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Synthesis of water-soluble aminosulfonamide ligands and their application in enantioselective transfer hydrogenation

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Abstract—Water-soluble analogues of Noyori's (1*S*,2*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine and Knochel's (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diaminocyclohexane, containing an additional sulfonic acid group, have been synthesised. The ruthenium catalysed reduction of aromatic ketones using enantiomerically pure catalyst derived from water soluble ligands and $[RuCl_2(p\text{-cymene})]_2$ has been examined. High enantioselectivity and moderate activity were observed in the 2-propanol/base system. The addition of water is necessary to stabilise the catalyst.

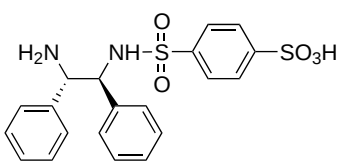
1. Introduction

Enantioselective transfer hydrogenation reactions of prochiral ketones have been achieved using a range of catalysts.[1] Amongst the best catalysts for these reactions are ruthenium complexes developed by Noyori[2] and Knochel.[3]

There has been considerable interest in the development of water-soluble ligands,[4] which allow metal catalysed reactions to take place in water,[5] other polar solvents, biphasic systems[6] and in supported polar phase catalysis.[7] We are interested in preparing water-soluble ligands, which would be effective in the enantioselective transfer hydrogenation of ketones. In this Letter, we report the successful synthesis of ligands **1**, **2** and **3** and their use in asymmetric catalysis.

2. Results and discussion

Ligand **1** was prepared as shown in Scheme 1. Sulfanilic acid **4** was first converted to the sodium salt of 4,4-dithiobisbenzenesulfonic acid **5** using a procedure previously described by Smith et al.[8] via diazotisation followed by quenching with disodium disulfide. The conversion of compound **5** into bissulfochloride **6** was effected using a mixture of PCl_5 and $POCl_3$ at reflux. Addition of (1*S*,2*S*)-diphenylethylenediamine (DPEN) **7** to a solution of **6** in (10:1) dichloromethane/triethylamine gave bissulfonamide **8** in high yield. Oxidation of



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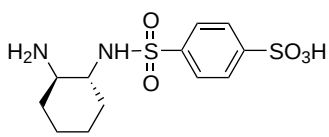

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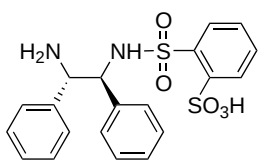

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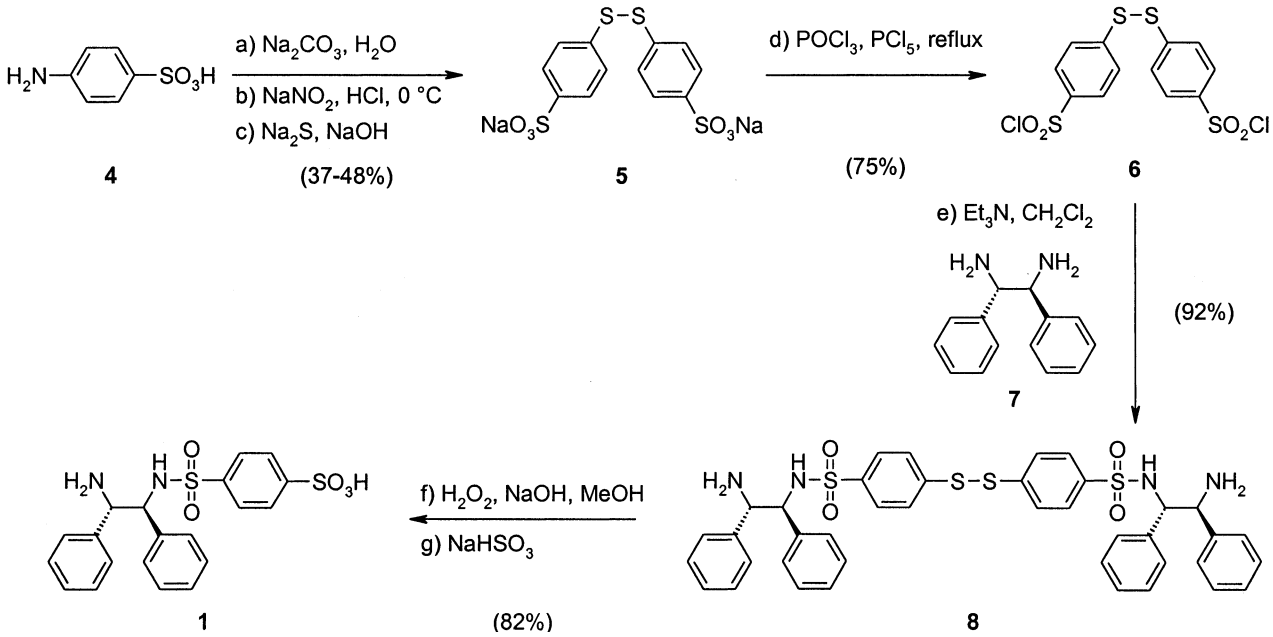
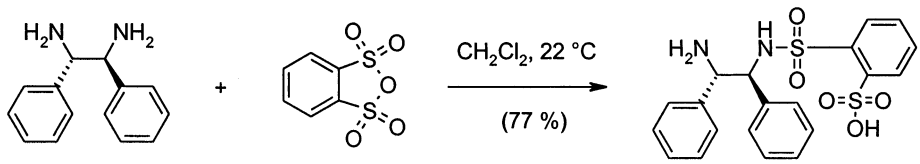
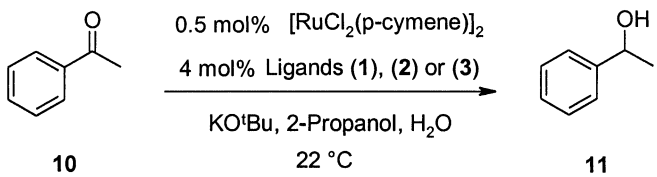


Scheme 1.



Scheme 2.

the disulfide bond with basic hydrogen peroxide produced ligand **1** in good yield. Ligand **2** was prepared in a similar manner using (1*R*,2*R*)-diaminocyclohexane in place of DPEN. As expected, ligand **2** has a higher water-solubility than ligand **1**. As a result of this a slightly lower yield was isolated.



Scheme 3.

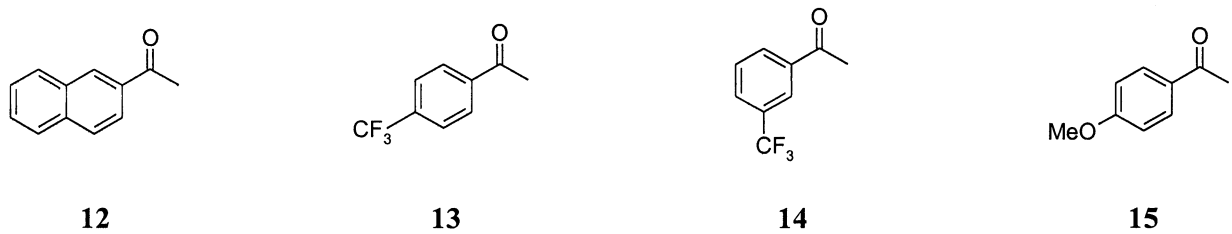


Table 1. Asymmetric transfer hydrogenation of aromatic ketones catalysed by polar ruthenium complexes

Ketone	Ligand	Reaction time (h)	Conversion (%)	Enantiomeric excess (%)	Configuration
10	**1**	48	96	94	*S*
10	**2**	48	91	88	*R*
10	**3**	48	11	91	*S*
12	**1**	72	94	95	*S*
12	**2**	48	87	90	*R*
13	**1**	4	100	81	*S*
13	**2**	4	100	88	*R*
14	**1**	24	90	87	*S*
14	**2**	24	91	81	*R*
15	**1**	42	31	91	*S*
15	**2**	42	35	83	*R*

Ligand **3** was prepared in one-step by the reaction of (1*S*,2*S*)-diphenylethylenediamine **7** with benzene-1,2-disulfonic acid anhydride[9] **9** as shown in Scheme 2.

The water-soluble amino sulfonic acid ligands **1**, **2** and **3** were tested in the ruthenium catalysed transfer hydrogenation using 2-propanol as the source of hydrogen. The enantiomerically pure ruthenium catalyst was prepared by reacting $[RuCl_2(p\text{-cymene})]_2$ with the required ligand in the presence of base at 40°C. Under standard conditions,[10] acetophenone **10** was converted into phenethyl alcohol **11** (Scheme 3). The aromatic ketones **12**, **13**, **14** and **15** were also reduced to the corresponding alcohols under identical conditions (Table 1).

Preliminary results indicate that ruthenium ligand **1** systems give rise to a higher enantioselectivity, whilst ruthenium ligand **2** systems demonstrate higher activity. As yet, little work has been carried out using ligand **3**; however, crystalline transition metal complexes of this ligand have been isolated and characterised by X-ray crystallography. As expected, electron deficient ketones **13** and **14** were reduced more rapidly than the electron rich ketone **15**.

In summary, the preparation of three new water-soluble ligands has been achieved. Initial experiments demonstrate that these function are effective chiral ligands in the reduction of various aromatic ketones under transfer hydrogenation conditions. It is anticipated that these ligands will enable the development of biphasic systems and ultimately, supported liquid phase catalysts. Our attention will now turn to this chemistry and results will be reported in due course.

Acknowledgements

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