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New chiral *N*-(*N*,*N*-dialkylamino)sulfamoyl-1,2-diamine ligands for highly enantioselective transfer hydrogenation of ketones

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Abstract—Chiral Ru(II) and Rh(III) complexes of *N*-(*N*,*N*-dialkylamino)sulfamoyl-1,2-diamine catalyze the transfer hydrogenation of various classes of aromatic ketones with high activity and excellent enantioselectivity.

1. Introduction

The search for economic industrial routes towards the preparation of enantiomerically pure alcohols still continues owing to their use in the production of pharmaceuticals and agrochemicals. A direct access to single enantiomer alcohols via catalytic reduction of ketones appears to be the most attractive, and various methods have been introduced.[1–3] Transfer hydrogenation with propan-2-ol or HCO_2H–Et_3N azeotrope is a very convenient process eliminating high hydrogen pressure or the need for hazardous reducing reagents.[4] Amongst some notable achievements for the reduction of aromatic ketones, Noyori et al. chiral Ru(II)-*N*-tosyl-1,2-diphenylethylenediamine catalyst (Ru(II)-Ts-DPEN) displays high enantioselectivity.[5] The reduction takes place through a pericyclic mechanism involving a Ru hydride.[6]

In our quest to optimize the Ru(II)-TsDPEN system for the reduction of various classes of ketones, we thought to modify the sulfonamide residue maintaining the NH_2 terminus unchanged. As a matter of fact, the polystyrene supported Ru(II)-TsDPEN of Bayston et al.[7] and the Ru(II)-*N*-perfluorosulfonyl-DPEN of Mioskowski et al.[8] showed in some cases higher enantioselectivities.

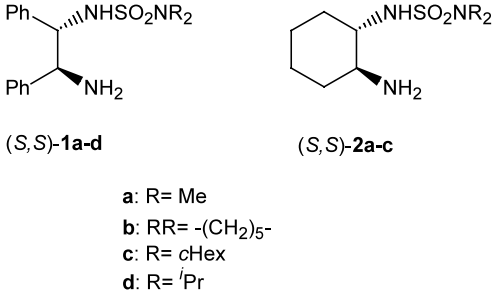
Various RSO_2-DPEN ligands for transfer hydrogenation were already prepared[5,8,9] with R = Ar, CF_3, R_F, but to our knowledge, R'_2N ligands have not been mentioned.

Herein, we disclose the preparation of new *N*-(*N*,*N*-dialkylamino)sulfamoyl-1,2-diamine type ligands and their application in Ru(II) and Rh(III)-catalysed asymmetric transfer hydrogenation of aromatic ketones.

2. Results and discussion

We prepared two series of *N*-(*N*,*N*-dialkylamino)sulfamoyl-1,2-diamine ligands **1a**–**d** and **2a**–**c** by reacting a dialkylsulfamoylchloride with DPEN and *trans*-1,2-diaminocyclohexane (CYDA), respectively (Scheme 1).

Their Ru(II) and Rh(III) complexes were prepared and tested against various models of aromatic ketones[10] under transfer hydrogenation conditions at 25°C using



(*S*,*S*)-**1a-d** (*S*,*S*)-**2a-c**

a: R= Me
b: RR= -$(CH_2)_5$-
c: R= *c*Hex
d: R= ^{i}Pr

Scheme 1. *N*-(*N*,*N*-Dialkylamino)sulfamoyl-1,2-diamine ligands.

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HCO_2H–Et_3N azeotrope (Table 1). The metal complexes were prepared by heating the metal precursor with the ligand (1.2 equiv. to the metal) at 80°C in the reaction solvent. Enantioselectivity and conversion were better in highly polar solvents such as DMF, DMA, NMP, 1,3-dimethyl-2-imidazolidinone, TMU compared to MeCN, CH_2Cl_2 and toluene. Increasing the temperature from rt to 50°C accelerated the reduction but gave lower enantioselectivity, while at 0°C prolonged reaction time was required and resulted in 1–2% higher ee.

Ligand **1c** gave up to 85% ee and 100% conversion for the reduction of methylbenzoylformate. In the case of ethyl benzoylacetate, ligand **1a** led to 98% ee and 100% conversion. Reduction of 2-carbomethoxy-1-indanone using the ligand **1a** led to the *anti*-product (>99% de) in >99% ee and 87% conversion. In the case of acetophenone, the reduction with the various ligands resulted in up to 96% ee but with moderate conversions.

The analysis of the above data with the different sulfamoyldiamine ligands does not show a specific trend in relation to the dialkylsulfamoyl residue bulkiness. However, ligands with the DPEN skeleton gave better results than the ones with CYDA ligands and the Ru complexes were found to give better results than the Rh complexes.

In summary, this work presents new chiral *N*-(*N*,*N*-dialkylamino)sulfamoyl - 1,2 - diphenylethylenediamine and *N*-(*N*,*N*-dialkylamino)sulfamoyl-1,2-cyclohexyldiamine ligands and their use in transfer hydrogenation of various classes of aryl ketones. In particular, the chiral Ru complex of *N*-(*N*,*N*-dimethylamino)-sulfamoyl-1,2-diphenylethyl-enediamine **1a** is an effective catalyst for the transfer hydrogenation of methylbenzoylformate, ethyl benzoylacetate and 2-carbomethoxy-1-indanone using HCO_2H–Et_3N azeotrope.

3. Experimental

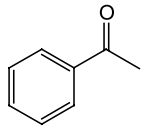
3.1. General

(1*S*,2*S*)-Diphenylethylenediamine, (1*S*,2*S*)-diaminocyclohexane and dimethylsulfamoylchloride are commercially available; *N*-chlorosulfonylpiperidine was prepared according to Denivelle;[11] dicyclohexyl and diisopropylsulfamoylchlorides were prepared according to Nakashima et al.[12] ^{1}H NMR (300 MHz, internal Me_4Si) spectra were recorded using a Varian VXR-300 instrument for solutions in $CDCl_3$.

3.2. General procedure for the preparation of ligands 1a–d and 2a–c

To a cold (0°C) solution of (1*S*,2*S*)-diphenylethylenediamine (212 mg, 1.0 mmol) in DCM (25 mL) was added dropwise dialkylsulfamoyl chloride (1.0 mmol). The mixture was stirred at rt overnight, washed with satd. aq. Na_2CO_3 (2×10 mL) and the organic layer dried over Na_2SO_4. The concentrated residue was

Table 1. Asymmetric transfer hydrogenation of various classes of ketones[a]



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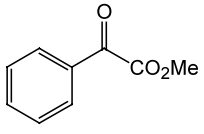

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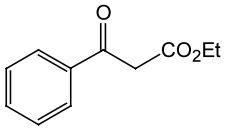

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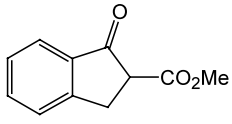

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Ketone	Ligand	Metal precursor	S/C ratio	Time (h)	Conv. (%)[b]	E.e. (%)[b]	Conf.[c]
3	**1a**	$[RuCl_2(cym)]_2$	100	48	67	96	*S*
3	**1a**	$[RuCl_2(cym)]_2$	100	72	80	96	*S*
3	**1b**	$[RuCl_2(cym)]_2$	100	24	51	95	*S*
3	**2a**	$[RuCl_2(cym)]_2$	100	24	25	94	*S*
4	**1a**	$[RuCl_2(cym)]_2$	200	2	100	72	*R*
4	**1a**	$[RuCl_2(cym)]_2$	200[d]	2	100	81	*R*
4	**1a**	$[RhCl_2Cp^*]_2$	200	1	100	72	*R*
4	**1c**	$[RuCl_2(cym)]_2$	200	3	100	85	*R*
4	**2a**	$[RuCl_2(C_6H_6)]_2$	200	5	100	33	*R*
5	**1a**	$[RuCl_2(cym)]_2$	200	24	100	98	*S*
5	**1a**	$[RhCl_2Cp^*]_2$	200	24	70	79	*S*
5	**1b**	$[RuCl_2(C_6H_6)]_2$	200	24	100	96	*S*
5	**1d**	$[RuCl_2(cym)]_2$	200	24	24	65	*S*
5	**2a**	$[RuCl_2(cym)]_2$	200	24	75	80	*S*
6	**1a**	$[RuCl_2(C_6H_6)]_2$	200	24	85	95	*anti*
6	**1a**	$[RuCl_2(cym)]_2$	200	48	87	>99[e]	*anti*

[a] Reactions were carried out with HCO_2H/Et_3N azeotrope in DMF at 25°C, unless otherwise noted.
[b] Determined by GC analysis using a Chirasil-DEX CB (25 m).
[c] Determined by comparison with available references.
[d] Reaction in TMU.
[e] >99% de.

purified by chromatography (DCM/EtOAc, 2:1) and the product was recrystallized from $^{i}Pr_2O$.

Similar reaction conditions were adopted for (1*S*,2*S*)-diaminocyclohexane (500 mg, 4.38 mmol) and the concentrated residue was purified by chromatography (DCM/^{i}PrOH/Et_3N, 6:1:0.01) and recrystallized from $^{i}Pr_2O$.

3.2.1. (1*S*,2*S*)-*N*-(*N*,*N*-Dimethylsulfamoyl)-1,2-diphenylethylenediamine, 1a. White powder (166 mg, 52%). Mp 94–96°C. $[\alpha]_{546}^{20}=-12.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 2.33 (s, 6H, 2×CH_3), 4.15 (d, 1H, C<u>H</u>NH_2; *J* 5.9 Hz), 4.44 (d, 1H, C<u>H</u>NH; *J* 5.9 Hz), 7.21–7.33 (m, 10H, 2×Ph). MS (FAB) *m*/*z* 320 (M+H)$^+$.

3.2.2. (1*S*,2*S*)-*N*-(Piperidyl-*N*-sulfonyl)-1,2-diphenylethylenediamine, 1b. White powder (197 mg, 55%). Mp 136–138°C. $[\alpha]_{546}^{20}=-5.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.24 (m, 6H, C<u>H</u>$_2$C<u>H</u>$_2$NC<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 2.70 (m, 4H, CH_2NCH_2), 4.16 (d, 1H, C<u>H</u>NH_2; *J* 5.7 Hz), 4.43 (d, 1H, C<u>H</u>NH; *J* 5.7 Hz), 7.19–7.35 (m, 10H, 2×Ph). MS (FAB) *m*/*z* 360 (M+H)$^+$.

3.2.3. (1*S*,2*S*)-*N*-(*N*,*N*-Dicyclohexylsulfamoyl)-1,2-diphenylethylenediamine, 1c. White powder (160 mg, 35%). Mp 145–147°C. $[\alpha]_{546}^{20}=-5.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 0.95–1.29 and 1.44–1.72 (2m, 20H, 2×C<u>H</u>$_2$C<u>H</u>$_2$CH(C<u>H</u>$_2$)$_3$), 2.96 (m, 2H, 2×C<u>H</u>C<u>H</u>$_2$), 4.06 (d, 1H, C<u>H</u>NH_2; *J* 6.0 Hz), 4.40 ('br t', 1H, C<u>H</u>NH; *J* 5.1 Hz), 5.58 (br d, 1H, CHN<u>H</u>; *J* 5.7 Hz), 7.10–7.31 (m, 10H, 2×Ph). MS (FAB) *m*/*z* 456 (M+H)$^+$.

3.2.4. (1*S*,2*S*)-*N*-(*N*,*N*-Diisopropylsulfamoyl)-1,2-diphenylethylenediamine, 1d. White powder (184 mg, 49%). Mp 112–114°C. $[\alpha]_{546}^{20}=-3.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 0.97 and 1.11 (2d, 12H, 2×CH(C<u>H</u>$_3$)$_2$; *J* 6.9 Hz), 3.40 (hept., 2H, 2×C<u>H</u>(CH$_3$)$_2$), 4.10 (d, 1H, C<u>H</u>NH_2; *J* 5.4 Hz), 4.39 ('t', 1H, C<u>H</u>NH; *J* 5.7 Hz), 5.65 (br d, 1H, CHN<u>H</u>; *J* 6.3 Hz), 7.16–7.32 (m, 10H, 2×Ph). MS (FAB) *m*/*z* 376 (M+H)$^+$.

3.2.5. (1*S*,2*S*)-*N*-(*N*,*N*-Dimethylsulfamoyl)-1,2-cyclohexanediamine, 2a. Light yellowish powder (269 mg, 42%). Mp 97–98°C. $[\alpha]_{546}^{20}=+55.1$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.09–1.33 (m, 4H), 1.71 (m, 2H), 1.95 (m, 1H), 2.23 (m, 1H), 2.37 (dt, 1H, C<u>H</u>NH_2; *J* 10.5, 3.6 Hz), 2.83 (m, 7H, 2×CH_3, C<u>H</u>NH). MS (FAB) *m*/*z* 222 (M+H)$^+$.

3.2.6. (1*S*,2*S*)-*N*-(Piperidyl-*N*-sulfonyl)-1,2-cyclohexanediamine, 2b. White powder (356 mg, 47%). Mp 85–87°C. $[\alpha]_{546}^{20}=+43.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.09–1.32, 1.49–1.78 (2m, 12H), 1.96 (m, 1H), 2.22 (m, 1H), 2.37 (dt, 1H, C<u>H</u>NH_2; *J* 10.3, 3.9 Hz), 2.80 (dt, 1H, C<u>H</u>NH; *J* 10.3, 3.9 Hz), 3.20 (t, 4H, C<u>H</u>$_2$NC<u>H</u>$_2$; *J* 5.4 Hz). MS (FAB) *m*/*z* 262 (M+H)$^+$.

3.2.7. (1*S*,2*S*)-*N*-(*N*,*N*-Dicyclohexylsulfamoyl)-1,2-cyclohexanediamine, 2c. White powder (674 mg, 65%). Mp 151–153°C. $[\alpha]_{546}^{20}=+37.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.00–1.96 (m, 27H), 2.25–2.39 (m, 2H), 2.78 (m, 1H, C<u>H</u>NH), 3.20 (m, 2H, 2×NCH), 4.49 (br d, 1H, NH, *J* 5.1 Hz). MS (FAB) *m*/*z* 358 (M+H)$^+$.

3.3. General procedure for asymmetric transfer hydrogenation

A mixture of the metal precursor ([$RuCl_2$(η^6-arene)]$_2$ or [$RhCl_2$Cp*]$_2$) and the chiral ligand (1.2 equiv. to the metal atom) was heated in DMF (0.5 mL) at 80°C for 20 min. The solution was cooled to 25°C and HCO_2H–Et_3N, 5:2 (0.44 g, 5 mmol HCO_2H) and the substrate (1 mmol) were subsequently added. The reaction mixture was stirred at 25°C for the time indicated in Table 1. Aliquots were diluted with $^{i}Pr_2O$ and analyzed by chiral GC on Chirasil-DEX CB (25 m) column.

3.3.1. 1-Phenylethanol. GC, 120°C: 9.0 min (*R*), 9.6 min (*S*). The stereochemistry was assigned by comparison with commercially available (*S*)-1-phenylethanol (Aldrich).

3.3.2. Methyl mandelate. GC, 135°C: 12.0 min (*R*), 12.5 min (*S*). The stereochemistry was assigned by comparison with commercially available methyl (*R*)-mandelate (Aldrich).

3.3.3. Ethyl 3-hydroxy-3-phenylpropanoate. GC, 140°C: 22.1 min (*R*), 23.0 min (*S*). The stereochemistry was assigned by comparing the specific rotation value with the literature data.[13]

3.3.4. 2-Carbomethoxy-1-indanol. GC, 160°C: 14.5 min and 14.8 min (*anti*), 17.9 and 19.2 (*syn*). A mixture of racemic *anti*- and *syn*-diastereomers was obtained by $NaBH_4$ reduction of 2-carbomethoxy-1-indanone.

Acknowledgements

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9. We have prepared various $ArSO_2$-DPEN ligands and their results will be communicated in due course.
10. The best results for transfer hydrogenation using Ru(II)-TsDPEN:
-with acetophenone:[5b] 98% ee, >99% conversion;
-with methyl benzoylformate: 63% ee, >99% conversion (this work);
-with ethyl benzoylacetate:[13] 94% ee, >99% conversion;
-with 2-carbomethoxy-1-indanone: >99% ee, >99% de, 48% conversion after 48 h (this work).
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