Article

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N-N Torsion Angle in BINAM-Mono and Bis(Sulfonamide) Ligands and its Effect on the Catalytic Asymmetric Transfer Hydrogenation (ATH) of Aromatic Ketones

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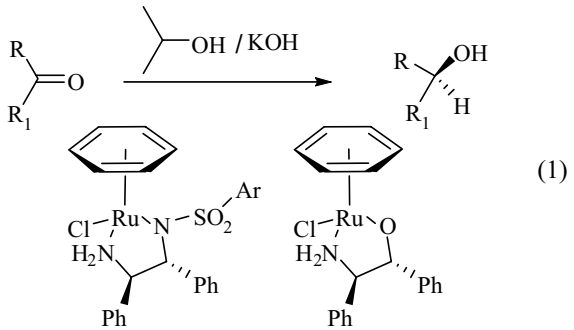
Resumen. Los ligandos **L1** y **L2** se sintetizaron a partir de (*R*)-(+)-1,1'-binaftil-2,2'-diamina comercialmente disponible y se probaron con $Rh^{III}Cp^*$ como catalizadores en la reducción asimétrica por transferencia de hidrógeno de cetonas aromáticas en formiato de sodio acuoso como la fuente de hidruro. Los resultados fueron comparados con los de los ligandos derivados de 1,2-, 1,4-, y 1,6-diaminas, y correlacionados con el tamaño del anillo quelato metal-ligando y los ángulos de torsión *N-N* determinados por cálculos teóricos.
Palabras clave: Transferencia de hidrógeno asimétrica, ligandos monosulfonamida, complejos $Rh^{III}Cp^*$, medio acuoso.

Abstract. Ligands **L1** and **L2** were synthesized from commercially available (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine and tested with $Rh^{III}Cp^*$ as catalysts in the asymmetric transfer hydrogenation of aromatic ketones in aqueous sodium formate. The results were compared with ligands derived from 1,2-, 1,4-, and 1,6-diamines, and correlated to the metal chelate ring size and the *N-N* torsion angles determined by theoretical calculations.
Keywords: Asymmetric transfer hydrogenation, monosulfonamide ligands, $Rh^{III}Cp^*$ complexes, aqueous media.

Introduction

Chiral secondary alcohols are valuable synthetic intermediates in the pharmaceutical, agrochemical, and flavor industries [1-3]. Catalytic reduction of ketones to single enantiomers appears to be the most attractive, and various methods have been introduced. Asymmetric transfer hydrogenation (ATH) with propan-2-ol, HCOOH-NEt_3 azeotrope and aqueous sodium formate as the hydride source is a very convenient process, eliminating the use of molecular hydrogen under pressure [4, 5]. The commonly used metals are Ru(II) and Rh(III) as complexes of chiral β-amino alcohols or 1,2-diamines as catalysts in this process (Equation 1) [4, 5].

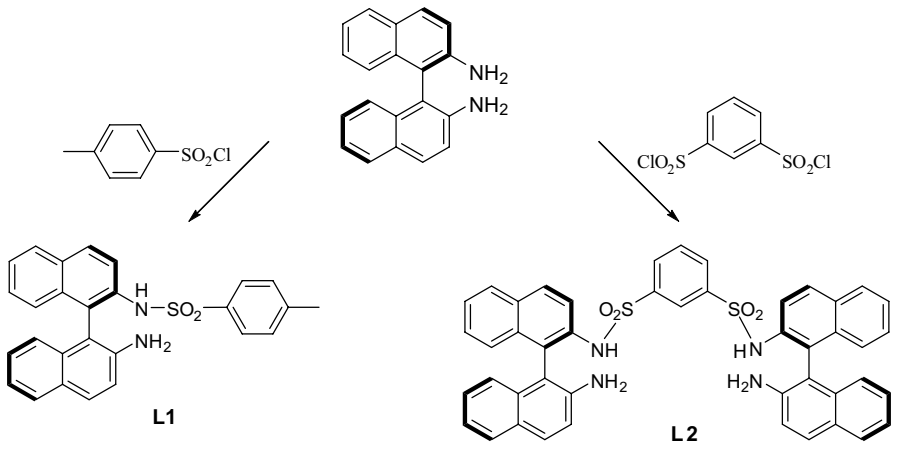


(1)

Although a variety of structurally different β-amino alcohols have been used in this reaction, the diamines gave the best results and have been confined to 1,2-diphenyl ethane (DPEN) and cyclohexane-1,2-diamine systems [4, 5]. These diamine-metal complexes have resulted in high enantioselectivity and yield of the alcohol. This high efficiency is attributed partly to the rigid five member ring formed between the chiral ligand and the metal ion, which makes the metal center itself chiral. Based on the success of 1,2-diamines as ligands, we set out exploring for other systems such as chiral 1,4-diamine ligands for possible application with Ru(II) and Rh(III) complexes in the ATH of ketones. Using ligands, other than 1,2-diamine, raised the obvious question of the effect of the metal chelate ring size on the enantioselectivity and yield in the ATH reduction of ketones. In order to test the role of the metal chelate ring size on enantioselectivity and yield in the ATH of ketones, we report herein the use of axially chiral compounds with biaryl backbones: (*R*)-1,1'-binaphthyl-2,2'-diamine-monosulfonamide (**L1**) and C_2 symmetric 1,1'-binaphthyl-2,2'-diamine-bis(sulfonamide) (**L2**) in the ATH of ketones. Commercially available (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine was reacted with the corresponding sulfonyl chloride using a previously reported method to give ligands **L1** and **L2** (Scheme 1) [5k], which were then tested in the ATH of aromatic ketones.

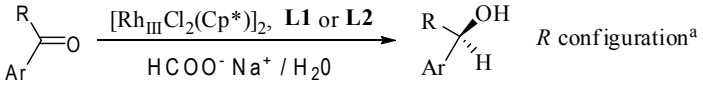
Results and discussion

Results obtained with the complex **L1**-$Rh^{III}Cp^*$ showed moderate enantioselectivities (52-77%) and yields (45-85%) in the ATH of ketones over a period of 15 h. Complex **L2**-$Rh^{III}Cp^*$ gave similar enantioselectivities (56-84%) and slightly better yields (70-80%, except for 2-acetonaphthalene) under identical reaction conditions (Table 1). The slightly better overall results may be due to the availability of two metallic centers in the catalyst.

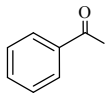
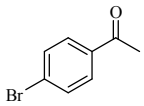
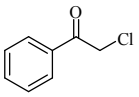
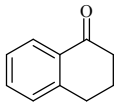
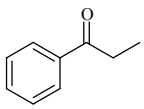
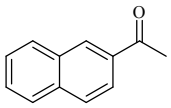
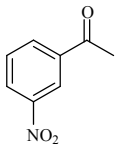


Scheme 1.

Table 1. Reduction of prochiral ketones by ATH with $[Rh^{III}Cp^*Cl_2]_2$ and chiral ligands **L1** and **L2** in aqueous sodium formate.



R configuration[a]

Ketone	L1		L2	
	Yield (%)[b]	ee (%)[c]	Yield(%)[b]	ee (%)[c]
	56	77	76	84
	59	52	74	70
	85	56	80	56
	68	70	74	70
	66	62	70	69
	45	52	21	51
	65	55	75	72

[a] Absolute configurations are all *R*, assigned by comparing optical rotations with literature values, [6] except for 2-chloroacetophenone [7] (compared with a chloro alcohol sample from Aldrich Sigma, rotation (–) for configuration (*R*), based on rotation (+) the configuration (*S*) is assigned).

[b] Reaction conditions: 15 h at 40 °C. S/C = 300.

[c] Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.

Reduction of acetophenone using the biphenyl ligand **L3** [8] (Figure 1), gave the alcohol in 93% yield and 64% enantioselectivity, whereas the reduction of *p*-bromoacetophenone gave the alcohol in 92% yield and 69% enantioselectivity. These results are comparable with those obtained with ligands **L1** and **L2**, except for the yields, suggesting the additional fused benzene ring system probably imposes some steric or electronic hindrance in the transition state. However ligand **L4** [9] with Rh(III) and acetophenone gave 20% yield and 2% enantioselectivity, while Noyori's monosulfonamide ligand **L5** [4b] gave >99% yield and 95% enantioselectivity. These results clearly suggest that increasing the chelate ring size from the rigid five member with **L5,** to conformationally flexible seven member with **L1**, **L2** and **L3,** and nine member with **L4** chelate ring systems (Figure 2) tends to lower the yields and enantioselectivities of the final alcohol.

Computational analysis

To support the hypothesis that the chelate ring size has an effect on yields and enantioselectivities obtained for the final alcohol and steric repulsion between the adjoining ring systems would influence the N-Rh bonds, calculations were carried out at the B3LYP density functional level of theory [11], using a cc-pVDZ basis set [12] for the main group elements and the CEP-121G basis and effective core potential of Stevens *et al*. for the metal [13]. This combination of method and basis sets has proven effective in reproducing the geometries of other organometallic complexes [14]. Theoretical calculations for the $N(C\text{-}C)_nN$ torsion angles of the two binapthayl and biphenyl rings, which can be related to the efficiency with which the ligand coordinates to the metal centre, are shown in Figure 3.

The large torsion angle of 86.6° for BINAM (as in **L1**) may not allow strong coordination to the rhodium centre, even though it involves a seven member ring, compared to cyclohexane-1,2-diamine which forms a rigid five member ring (as in **L5**). To test this hypothesis, we added monosulfonamide of cyclohexane-1,2-diamine ligand (**L5**) to the catalytic reaction (Equation 2), which led to acceleration of the reaction leading to enantioselectivity >92% and yield >95% in 1h with the elimination of BINAM. This observation is further supported by a recent report by Faller and Fontaine who have shown the displacement of BINAM by DPEN from a ruthenium complex [10].

The results in Table 2 demonstrate that, unlike **L5**, ligands **L1** and **L3** must deform substantially in order to attain M-N separations as low as 2.2 Å. Ligand **L3** accomplishes this with a

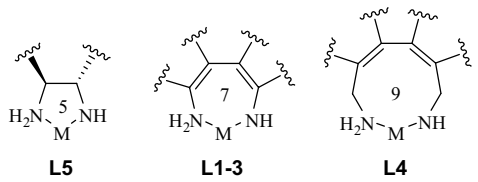
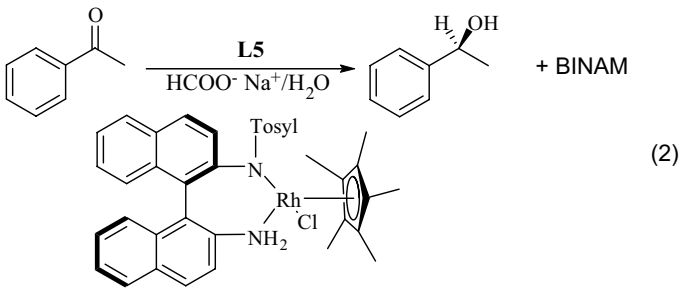


Fig. 2. Metal chelate ring size.

L1 = 86.6°, **L3** = 62.2°, **L5** = 53.9°

Fig. 3. Calculated torsion angles of the free ligands **L1**, **L3** and **L5**.



(2)

torsion of the tosyl group, reducing the N-N separation by 0.1 Å and arriving at Rh-N bond distances 0.01 to 0.06 Å larger than those found with **L5**. For **L1**, the deformation is more severe, requiring a torsion of 20° in the NCCN dihedral and arriving at Rh-N distances 0.06 and 0.08 Å longer than those with cyclohexane. Therefore, although the complexes are stable, the ligands are under considerable strain and easily displaced.

If we attempt to force the complexed **L1** to adopt a smaller dihedral angle, the energy is predicted to climb rapidly at angles below 60 degrees. The energy as a function of this dihedral angle was evaluated by a relaxed potential energy scan, fixing the dihedral angle to different values and optimizing all the other parameters. The results are shown in Figure 4. This shows that bonding to the metal is insufficient to overcome the strain induced by trying to make the ligand more planar.

Conclusion

We have synthesized mono- and C_2-symmetric bis(sulfonamide) ligands from (*R*)-BINAM and used them in the ATH of aro-

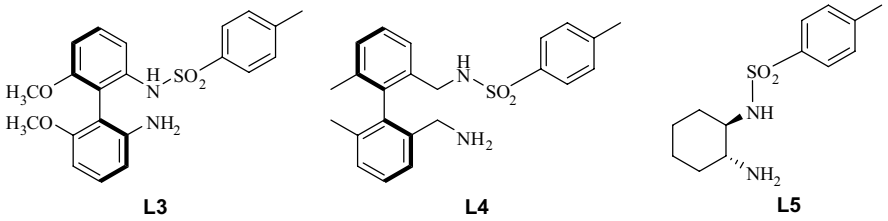


Fig. 1. Ligands **L3-5**.

Table 2. Calculated bond lengths and torsion angles in free and complexed ligands **L1**, **L3** and **L5**.

Ligand	Uncomplexed		Complexed			
	N---N distance	$N(C\text{-}C)_nN$ torsion angle	N---N distance	$N(C\text{-}C)_nN$ torsion angle	Rh–NH_2 bond length	Rh–N-Tos bond length
L1	3.65	86.6	2.95	66.5	2.23	2.23
L3	3.03	62.2	2.94	64.2	2.21	2.18

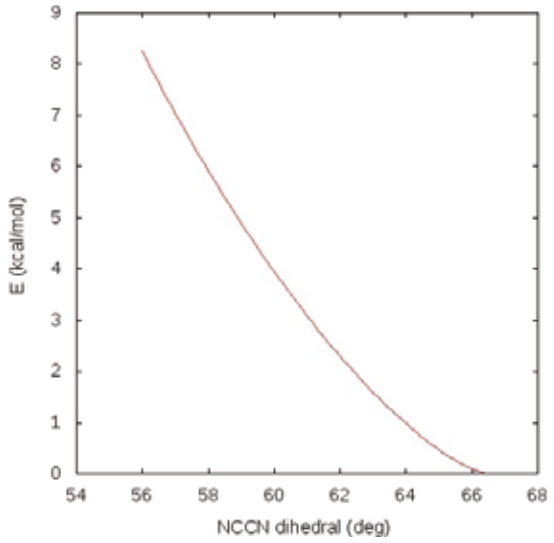


Fig. 4. Relaxed B3LYP/cc-pVDZ,CEP-121G potential energy scan along the NCCN dihedral angle of **L1**.

matic ketones. Good yields and moderate enantioselectivities of the chiral secondary alcohols were obtained. Comparing these results with ligands **L3**, **L4** and **L5**, suggests that a large $N(C\text{-}C)_nN$ torsion angle leads to lower yields and enantioselectivities, probably due to conformational ring flexibility. Our experimental results are supported by theoretical calculations. In summary, the rigid five member chelate ring formed by **L5**, with a torsion angle of 47.6° appears to offer the best performance in the ATH of aromatic ketones.

Experimental

Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Perkin-Elmer FT-IR 1600 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Nova 500 MHz spectrometer. Rotation was measured with a Perkin-Elmer 343 Polarimeter. Elemental analyses were conducted by NuMega San Diego.

***N*-(2'-Amino-[1,1']binaphthalenyl-2yl)-4-methyl-benzenesulfonamide (L1).** *p*-Toluenesulfonyl chloride (420 mg, 2.2 mmol) in 5 mL of CH_2Cl_2 was added drop wise to a mixture of (1*R*,2*R*)-2,2'-diamino-1,1'-binaphthalene (569 mg, 2.0 mmol) and pyridine (2.0 mL, 24.0 mmol) in 15 mL CH_2Cl_2. The reaction mixture was stirred for 24 h at room temperature and then purified by preparative TLC with petroleum ether/ethyl acetate 6:1 to afford a white crystalline solid: mp 169-170 °C; 84% yield; $[\alpha]_D$ $+8^0$ (c 0.72, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3365, 3051, 1621, 1595, 1403, 1316, 1164, 1091, 977, 814, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.11 (1H, d, *J* = 9.0 Hz), 7.93 (1H, d, *J* = 9.0 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 9.0 Hz), 7.74 (1H, d, *J* = 8.0 Hz), 7.35-7.42 (3H, m), 7.17-7.22 (2H, m .91-7.06 (5H, m), 6.67 (1H, s, NH), 6.40 (1H, d, *J* = 8.5 Hz), 3.37 (2H, brs, NH_2), 2.29 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.6, 142.7, 135.8, 134.3, 133.7, 133.6, 132.7, 130.7, 129.7, 129.4, 128.2, 128.1, 127.1, 127.0, 125.7, 125.4, 123.3, 122.5, 121.6, 119.5, 118.0, 109.6, 21.5; FABMS *m/z* (rel. int.): 439 $[M+H]^+$ (100). C, 73.98%; H, 5.05 %, calcd for $C_{27}H_{22}N_2O_2S$, C 73.95 %, H 5.06%.

Benzene-1,3-disulfonic acid bis-[(2'-amino-[1,1']-binapthalenyl-2yl)-amide] (L2). 1,3-Benzenedisulfonyl chloride (0.274 g, 1.0 mmol) in 5 mL of CH_2Cl_2 was added drop wise to a mixture of (1*R*,2*R*)-2,2'-diamino-1,1'-binaphthalene (569 mg, 2.0 mmol) and pyridine (2.0 mL, 24.0 mmol) in 15 mL CH_2Cl_2. The reaction mixture was stirred for 24 h at room temperature and then purified by preparative TLC with petroleum ether/ethyl acetate 6:1 to afford a white solid: mp 202 °C; 80% yield; [α] $+20^0$ (c 0.26, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3451, 3379, 1620, 1401, 1177, 816, 573 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.95 (2H, d, *J* = 9.0 Hz), 7.89-7.71 (10H, m), 7.39-6.95 (14H, m), 6.81 (2H, brs, NH), 6.41 (2H, d, *J* = 8.4 Hz), 3.72 (4H, brs, NH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.3, 140.3, 139.2, 133.4, 132.6, 131.6, 130.9, 130.8, 130.6, 129.9, 129.3, 129.0, 128.3-128.0, 127.5, 127.3, 127.2, 125.9-125.5, 123.1, 122.9, 122.8, 120.0, 118.1; FABMS *m/z* (rel int.) 771 $[M+H]^+$ (100), 683 (5), 491 (15), 435 (10), 271 (25). Anal. C, 71.67%, H, 4.45%, calcd for $C_{46}H_{34}N_4O_4S_2$, C 71.72%, H 4.50%.

General Procedure for the Asymmetric Transfer Hydrogenation of Ketones in Water

A mixture of the metal precursor $[Rh^{III}Cl_2Cp^*]_2$ (0.0039 mmol) and the chiral ligands **L1**, **L3**-**L5** (0.0039 mmol) or ligand **L2** (0.0078 mmol) was heated in water (2 mL) at 40 °C for 1 h in air without a base. HCOONa (5.70 mmol) and the substrate (1.17 mmol) were subsequently added. The reaction mixture was stirred at 40 °C for 15 h for each individual reaction. The reaction mixture was extracted with ether (3 × 10 mL). The ether layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue containing the alcohol was acetylated using acetic anhydride and 4-DMPA (4-*N*,*N*-dimethylamino-pyridine).

Acknowledgements

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