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Rhodium complex with Unsymmetrical VicinalDiamine Ligand: Excellent Catalyst for Asymmetric Transfer Hydrogenation of Ketones

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Abstract. New unsymmetrical vicinal diamine ligands with systematic variation in regio and stereo positions in amine and sulphonamide groups were synthesized from cheap starting material such as norephedrine. Catalytic Asymmetric Transfer Hydrogenation (ATH) of aromatic alkyl ketones has been investigated using transition metal complexes and new derivatives of monotosylated unsymmetrical vicinal diamine ligands using sodium formate as the hydrogen source, in water and methanol medium. Chiral secondary alcohols were obtained with excellent enantioselectivity (>95% ee) and conversions of ketones (>95%) with $[Rh(Cp^*)Cl_2]_2$ and ligand 4 as a catalyst. Enantioselectivity was found to be slightly higher with the use of methanol as a solvent for ATH of ketones with sodium formate as the hydrogen source compared to water as a solvent and was found to be consistent with all the ketones investigated. The reaction mixture is homogeneous in methanol unlike in water, where substrate and product are insoluble in water and form separate phases, sodium formate being soluble in water. The activity and enantioselectivity obtained for ATH of ketones using $[Rh(Cp^*)Cl_2]_2$ and unsymmetrical vicinal diamine ligand as catalyst was comparable with the C2 symmetric benchmark ligands like TsDPEN (1R,2R)-N-(*p*-tolylsulfonyl)-1,2-diphenylethylene-diamine),and TsCYDN (1R,2R)-N-(*p*-tolylsulfonyl)-,1,2-cyclohexyl,diamine) under similar reaction conditions. To the best of our knowledge, this is first example on the ATH of ketones with good activity and high enantioselectivity with $[Rh(Cp^*)Cl_2]_2$ and unsymmetrical vicinal diamine ligands as catalyst systems.

Keywords: Asymmetric Transfer Hydrogenation, Rhodium, Unsymmetrical Vicinal Diamine, ketones.

1. Introduction

Catalytic asymmetric transfer hydrogenation (ATH) of ketones is one of the important transformations in organic chemistry and a large number of catalytic methods are available to achieve this goal[1-4].One of the most significant breakthroughs in transfer hydrogenation was reported by Noyori et al. with the use of Ruthenium, Rhodium and Iridium complexes with chiral monoarylsulfonylated-1, 2-diamine[5-10] or β-amino alcohols[11, 12] as ligands.

Majority of work on ATH of ketones has been carried out using TsDPEN and TsCYDN (1R, 2R)-N-(*p*-tolylsulfonyl)-1,2-cyclohexyl,diamine) ligands in organic media (formic acid-triethylamine (FA/TEA) as hydrogen donor) as well as in water and under aerobic conditions (FA/TEA or sodium formate as hydrogen donors).[13-16]

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Transition metal complex/ligand combination used is important for achieving good activity and enantioselectivity in ATH of ketones[17]. Rh-complexes were found to be a better catalyst than Ru-complexes (of TsDPEN andTsCYDN ligands) in theseconditions with very high activity and enantioselectivity for various ketones.(Scheme **1).**[15,16,18]

This key development has led to intense exploration of catalyst systems with the aim of designing more efficient ligands, improving catalytic activity and broadening the scope of asymmetric transfer hydrogenation reaction. However; there are limited reports on structurally versatile monosulfonated diamine ligands. Importantly, most of these reports are restricted to modifying the substitution on either sulphonamide group or on the phenyl group without disturbing the real C2 symmetric backbone of TsDPEN or TsCYDN[7,-10] (Scheme **2a A-D**).

There are very few examples on the synthesis and use ofunsymmetrical diamine ligands with transition metal catalysts for ATH of ketones.[19-22] Wills et al.[19] synthesized new unsymmetrical monosulfonated vicinal diamines from cis 2 amino indanol (Scheme **2 b, E**) and observed good results for ligandwith syn orientation.[19]Though,it was proposed later that anti-substitution of amine and sulphonamide groups is important for activity and enantioselectivity.[20] Very recently Ming-hua-xu and co-workers[21] synthesized new analogues of unsymmetrical vicinal diamines and showed that it is essential to have one phenyl group attached to

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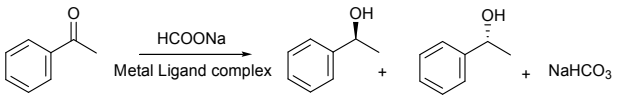
carbon bearing the sulphonamide group and a bulky substituent on the carbon bearing amine for high activity andenantioselectivity for ATH of ketones[21](Scheme **2 b, F**). Roszowski etal. synthised derivatives of unsymmetrical vicinal diamines from limonene and used in ATH of ketones with $[Ru(p\text{-cymene})Cl_2]_2$, (Scheme **2 b, G**).[22]

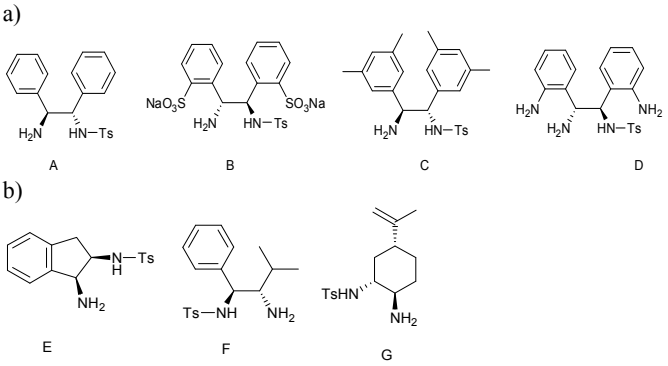
Careful observation of these resultsindicated that there is no clear view on the type of substituent and its position in the ligand and itsinfluence on the activity andenantioselectivity. Further, these reports were restrictedto the useof $[Ru(p\text{-cymene})Cl_2]_2$ as the metal complex for ATH and no other transition metal complex was explored.

With this background in mind, unsymmetrical vicinal diamine ligands starting from cheap and easily available norephedrine were prepared and tested in ATH of ketones. Diamine derivatives with different stereo and regio positions of amine and sulphonamide groups, along with different positions of phenyl and other methyl group were synthesized (Scheme **3**). For this purpose a synthesis strategy was designed and ligands were synthesized using three different reaction schemes (Schemes **4, 5** and **6**). To the best of our knowledge this is the first report on use of Rhodium complex with unsymmetrical vicinal diamine ligands for ATH of ketones with good activity and enantioselectivity.



Ligand = 1,2 Monotosylated diamines

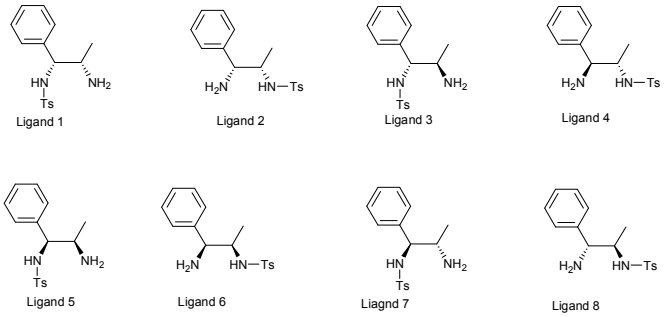
Scheme 1: **Asymmetric transfer hydrogenation of ketones using unsymmetrical vicinal diamines**



Scheme 2. Structure of Different Monotosylated vicinal diamines a) with C2 symmetry b) Unsymmetrical diamines

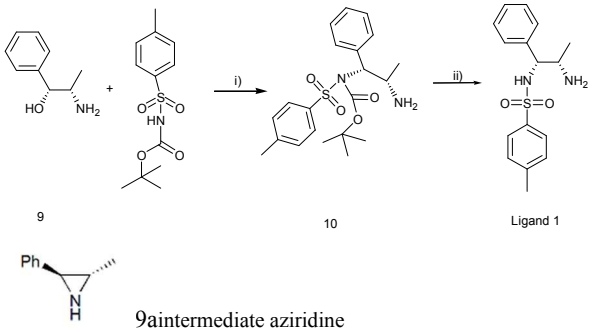
2. Results and Discussion

1R, 2S norephedrine and its enantiomer 1S, 2R norephedrine were used as key starting materials to synthesize various regio and stereo isomers (Scheme **3**) of unsymmetrical vicinal dimaine ligands. Ligand **1** was synthesized using the reaction of N-BOc (*tert*-butyloxycarbonyl) sulfonamide with 1R, 2S norephedrine under Mitsunobu conditions[23] (Scheme **4**).Intermediate aziridine (**9a**) is formed with intramolecular cyclisation and inversion at the hydroxyl carbon.The ring opening of intermediate is caused by the N-BOc sulfonamide again with inversion of configuration to get the compound **10** (efforts on the isolation of the intermediate 10 in pure form failed).



Scheme 3. Various Unsymmetrical vicinal diamine ligands synthesized.

During the isolation **10**, it was partially converted to Ligand **1**. Subsequent deprotection of BOc group in compound **10** with HCl in dioxane gave the ligand**1** with overall retention of the configuration. ^{1}H NMR spectrum showed the coupling constant of the vicinal hydrogen to be 4 Hz, indicating the sulfonamide and amine geometry to be cis with respect to each other. Similar observation with inversion of configuration at hydroxyl carbon for Mitsunobu reaction of amino alcohols and ephedrine was reported by Jules Freedman and others.[24, 25]



9aintermediate aziridine

Scheme 4: Synthesis of ligand 1
Reaction conditions: i) DEAD,(Diethyl azodicarboxylate) Triphenyl phosphine in Dichloromethane, ii) 4N HCl in Dioxane

Synthesis of ligand **2** has been carried as per the literature procedures[26, 27] (Scheme **5)** andreduction using triphenyl phosphine and water. In the first step, norephedrine (compound **9**) was tosylated using *p*-toluene sulfonyl chloride to get compound **11**. Mitsunobu reaction was carried out with compound **11** to get compound **12**. Intramolecular cyclisation occurs with inversion of configuration at the hydroxyl carbon as observed and reported in the literature.[26, 27]

Ring opening of tosylated aziridine (compound**12**) was carried out using sodium azide in a mixture of water and acetonitrile (20:80 volume ratio) to obtain compound **13** as the product.[26] The ring opening of this tosylated aziridine occurs with complete inversion at the phenyl carbon resulting in overall retention of the configuration (w.r.t starting norephedrine configuration, compound **9**).Reduction of compound **13** with triphenyl phosphine and water gave ligand **2**. The sulfonamide and amine geometry in ligands **1** and **2**is cis with respect to position of amine and sulfonamide groups.

To prepare the isomers with trans geometry, synthetic methodology as shown in Scheme **6** was followed. Chlorination of norephedrine (Compound **9**) was carried out using thionyl chloride as per the procedure described in literature.[28]

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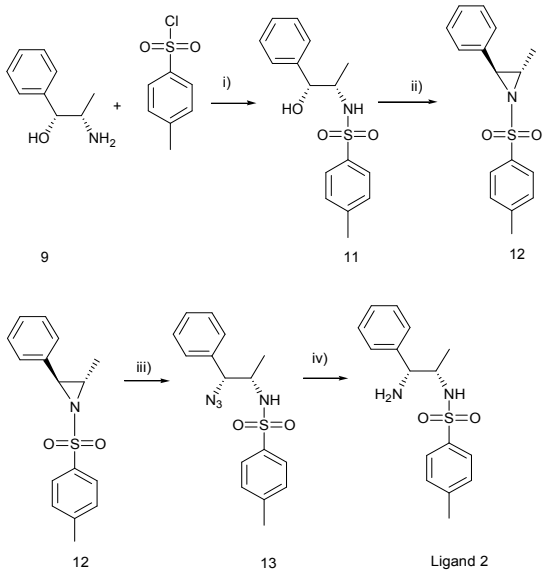
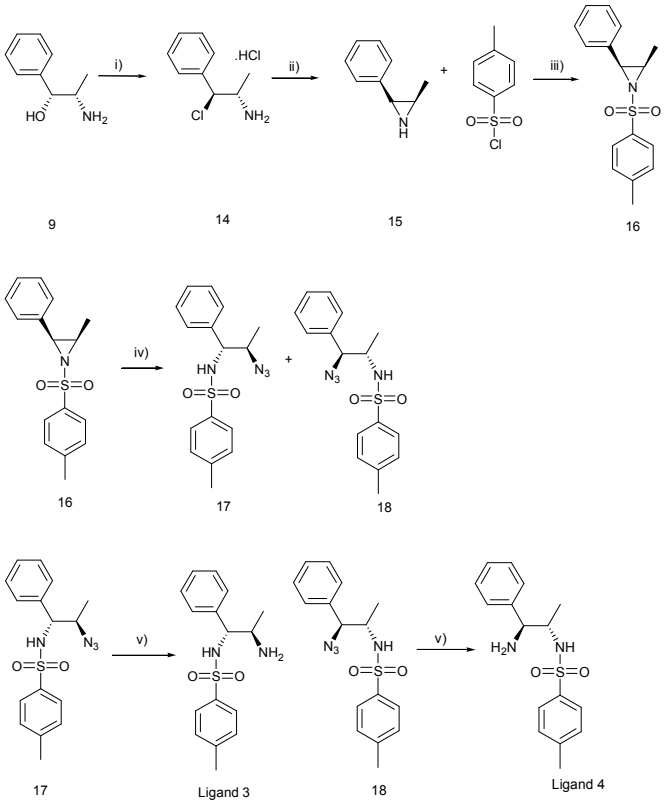


Scheme 5: Synthesis of ligand 2

Reaction conditions: i) Triethyl amine in t-Butyl methyl ether ii) DEAD,(Diethyl azodicarboxylate) Triphenyl phosphine in THF(Tetrahydrofuran) iii) Sodium azide in Acetonitrile: water, iv) Triphenyl phosphine in THF and water

The chloro norephedrine, compound **14** was formed with the inversion of configuration at the carbon bearing hydroxyl group.[28] The chloro norephedrine hydrochloride (compound **14**) was treated with sodium hydroxide, resulting in the formation of compound **15**. This transformation again takes place with the inversion of configuration at benzylic carbon to form aziridine[25, 29] (compound **15**). The aziridine was reacted with*p*-toluene sulfonyl chloride and pyridine to get compound **16**. The ring opening of sulfonated aziridine (compound **16)** was carried out using 1,4-diazabicyclo[2.2.2]octane**(**DABCO) in 2 equivalence and Trimethylsilyl azide(TMS azide) as a nucleophile and azide source. Two compounds (compound **17** and compound **18**) were formed during this reaction (in a 60:40 ratio checked by NMR).

Please note that in Scheme **5**, aziridine with trans geometry gave only one product (compound **12**).[26, 27] Phenyl and methyl groups in sulfonated aziridine (Scheme **5**, compound **12**) are trans with respect to each other. Thus, ring opening of compound **12** produces only one compound with complete regio and stereo specificity. In compound **16**, (Scheme **6**), geometry of phenyl and methyl is cis w.r.t each other. The ring opening of aziridine and activated aziridine in ephedrine type compounds is governed by the stereochemistry of the phenyl and methyl groups. Compound with cis geometry is known to produce regioisomers because of attack from both the sides.[24, 25]This probably results in attack of nucleophile from both the sides producing 2 compounds(compounds **17** and **18**). These two compounds were found to be very difficult to separate by column chromatography or crystallization methods. The purification by flash chromatography was developed for the separation of these two compounds. The detailed structural analysis of these compounds was carried out. The NMR spectrum of compound **17**clearly showed that benzylic proton had an additional coupling constant (8 Hz) and is coupled to the NH proton of the sulfonamide group. (Confirmed with 2D ^{1}H-^{1}H COSY (Correlation Spectroscopy) and ^{1}H-^{15}NHMBC) (Supporting Information, page number, 38 section 4). This indicated the ring opening of sulfonated aziridine (compound **16**), is proceeding from methyl side also.



Scheme 6: Synthesis of ligand 3 and 4

Reaction conditions: i) $SOCl_2$, ii) 4N NaOH, in Methanol, iii) Pyridine in t-butyl methyl ether iv) 1,4-diazabicyclo[2.2.2]octane (DABCO) and Trimethylsilyl azide (TMS azide), v) Triphenyl phosphine in THF and H_2O

In compound **18**azide is attached to the carbon having phenyl group (formed due to ring opening of the sulfonated aziridine **16**from phenyl side) and sulfonamide group is attached to carbon having methyl group and showed coupling constant of 5.8 Hz. Thetrans geometry of azide and sulfonamide in azide (compound **18a** enantiomer of **18)** was confirmed by X ray single crystal structure. ORTEP diagram for the azide intermediate compound **18a** is presented in Figure **1. (**details in supporting information, page number 39 section 5).The reduction of azide compounds (**17** and **18**) was carried out using triphenyl phosphine/water. Acid base work up was used to isolate ligand **3**as a white solid. In case of ligand **4** however, this purification procedure gave gummy mass which on standing for two days became off white sticky solid. Therefore, ligand **4** was prepared as hydrochloride salt using 4N HCl in dioxane to obtain free flowing solid. Enantiomers of these ligands (Ligands **5-8**) were prepared by using the same procedure using 1S, 2R norephedrine as a starting material.

2.1 ATH of ketones in water

ATH of acetophenone using sodium formate as hydrogen donor and water was investigated using Ru, Rh and Ir metal complexes as catalyst precursors with eight monosulfonated diamine ligandsprepared as described. The results are presented in Table 1. The results showed that the catalysts prepared with monosulfonateddiamine ligands (Table **1**, Sr. No. 1-8) were active and selective for asymmetric transfer hydrogenation of acetophenone.It was also observed that ligand-metal complex combination was important for high activity and enantioselectivity.Rh catalyst showed excellent conversion (>97%) and enantioselectivity (>90%) with ligands **3** and **4** (Table 1 entry 3,4,7,8) and very low conversion with ligands **1** and **2**,while Ru (10

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to 36%) and Ir (10 to 22 %) catalysts showed lower activity with all the ligands.

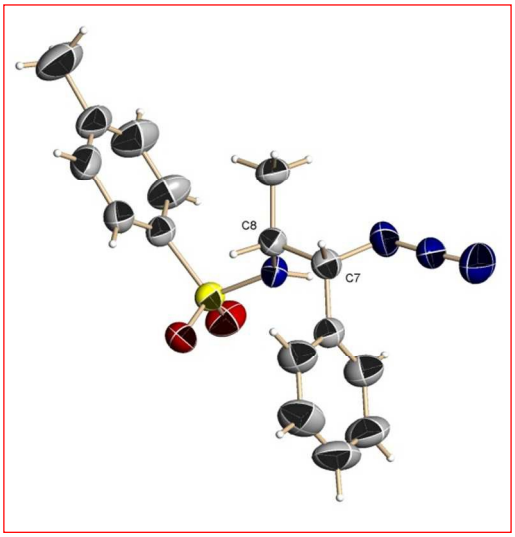


Figure 1. ORTEP diagram of compound 18a Ellipsoids are drawn at 50% probability (CCDC Depositary number CCDC 1018428, Details supporting information page number 38)

Enantioselectivity for all the metal complexes and all ligands was good to excellent and was in a range of 68 to 92%. Relative stereochemistry of the amine and sulfonamide group of ligand was found to be critical in deciding the activity of the catalyst system. For example Ligand **1** and **2** having syn geometry of the amine and sulfonamide groups were less reactive irrespective of the metal complex used. Thus, ruthenium, rhodium and iridium complexes used in this study showed < 30 % conversion with moderate to good ee. (67-90%.).Similar observation is noted by other research groups for compounds having syn or cis geometry. However, indane based sulfonamide ligands showed high conversion and ee (96%, and 83% ee),[19]though amine and sulfonamide configuration in these ligands was cis w.r.t each other. Ligands having anti or trans geometry (ligands **3** and **4**) showed high conversions and ee (>90%) for the $[Rh(Cp^*)Cl_2]_2$ catalyst (Table 1, Sr. No. **3** and **4)**.

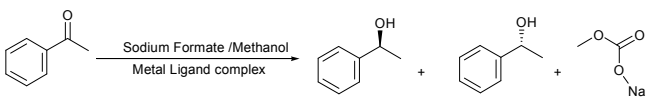
The structure activity relationship showed that along with stereochemistry of the amine and sulfonamide groups, their regio position is also important. In ligand **3** sulfonamide group is attached to the carbon having phenyl group and amino group is attached to the carbon having methyl group. In ligand **4** the amino group is attached to the carbon having the phenyl group and sulfonamide group is attached to the carbon having the methyl group. The results showed that ligand **4** and its enantiomer (Table 1, entry 4 and 8) were most active for all the catalysts screened and best results were observed with $[Rh(Cp^*)Cl_2]_2$ (99% conversion with 92 % ee in 1.25 h). The activity was marginally higher than ligand **3** and its enantiomer for $[Rh(Cp^*)Cl_2]_2$(97 % conversion with 92 % ee in 2h,entry 3 and 7). The difference in activity between ligand **3** and **4** was probably because of the different positions of the amine and sulfonamide group. The enantioselectivity using both the ligands **3** and **4** was same, indicating that methyl and phenyl group attached to the carbon having sulfonamide group do not influence enantioselectivity. It was found that the configuration of the resultant alcohol was having the same configuration as that of the carbon bearing sulfonamide group. Thus, for all the entries it was observed that irrespective of the activity shown by ligand, configuration is driven by the carbon bearing sulfonamide group. These observations were found to be consistent with the observed literature reports.[20-22,30]The position of amine and sulfonamide groups with respect to each other had significant impact on conversion, but lower effect on enantioselectivity.Best results (99 % conversion in 1.25 h with 92 % ee) were obtained using Rh-ligand **4** catalyst systemwith $[Rh(Cp^*)Cl_2]_2$ and further screening of ketones was done withRh-ligand **4** catalyst system.

Comparison of the results obtained with $[Rh(Cp^*)Cl_2]_2$ and ligand 4 in the present work with literature reports with$[Rh(Cp^*)Cl_2]_2$ TsDPEN, and TsCYDN, indicated that enantioselectivity was slightly lower (97 % for TsDPEN,[15] 94 % for TsCYDN[18] vs 92 % for ligand **4,** Table 1 entry 4).

2.2 Screening of ketones using $[Rh(Cp^*)Cl_2]_2$ligand 4 complex

Various ketones were screened for ATH using Rh-ligand **4** catalyst system with sodium formate as the hydrogen donor in water. The results are presented in Table 2. With acetophenone; 95 % conversion was observed with 91 % ee in 1 h. With the presence of electron withdrawing groups in para position (*p*-chloro acetophenone and *p*-bromo acetophenone), the conversions as well as enantioselectivity were slightly lower compared to acetophenone, (Table 2, entry 2 and 3). With electron donating groups in para position (methyl and isobutyl acetophenone), conversions were significantly lower, 90 % and 87 % in 2 h and 6 h respectively. The enantioselectivity however was higher for methyl acetophenone (97 %) compared to acetophenone (91 %) (Table 2 entry 5). For isobutyl acetophenone the enantioselectivity was found lower (89%).4-methoxy acetophenone is known to be a challenging substrate for ATH reaction, probably because of its low redox potential[5]. In the present work 4-methoxy acetophenone was also reduced with very good conversion (82 % in 2h) and excellent enantioselectivity (97%). Although to reach more than 90 % conversion it took nearly 12 h (Table 2 entries 6). Cyclic ketones like indanone and tetralone were reduced at much faster rate but lower than acetophenone and with significantly lower enantioselectivity (98 % conversion in 1.5 h with 84 % ee for indanone, 95 % conversion in 2 h with 88 % ee for tetralone) (Table 2, entry 8 and 9). For 6-methoxy-2-acetyl naphthalene (Table 2, entry 10), however only 5 % conversion was observed with 98 % ee even after prolonged reaction time of 12 h. For this reaction it was observed that, substrate is insoluble in water and floats on water.

Since 6-methoxy-2-acetyl naphthalene is a solid, it is not forming a separate layer along with the catalyst as found in the case of other ketones. Because of this the reaction cannot take place at the interface of aqueous phase and organic phase (ketone)[13].The use of appropriate solvent to solublise such substrates and make a homogeneous phase would be helpful in driving the reaction forward. With this idea in mind ATH of ketones was investigated with methanol as a solvent(Scheme **7**). Before initiating this activity, the role methanol only as solvent was confirmed using deutarated methanol as solvent and reactant. (Supporting information, section 2.1, page number 16).



Scheme 7: ATH of ketones using Sodium formate in methanol

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Table 1: ATH of acetophenone using monosulfonated unsymmetrical diamines and transition metal complexes

Entry	Ligand	([Ru(*p*-cymene)Cl_2]$_2$			[Rh(Cp*)Cl_2]$_2$			[Ir(Cp)*Cl_2]$_2$		
		Conv. [%]	ee %	Config	conv. %	ee %	Config.	Conv. [%]	ee	Config.
1	1	12	68	R	23	78	R	10	86	R
2	2	<10	70	S	18	82	S	<10	75	S
3	3	22	90	R	**97**	**92**	**R**	22	82	R
4	4	36	85	S	**99***	**92**	**S**	22	90	S
5	5	10	70	S	21	80	S	10	85	S
6	6	<10	72	R	15	83	R	<10	77	R
7	7	21	91	S	**97**	**92**	**S**	20	80	S
8	8	32	83	R	**99***	**92**	**R**	20	88	R

Reaction conditions: Metal complex, 0.005mmol; Ligand,0.01mmol; sodium formate 5 mmol; acetophenone, 1mmol;water 2cm^3 ; Temperature: 25^{0}C; Time 2 h, * 1.25 h

Table 2: ATH of various ketones using [Rh (Cp*)Cl_2]$_2$and ligand 4

Entry	Ketone	Reaction time (h)	Conv. %	FinalTOF,h^{-1}	%ee
1	Acetophenone	1	95	94	91
2	4-Bromo Acetophenone	1.5	99	66	88
3	4-Chloro Acetophenone	1.5	99	66	88
4	2,4 Dichloro acetophenone	2	95	48	86
5	4-methyl acetophenone	2	90	46	97
6	4-isobutyl acetophenone	6	87	12	89
7	4-Methoxy acetophenone	3(12)	82(95)	28	97
8	1 Indanone	1.5	98	66	84
9	1-tetralone	2	95	48	88
10	6-methoxy2-Acetylnaphthalene	12	5	-	98

Reaction conditions: Rh(Cp*)Cl_2]$_2$, 0.005 mmol; Ligand, 0.01 mol; ketone,1 mmol; sodium formate 5 mmol; water,2 cm^3; Temperature: 25^{0}C

2.3 ATH of ketones with methanol as a solvent

ATH of acetophenone in methanol as a solvent (Scheme**7**) was investigated in detail using [Rh (Cp*)Cl_2]$_2$ as a catalyst precursor and ligands **1-8** (Table 3). The trends for activity observed were similar to that observed in water and sodium formate for all ligands with high activity for ligands**3** and**4**(ligands with trans geometry of amine and sulfonamide groups)**.**Alsoin general the ee values obtained in methanol were higher for all the ligands than thoseobtained in water (compare results in Table 1 and Table 3).Methanolic solution became turbid as reaction progressed due to the formation of sodium methyl carbonate and 18 electron hydride complex which is a catalyst precursor in ATH of ketones as reported by Noyori.[8](For details see supporting information page number 15 section 2).Ligand**4** showed better activity than ligand**3**(97% in 2h, Vs 82 % in 2h respectively). The enantioselectivity obtained however was similar for both the ligands (96% and 95% respectively) (Table 3, entry 3, 4, 7, 8). The activity for ATH of acetophenone with ligands **1** and **2** (ligands with cis geometry of amine and sulfonamide groups) with Rh catalyst was very low. However,the reaction mixture became turbid after 2 h, indicating the formation of sodium methyl carbonate and Rh-hydride

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complex(similar to that observed in case of ligands**3** and **4**). It was not possible to get similar observations in water as sodium hydrogen carbonate generated is water soluble. Xiao et al[16,] have proposed that rate determining step may not be the one with metal hydride formation but transfer of hydride to ketonic substrate via six membered transition states[14-16].Thus geometry of 18 electroncomplex could be critical in deciding the activity and enantioselectivity in ATH of ketones.

Finally the results obtained for ATH of acetophenone with Rh-ligand **4** were compared with benchmark ligands like Rh-TsDPEN and Rh – TsCYDN (Fig.2.) with methanol as solvent. It was observed that initial activity of Rh-TSDPEN is slightly higher than Rh-ligand **4** complex, but comparable with Rh-TsCYDN (Fig. 2c TOF, h^{-1} at 15 mins 213, 170 and 167 respectively). Similar effect in the ee was observed. Rh–TsDPEN showed marginally higher ee than Rh-TsCYDN and Rh-Ligand 4 complex (98% vs 96 % receptively).

Table 3: ATH of acetophenone in methanol as solvent

Entry	Ligand	Time (h)	Conv %	Final TOF,h^{-1}	ee %	Config
1	1	2	10	-	85	R
2	2	2	18	-	85	S
3	3	2(4)	82(98)	24	95	R
4	4	2	97	49	96	S
5	5	2	10	-	85	S
6	6	2	18	-	85	R
7	7	2(4)	82(98)	24	95	S
8	8	2	97	49	96	R

Reaction conditions: [$Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol; acetophenone 1 mmol ; sodium formate 5 mmol; Temperature: 25^0C;Methanol, $2cm^3$

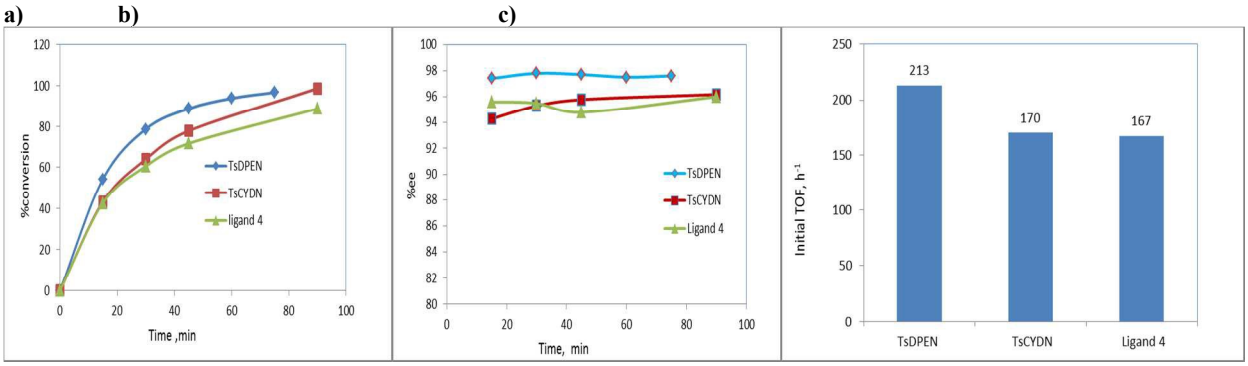

Figure 2: Comparative data, for Ligand 4 with benchmark ligands TsCYDN, TsDPEN, a) conversion, b) ee c) Initial TOF, h^{-1} (15 mins)

Reaction conditions: $[Rh(Cp^*)Cl_2]_2$, 0.005 mmol; ligand 0.01 mmol; sodium formate 5 mmol,; Temperature, 25^0C; Methanol 1.88 cm^3 acetophenone,1mmol

2.4Comparison of results in water and methanol

Various ketones were screened using $[Rh(Cp^*)Cl_2]_2$/ligand-**4** catalyst system with methanol as solvent and the results are presented in Table 4.All theketones were reducedwith excellent conversion and enantioselectivity and the activity trends observed were similar to those observed with water as solvent, (compare Tables2 and 4). However, consistently higher ee was observed for all the ketones investigated, with slightly lower activity than observed in water.Cyclic ketone like Indanone (table 4, entry 7) was reduced within 2 h with 98% conversion and 97% ee, (vs 84 % ee in water,table 3 entry 9).Tetralone was reduced within 3 h with more than 98 %ee, vs 88% ee in water, table 3 entry 9.2-acetyl-6 methylnaphthalenegave55% conversion with 98% ee in 2 h reaction time in methanol as solvent, compared to just 5% with water as a solvent.Comparison of the results with Rh-ligand **4** catalyst system showed that activity for all the ketones screened was higher with water as a solvent,(Table 2 and 4) but the enantioselectivity in methanol was consistently higher by ~5 %. For cyclic ketones like indanone and tetralone the enantioselectivity was higher by 10-12%

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Table 4: ATH of various ketones using ligand4 and $[Rh\ (Cp^*)Cl_2]_2$ catalyst using methanol as solvent

Entry	Ketone	Time (h)	Conv. %	Final TOF, h^{-1}	ee %
1	Acetophenone	2	97	49	96
2	4-Bromoacetophenone	2	99	50	96
3	4-chloroacetophenone	2	99	50	96
4	2,4 Dichloroacetophnenone	2	95	48	92
5	4-Methyl acetophenone	2	94	47	97
6	4-Isobutyl acetophenone	6	97	16	97
7	4-Methoxy acetophenone	8	74	9	97
8	1-Indanone	2	98	49	97
9	1-Tetralone	2(3)	92(98)	46	98
10	2-Acetyl pyridine	12	88	7	86
11	3-Acetyl pyridine	14	98	7	98
12	p-Bromopropiophenone	2	88	44	92
13	2-Acetyl 6 Methoxy naphthalene	2	55	28	98

Reaction Conditions:$[Rh(Cp^*)Cl_2]_2$,0.005 mmol; Ligand,0.01mmol; ketone 1 mmol; sodium formate 5 mmol; Temperature: 25^0C; Methanol $2cm^3$

3Experimental Section.

All the experiments were carried out using oven-dried glassware in open air. All the ketones used except 2-Acetyl-6-methoxy naphthalene were procured from Aldrich. 2-Acetyl-6-methoxy naphthalene was obtained as a free sample from private company and purity of the compound (>98%) was confirmed by GC and GC-MS analysis. All solvents used were reagent grade. $[Rh(Cp^*)Cl_2]_2$was purchased from Strem Chemicals. The NMR spectra were recorded on a 400 MHz Bruker spectrometer. HPLC analysis was carried out using Waters HPLC instrument with quaternary gradient pump, diode array detector and auto sampler. GC-MS analysis for conversions of ketones was carried out using Thermo Trace GC DSQ and HP-5columnpurchased from Agilent Technologies.HR-MS analysis was done using Agilent 6520 Q-TOF instrument. The analytical methods used for chiral analysis of alcohols are taken from earlier available literature.[6,9-11,15]

3.1 Preparation of precatalyst /catalyst

The procedure described by Noyori[6] and Xiao et al[13-15, 18] was used to prepare the precatalyst. In a typical experiment Rhodium complex (5mmol, 3.09 mg) and ligand (10 mmol, 3.1 mg) were mixed in water/methanol (2ml). The contents were heated at 40^0C for 1h.To the same solution ketone 1 mmol and sodium formate 5 mmol wereadded and reaction was initiated.

4 Conclusions.

New unsymmetrical vicinal diamines were synthesized having different regio and stereo positions of amine and sulphonamide groups. The ATH of ketones using sodium formate as a hydrogen source and water and methanol as solvents was studied. Unsymmetrical vicinal dimaines synthesized from norephedrine in combination with $[Rh\ (Cp^*)Cl_2]_2$ as catalyst is effective for ATH of various ketones, using water as well as methanol as solvent. The ATH proceeds smoothly with conversion ranging between 88 to 98 % and enantioselectivity between 86 %- 97%. The structure activity relationship was studied and excellent enantioselectivity has beenobtained using ligand where phenyl group is attached to the carbon bearing amine group and methyl group is attached to the carbon bearing sulphonamide group. Enantioselectivity for all ketones screened was consistently high except for pyrydyl ketones. The enantioselectivity was found to be consistently higher by small but measurable amount for ATH various ketones with methanol as solvent. The results obtained with Rh-ligand 4 complex werecomparable with benchmark ligands like Rh-TsDPENand Rh – TsCYDN. To the best of our knowledge this is the first example of a $[Rh(Cp^*)Cl_2]_2$ and unsymmetrical vicinal diamine catalyst system used in ATH of ketones with very high conversions and enantioselectivity. The use of methanol makes this reaction truly homogeneous. This homogeneity of reaction in methanol providesfurther opportunity to study the mechanistic and kinetic details of the

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reaction much more easily than in water. Further work on ATH ofketones is in progress in our laboratory..

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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