faster than those in isopropanol/KOH.

Chiral secondary alcohols are valuable intermediates in the synthesis of physiologically active pharmaceuticals,[1] agrochemicals[2] and flavor ingredients.[3] In response to the increasing demand for optically active secondary alcohols, a variety of powerful catalytic procedures have been developed. One such method involves the use of monotosylated 1,2-diamines or amino alcohols as ligands for ruthenium(II) catalyzed asymmetric transfer hydrogenation (ATH) of ketones, a method developed by Noyori and co-workers.[4]

Since this discovery, a significant number of new ligands have been reported for the ATH with ruthenium(II).[5–8] Recently, iridium and rhodium-Cp* based catalysts have also been shown to be efficient catalysts in the ATH of ketones. Xiao,[5] Ikariya (**1**),[9] Gavriilidis (**2**),[10] and Wills (**3**)[11] have independently shown Cp*–Rh-diamine/aminoalcohol complexes (Eq. 1) to be excellent catalysts in the ATH (isopropanol/KOH or $HCOOH/NEt_3$) of ketones, leading to high enantioselectivities and yields. Further, Xiao and other researchers have reported the ATH of ketones under environmentally friendlier conditions. Using aqueous sodium formate, secondary alcohols were obtained in excellent enantioselectivities and yields.[5,6e–j]



(1)

Binuclear complexes are known to give higher activities and selectivities as compared to the mononuclear complexes. This effect has been attributed to cooperative activation of the substrate and reactants, enhancing product formation through steric or electronic effects.[12a] Base on this association, we prepared rhodium and ruthenium bis(sulfonamide) complexes as part of our continuing interest in this subject.[12b,c] The chiral C_2-symmetric bis(sulfonamide) ligands were derived from the readily available *trans*-cyclohexane-1,2-diamine and complexed to Cp*Rh and $[(arene)RuCl_2]_2$ and their

Keywords: Bis(sulfonamide) ligands; RhCp* complex; Asymmetric transfer hydrogenation; Ketones.
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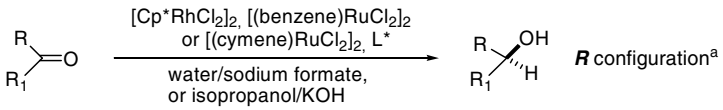
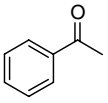
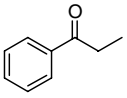
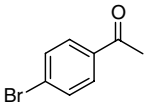
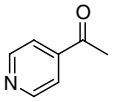
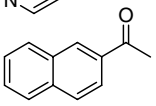
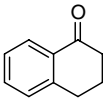
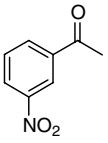
Table 1. Asymmetric transfer hydrogenation of ketones with chiral ligands **1**, **4**–**7**, and metal complexes



Ketone	Ligand	*t* (h)	[(Benzene)$RuCl_2$]$_2$			[(Cymene)$RuCl_2$]$_2$			[Cp*$RhCl_2$]$_2$		
			S/C	ee (%)[b]	Yield (%)	S/C	ee (%)[b]	Yield (%)	S/C	ee (%)[b]	Yield (%)
	**4**[c]	0.25							100	92	100
	4[d]	5	33	91	70	33	94	89	100	99	99
	4[e]	16	33	88	95	33	94	74	100	89	84
	5	16	25	76	92	—	—	—	25	67	25
	6	16	25	73	87	—	—	—	25	50	15
	7[f]	12	—	—	—	—	—	—	100	94	92
	7[g]	24	—	—	—	33	89	97	—	—	—
	**4**[c]	0.25							100	92	76
	4[d]	5	33	81	47	33	85	54	100	66	71
	**4**[c]	0.25							100	90	98
	4[d]	5	33	78	87	33	89	94	100	89	87
	**4**[d]	5	33	66	98	33	91	99	100	88	83
	**4**[c]	0.25							100	97	50
	4[d]	5	33	91	51	33	99	89	100	97	90
	**4**[c]	0.25							100	>99	86
	4[d]	5	33	99	28	33	99	74	100	99	60
	**4**[c]	0.25							100	>99	100
	4[d]	5	33	80	89	33	99	99	100	99	56

[a] Absolute configurations were assigned by comparing optical rotations with the literature values.[5,6l]
[b] Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.
[c] 40 °C using a mixture of water/sodium formate in air and without base.
[d] 25 °C using a mixture of isopropanol/KOH.
[e] 28 °C using a mixture of formic acid/triethylamine in DMF.
[f] Ref. 10.
[g] Ref. 15.

applications in the ATH of aromatic ketones in aqueous and isopropanol solvents were studied. We coupled commercially available 1,3-benzenesulfonyl chloride and resolved *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine to give C_2-symmetric bis(sulfonamide) **4** in 95% yield.[13a,b] This ligand proved to be an excellent candidate in the ATH with RhCp* and Ru(arene)-based catalysts, giving high enantioselectivity and yields with a variety of aromatic ketones. Importantly, higher enantioselectivities, shorter reaction times and similar yields were obtained with aqueous sodium formate solution than with isopropanol (Table 1). With ligand **4**, acetophenone ATH was complete in 15 min with 92% enantioselectivity and 100% yield in aqueous sodium formate, as compared to 5 h in isopropanol/KOH. When the acetophenone is made bulkier: propiophenone, α-tetralone, and 2-acetonaphthone, the reaction in isopropanol/KOH was sluggish and reasonable yields were obtained after 5 h. On

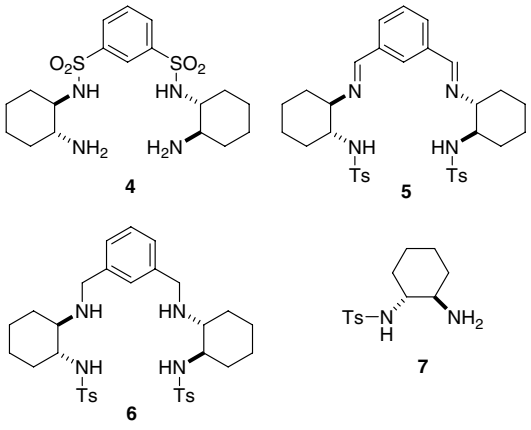


Figure 1. Structurally similar ligands.

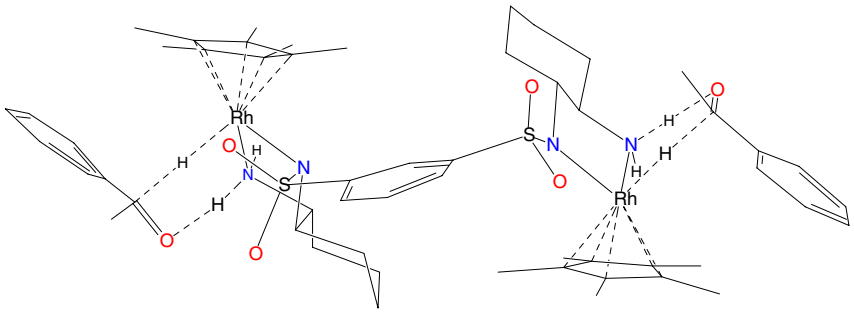


Figure 2. *anti*-Cp*Rh bis(sulfonamide)–acetophenone transition state in the *pro-R* conformation.

the other hand, using ligand **4**-Cp*Rh and aqueous sodium formate, the reaction gave high enantioselectivity and >95% yield in 30 min. Interestingly, under the same reaction conditions, 3-nitroacetophenone gave >99% enantioselectivity and 100% yield. This suggests a probable role of the polar nitro group as a surfactant, enhancing the reactivity. Aliphatic ketones gave much lower enantioselectivities and yields. 4-Acetylpyridine also gave low yield when used with ligand **4**/aqueous sodium formate, but (cymene)$RuCl_2$/isopropanol/KOH gave 91% enantioselectivity and 99% yield. These results show the versatility of the bis(sulfonamide) ligand **4** with Rh(III) or Ru(II) as catalysts in the ATH of ketones under aqueous sodium formate and isopropanol/KOH conditions.

The importance of a primary amine functional group and its location in the C_2-symmetric ligand **4** is evident, based on comparison to the results with the structurally similar ligands **5** and **6** (Fig. 1). Ligand **4** gave 99% ee/99% yield, while ligands **5** and **6** gave 67% ee/25% yield and 50% ee/15% yield, respectively, in the ATH of acetophenone using $[Cp^*RhCl_2]_2$ as the catalyst with a significant depression of rates using isopropanol/KOH. However, with $[(benzene)RuCl_2]_2$, ligands **5** and **6** gave 76% ee/92% yield and 73% ee/87% yield, respectively. Comparing ligand **4** to the monosulfonamide **7** with $[Cp^*RhCl_2]_2$[10] and $[(benzene)RuCl_2]_2$[14] in the ATH, overall the former gave higher enantioselectivities and yields. Other major differences included the rates: ligand **7** requires between 12 and 24 h to complete the reaction using isopropanol/KOH, compared to 4 h with ligand **4**.

To understand the factors that control the enantioselectivity of these catalysts better, we modeled the more selective Cp*Rh analogs using both molecular mechanics and the semi-empirical ZINDO program. *Pro-S* complexation is disfavored due to repulsion between the arene ring of the ketone and the sulfonamide group. In addition, these complexes show an increased positive charge on the methyl groups of the Cp* ligand, as compared to the uncomplexed ligand, which are in close proximity to the ketone arene ring in the *pro-R* complex. The *anti* arrangement of the *pro-R* complex was calculated to be approximately 1 kcal/mol more stable than the alternate *syn* conformer transition state (Fig. 2). The interaction between the aryl ketone and the metal–ligand complex appears to be largely controlled by electronic factors with minimal steric factors.

In conclusion, our results show that bis(sulfonamide) ligand **4**-Cp*Rh(III) complex is an excellent catalyst in the ATH, delivering fast reactions, high enantioselectivities and high yields using sodium formate as the hydrogen source, providing an alternative method for conducting ATH in a less costly, simpler and 'greener' manner.

Acknowledgements

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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.2006.09.141.

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