RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 46351

Received 1st August 2014
Accepted 5th September 2014

DOI: 10.1039/c4ra07964g

www.rsc.org/advances

Asymmetric transfer hydrogenation of imines in water/methanol co-solvent system and mechanistic investigation by DFT study†

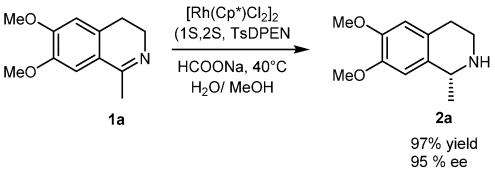
Vaishali S. Shende,[a] Savita K. Shingote,[a] Sudhindra H. Deshpande,[a] Nishamol Kuriakose,[b] Kumar Vanka*[b] and Ashutosh A. Kelkar*[a]

Asymmetric transfer hydrogenation of various cyclic imines proceeded efficiently with water/methanol co-solvent media in 20 min with excellent yields and enantioselectivities by employing Rh–TsDPEN catalyst and sodium formate as a hydrogen donor. The role of the co-solvent in enhanced productivity of the reaction was investigated by DFT. The mechanism for ATH of the imines has been discussed on the basis of the DFT study.

Optically active amines are important building blocks for biologically active molecules in medical, pharmaceutical, agricultural sciences, flavor and fragrance industries.[1] Different methods have been developed for the preparation of enantiomerically pure amines in the past few years.[2] Asymmetric transfer hydrogenation (ATH) of imines is one of the most popular methods used for the preparation of chiral amines. Various chiral catalysts have been investigated for ATH of imines, but the most noteworthy to date are the ruthenium and rhodium complexes with optically active *N*-toluenesulfonyl-1,2-diphenylethylenediamine (TsDPEN) ligand[3] in organic solvents with formic acid–triethylamine azeotrope as a hydrogen donor.[2,4] There are very few reports on the ATH of imines in water[5] but major efforts were focused on the development of the water soluble ligands[5a–c,f] and the use of additives/surfactants[5a,d] to improve the activity of ATH of imines in water. However, longer reaction time is the major problem of all these investigations. Herein we wish to report the role of methanol as a co-solvent in achieving rapid ATH of imines with $[Rh(Cp^*)Cl_2]_2$–TsDPEN catalyst system in water with sodium formate as a hydrogen donor. Various co-solvents were screened and methanol was found to be the best co-solvent. Thus 97% yield of **1a** with 95% ee was achieved with H_2O–MeOH (1 : 1, v/v) as a solvent in just 20 min (TOF: 295 h^{-1}) (Scheme 1). The reactions were carried out in air, and excellent enantioselectivities were observed for various imine substrates.

We initiated our study on ATH of model substrate, 1-methyl-6,7-dimethoxy-3,4-dihydroxisoquinoline (**1a**) with Rh–TsDPEN as the catalyst[6] and HCOONa as a hydrogen donor in water at 40 °C with a substrate/catalyst (*S*/*C*) ratio of 100 : 1 (**1a**: 0.5 mmol, HCOONa: 5 equiv., water: 2 ml). In all these studies Rh–TsDPEN catalyst was generated *in situ* by reacting $[Rh(Cp^*)Cl_2]_2$ and 1.5 equiv. of TsDPEN in 1 ml distilled water for 1 h at 40 °C.[7] Within 5 h ATH of **1a** proceeded with 85% conversion and 95% enantioselectivity (Table 1, Entry 1). Effect of temperature on the activity and enantioselectivity was investigated (Table 1). Conversion of **1a** increased with increase in temperature (85% at 40 °C to 91% at 60 °C) with the drop in enantioselectivity from 95% at 40 °C to 88% at 60 °C. Hence the temperature of reaction was maintained at 40 °C for further study.

At the start of experiment with water as a solvent, reaction mixture became slightly turbid after the addition of substrate and sodium formate to pre-catalyst solution and as the reaction progressed there was product separation with brown colored globules floating on the aqueous layer and thus resulting in a biphasic reaction system. In order to increase the solubility of substrate and avoid product separation during the reaction, methanol was added as a co-solvent in 1 : 1 (v/v) ratio and to our surprise the reaction achieved 98% conversion and 95% enantioselectivity within 20 min (Table 1, entry 4; See ESI, Fig. S1,†



1a **2a**
97% yield
95 % ee

Scheme 1 ATH of **1a** in water using methanol as a co-solvent.

[a]*Chemical Engineering and Process Development, National Chemical Laboratory, Pune 411008, India. E-mail: aa.kelkar@ncl.res.in; Fax: +91 20 25902621*

[b]*Physical and Materials Chemistry Division, National Chemical Laboratory, Pune 411008, India. E-mail: k.vanka@ncl.res.in; Fax: +91 20 25902636*

† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra and HPLC traces of the products, computational details, electronic energies in au and in kcal mol^{-1} (Tables S3–S6) and the *xyz* coordinates of all the structures discussed in the manuscript. See DOI: 10.1039/c4ra07964g

Table 1 ATH of **1a** in water and methanol[a]

Entry	Solvent	Temp (°C)	Time (min)	Conv[d] (%)	ee[e] (%)
1	H_2O	40	300	85	95
2	H_2O	50	300	88	91
3	H_2O	60	300	91	88
4[b]	H_2O/MeOH	40	20	98	95
5	MeOH	40	300	35	94
6[c]	MeOH	40	300	5	nd[f]

[a] Reaction conditions: **1a** (0.5 mmol), $[Rh(Cp^*)Cl_2]_2$ (0.0025 mmol), (1S, 2S)-TsDPEN(0.0075 mmol), HCOONa (2.5 mmol), solvent (2 ml). [b] H_2O–MeOH (v/v, 1 : 1). [c] Reaction carried out without HCOONa. [d] Determined by GC. [e] Determined by chiral HPLC. [f] Not determined.

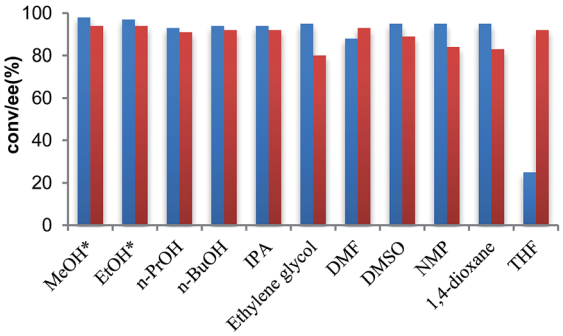


Fig. 2 Co-solvent screening for ATH of **1a** catalyzed by Rh–TsDPEN Conv (■), ee (■), reactions were carried out on a 0.5 mmol scale in a 2 ml water–co-solvent (1 : 1, v/v) at 40 °C, time: 30 min, * time: 20 min.

C-T profile of ATH of **1a**). When ATH of imine **1a** was carried out in pure methanol with HCOONa as a hydrogen donor (Table 1, entry 5) only 35% conversion with 94% enantioselectivity was observed in 5 h. Experiment was carried out with only methanol (without sodium formate) to check the role of methanol as a hydrogen donor (Table 1, entry 6). In this reaction 5% conversion of **1a** was observed in 300 min indicating that methanol worked just as a solvent in this reaction.

To figure out the optimum amount of methanol necessary as a co-solvent for this reaction, ATH of **1a** was carried out by varying the amount of methanol in water from 25% to 75% and the results are presented in Fig. 1. Total quantity of solvent was kept constant at 2 ml. From the Fig. 1, it can be seen that conversion of **1a** increased with increase in methanol concentration till 50% methanol (98% conversion in 20 min) and reaction mixture was homogeneous throughout the course of reaction. However, with further increase in methanol concentration to 75% conversion of **1a** decreased considerably (92% in 30 min). Enantioselectivity was not affected by a change in methanol concentration (94–95%).

Various co-solvents were screened (co-solvent: water ratio 1 : 1) for ATH of **1a** and the results are presented in Fig. 2 (for details see ESI, Table S1†). Among all co-solvents screened, methanol achieved 98% conversion with 95% enantioselectivity in 20 min. Alcoholic solvents like propanol, butanol and isopropanol also showed conversions ranging from 93% to 95% within 30 min reaction time with enantioselectivity value of 91–92%. Polar aprotic solvents like DMF, DMSO and NMP achieved conversion from 88% to 95% and showed enantioselectivities from 84% to 93% in 30 min reaction time. However, with THF just 25% conversion was observed in 30 min with 92% ee. Use of coordinating solvent THF leads to deactivation of catalytic system resulting in decreased conversion.[8] Best results (98% conversion with 95% enantioselectivity in 20 min) were obtained with water as solvent and methanol or ethanol as co-solvents (water : co-solvent, 1 : 1 v/v) and further work was carried out with methanol as a co-solvent.

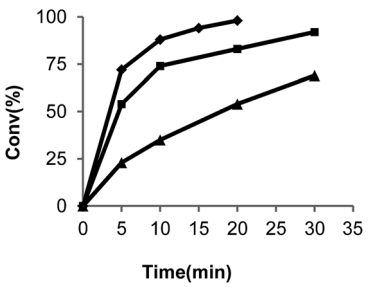


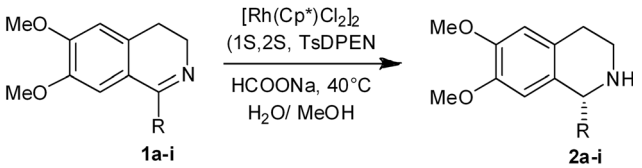
Fig. 1 Effect of methanol content in water on ATH of **1a**: 25% MeOH in water (▲), 50% MeOH in water (◆), 75% MeOH in water (■); **1a** (0.5 mmol); HCOONa (2.5 mmol); temp: 40 °C, solvent: 2 ml.

The efficiency of the water/methanol (1 : 1, v/v) solvent media was demonstrated for ATH of various cyclic imines using Rh–TsDPEN catalyst system with excellent yields and enantioselectivities as presented in Table 2. The chain length of the alkyl substituent at the 1-position of imine group had little effect on the enantioselectivity (Table 2, Entries 1–3). Imine derivatives having bulky phenyl group on imino carbon are hard to reduce (Table 2, Entries 8, 9), where second aromatic system apparently interferes with selective catalyst binding; resulting in low yield and enantioselectivity.[2b] Notably the enantioselectivities for ATH of imines achieved with Rh–TsDPEN catalyst system in water–methanol solvent in the present work (95–99% ee) are better than those reported in literature with FA–TEA hydrogen donor in organic solvents (89–99% ee).[4]

Co-solvents are known to have hydrogen-bond donor and/or acceptor groups for aqueous solubility and a small hydrocarbon region that serves to disrupt the strong hydrogen-bond network of pure water, thereby increasing the solubility of reactants/products.[9] In the present work methanol helps in solubilising the reactant **1a** and product **2a** in aqueous reaction mixtures by forming hydrogen bonds with the imino and amino nitrogen atoms. Several DFT calculations have been performed for ATH reaction of ketones and aldehydes which explain the role of solvent in the transition state of hydrogen transfer through hydrogen bonding and thereby ATH in water to proceed with accelerated rate.[10–12] It can be feasible for imines also; that the solvent present in the reaction mixture helps in accelerating the ATH of **1a** by forming local hydrogen-bonding network.[13]

In order to understand the co-solvent effect of methanol on the activity of the ATH of **1a**, density functional theory (DFT) calculations were performed, at the B3LYP/TZVP//PBE/TZVP level of theory. In order to ensure that the results are reliable; all

Table 2 ATH of imines catalyzed by Rh–TsDPEN in H_2O–MeOH (1/1, v/v) with sodium formate as hydrogen donor[a]



1a-i 2a-i

1a:R= Me 1d:R= iP 1g: R= cyclohexyl
1b:R= Et 1e: R= Bu 1h: R=Ph
1c:R= Pr 1f : R= cyclopentyl 1i: R=3,4-DiMeOPh

Entry	Imine	Time (min)	Yield[b] (%)	ee[c] (%)
1	**1a**	20	97	95
2	**1b**	20	95	94
3	**1c**	20	94	96
4	**1d**	20	94	99
5	**1e**	20	94	93
6	**1f**	20	95	97
7	**1g**	20	94	99
8	**1h**	180	40[d]	17
9	**1i**	180	15[d]	14

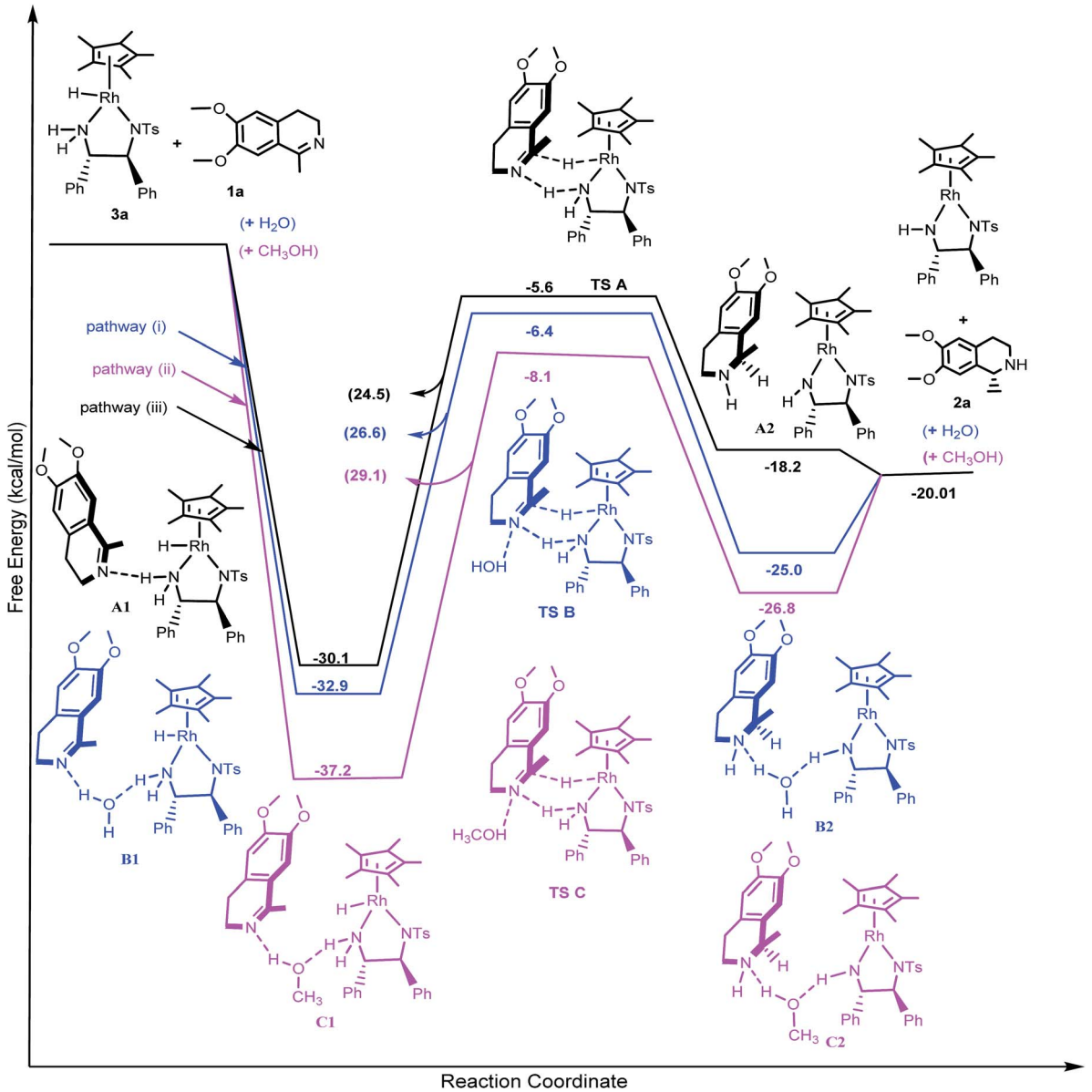
[a] Reaction conditions: **1** (0.5 mmol), $[Rh(Cp^*)Cl_2]_2$ (0.0025 mmol), (1S, 2S)-TsDPEN (0.0075 mmol), HCOONa (2.5 mmol), H_2O–MeOH(1 : 1, v/v, 2 ml), temp: 40 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Conversion determined by GC.

the calculations were performed with the real system **3a** (see Scheme 2 and ESI† for details on DFT study). Previous studies on the Ru-catalyzed ATH of formaldehyde[10] and ketones[14] suggests a sequential mechanism for transfer of hydrogen to the substrate molecule by the incorporation of implicit/explicit solvent molecules which involves a highly unstable alkoxide-like intermediate. However, in the present study of imines such a step-wise mechanism with an analogous intermediate was not observed. Based on the DFT calculations Xiao *et al.* have proposed that, a solvent water molecule could hydrogen bond with the substrate and thereby affect both the thermodynamics and the kinetics of the ATH of ketones.[12] Based on the above study three possible transition states shown in Fig. 5 were considered for imines with three different pathways (i) the presence of hydrogen bonding water molecule **TS-B** (ii) the presence of hydrogen bonding methanol molecule **TS-C** (iii) the absence of hydrogen bonding solvent molecule **TS-A** (Scheme 2). We have also considered the possibility that the solvent (water or methanol) can be a direct part of the hydrogen transfer pathway *via* an eight membered transition state. We have compared this possibility with a concerted pathway involving a six-membered transition state that would be formed between the rhodium catalyst system and the substrate (Fig. 3). As the figure indicates, the barriers are significantly lower for the six-membered transition state without participation of the solvent in the transition state. Hence, the reaction pathway involving the six-membered transition state has been considered, with the solvent molecule playing the role of a hydrogen bonding agent.

For pathway (iii), without the aid of any hydrogen bonding solvent molecule, the complex formed between the rhodium complex **3a** and imine **1a** (Scheme 2, **A1**) is 7.1 kcal mol^{-1} less stable than the analogous complex that would be formed with the aid of the hydrogen bonding methanol solvent (Scheme 2, **C1**). Also, for pathway (i) the complex formed with the aid of the hydrogen bonding water molecule (Scheme 2, **B1**) is 4.3 kcal mol^{-1} less stable than the hydrogen bonded methanol complex (Scheme 2, **C1**). This result indicates that the choice of the pathway that would be most likely to be followed would be determined at the inception of the reaction (Scheme 2). By employing the formula $\Delta G = -RT \ln K$, it can be estimated that the possible reason for the increased rate of reaction in water–methanol (1 : 1) solvent media is the pathway which involves **TS-C** and it is 137 600 times more likely to occur over pathway which involves **TS-A** and 1300 times more likely to occur over pathway which involves **TS-B** (see Scheme 2) (see computational details in the ESI† file for the calculation details). Moreover, the presence of hydrogen bonding methanol molecule leads to greater stability of the product complex (Scheme 2, **C2**), by 1.8 kcal mol^{-1} in pathway (ii) over the product complex with hydrogen bonded water (Scheme 2, **B2**) in pathway (i) and by 6.8 kcal mol^{-1} over the product complex without solvent molecule (Scheme 2, **A2**) in pathway (iii) (Scheme 2).

Interestingly, as the values along the three potential energy surfaces indicate, the difference between the barriers in the three cases is significantly closer than in the case of the ruthenium based catalyst studied by Xiao *et al.*, where the barrier heights dropped by 6.21 kcal mol^{-1} when a solvent molecule was considered.[12] For the current case, inclusion of the hydrogen bonding solvent molecule was seen to actually increase the barrier by 2.1 kcal mol^{-1}, in comparison to the non-hydrogen bonded case (see Scheme 2) for pathway (i), and by 4.6 kcal mol^{-1} for pathway (ii) (see Scheme 2). The explanation for this is that the favourable hydrogen bond between the two reactant species **1a** and **3a** is broken at the transition state, which leads to the observed higher barriers. Thus the driving factor in determining the productivity of the systems for ATH of **1a** in water–methanol (1 : 1) mixture is the thermodynamics, and not the kinetics. It is likely that the initiation of the reaction, *via* the formation of the complex between metal–ligand complex **3a** and imine **1a**, is a significant factor in determining its success, and the likelihood of initiation is significantly enhanced in the presence of methanol (potential energy surfaces shown in Scheme 2).

It may be noted that the reaction with pure methanol as a solvent was not taken into consideration because of the low solubility of the sodium formate in pure methanol. This would significantly impact *in situ* formation of the rhodium complex. Also, results clearly suggest that the reaction is facile in a 1 : 1 water–methanol mixture than in pure methanol or water. For the product structures, we have considered the possibility of hydrogen bonding between N–H of the product amine (**2a**) and the sulfonyl oxygen of the rhodium complex (see B and D of Fig. 4) and also the hydrogen bonding between the nitrogen atom of the product amine (**2a**) and the protic hydrogen of the methanol or water solvent molecules (see A and C of Fig. 4). It



Scheme 2 Energy profiles for asymmetric transfer hydrogenation of imine calculated by the DFT method (energy difference in kcal mol^{-1}).

was found that the latter case was energetically favorable by 1.3 kcal mol^{-1} for water and 3.0 kcal mol^{-1} for methanol respectively (see Fig. 4).

In this way methanol used as a co-solvent reduces the activation barrier in transfer hydrogenation of imine and overall result is the increased reaction rate for ATH of imine **1a**. Since all the calculations were carried out by taking the temperature as $T = 298.15$ K, we have also calculated the effect of temperature in the thermodynamic and the kinetic energies by adding the temperature correction at $T = 313.15$ K. The calculations suggest that the energy values changes only by 0.1–0.9 kcal mol^{-1} (Table S1 in the ESI†). The current calculations therefore provide insights into the nature of the ATH mechanism in different solvents, and showcase the importance of the role of hydrogen bonding in improving the activity of the process and stability of the products formed.

In ATH of imines, hydrogen transfer can follow either an outer-sphere pathway, proposed for carbonyl reduction[12,14] or an inner-sphere mechanism in which imine coordinates to the metal prior to hydrogen transfer.[15] Blacker *et al.* have found that the hydride and the proton are delivered to the substrate in a stepwise manner.[16] Nova *et al.* have explained the importance of two different substituents on the chelating bis(amido) ligand for transfer hydrogenation by bifunctional Cp*Rh(III) catalysts where the 16-electron Rh complex + formic acid are shown to be in equilibrium with the formate complex, but the latter lies outside the pathway for dehydrogenation.[17] Blackmond *et al.* have suggested that reductions of imines with Rh–di-amine catalysts might proceed *via* the unprotonated imine.[18] Wills *et al.* have proposed that the reductions of cyclic imines proceed by the ionic "*anti*" mechanism and a transition state structure for imine reduction is also proposed.[19] Based on literature

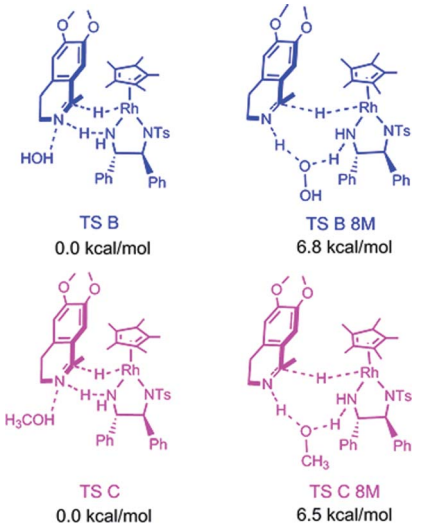


Fig. 3 Structures of six membered and eight membered (8M) transition state for asymmetric transfer hydrogenation of imine (energy difference in kcal mol^{-1}).

reports[14–19] and results presented in DFT study we have proposed a plausible mechanistic pathway for the ATH of **1a** in an aqueous-methanolic solution (Scheme 3) and possible proposed transition states are depicted in Fig. 5.

Precatalyst Rh–TsDPEN **3** is generated *in situ* from $[Rh(Cp^*)Cl_2]_2$ and TsDPEN in water and then it reacts with HCOONa forming formato complex **4**. The reduction proceeds *via* the formato intermediate **4**, followed by decarboxylation to give

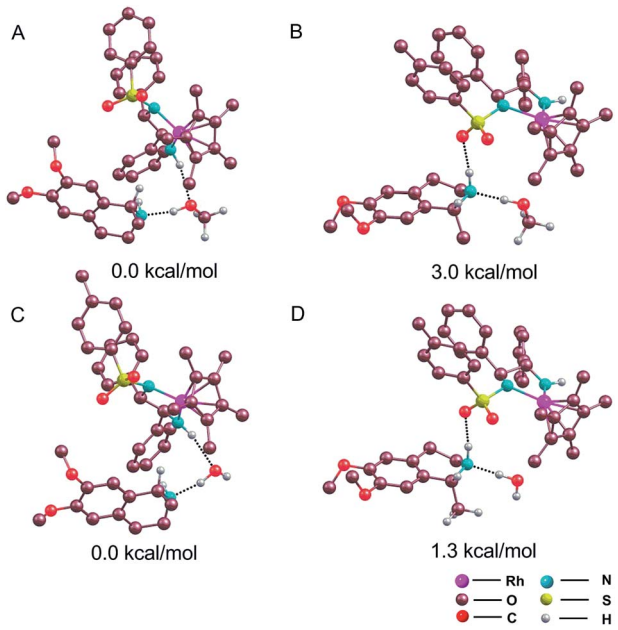
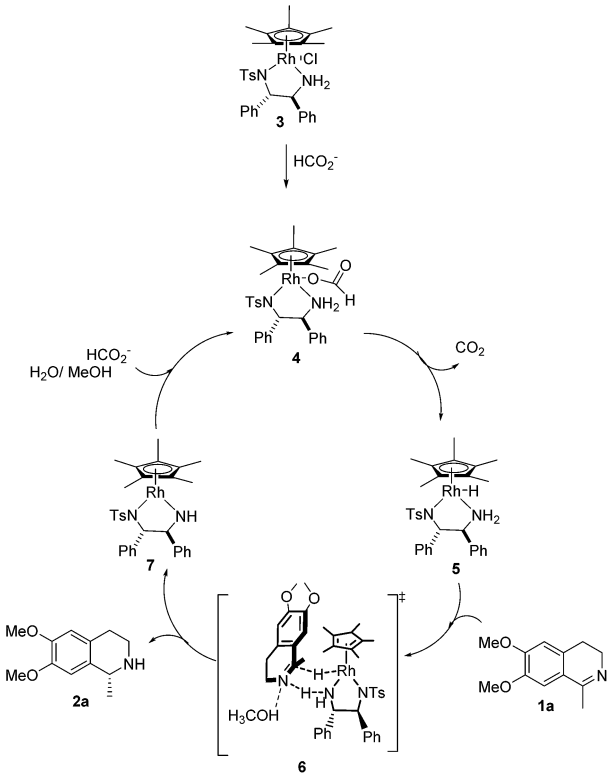


Fig. 4 Optimized geometry structures of product; (A): N–H of product **2a** hydrogen bonding only with methanol, (B): N–H of product **2a** hydrogen bonding with sulfonyl oxygen of the TsDPEN ligand, (C): N–H of product **2a** hydrogen bonding only with water, (D): N–H of product **2a** hydrogen bonding with sulfonyl oxygen of the TsDPEN ligand; energy difference in kcal mol^{-1}.



Scheme 3 Proposed mechanism for ATH of imine **1a** with Rh–TsDPEN in water–methanol (1 : 1, v/v) solvent system.

Rh–hydride intermediate **5** and the coordinatively unsaturated intermediate **7** (Scheme 3). It has been confirmed by DFT calculations that transition state in which the methanol solvent molecule provides activation of imine substrate *via* hydrogen bonding *i.e.* **TS-C** (Fig. 3) will be operating in mechanism for ATH of **1a** and in this way reductions proceed by the ionic "*anti*" mechanism proposed by Wills *et al.*[19] Thus **TS-C** in DFT study

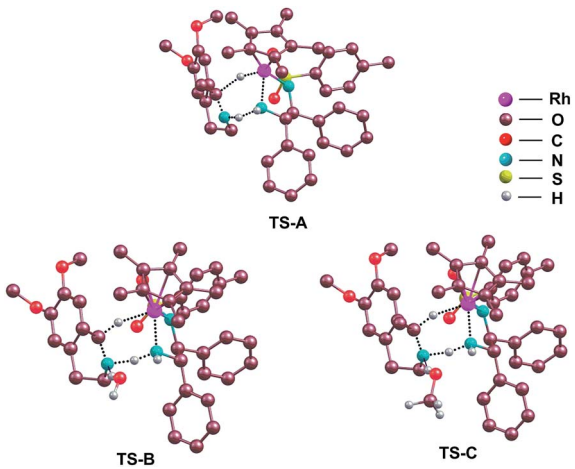


Fig. 5 Proposed transition states without participation of solvent molecules (**TS-A**) and with participation of water (**TS-B**) and with participation of methanol (**TS-C**) (hydrogen atoms have been omitted for the purpose of clarity).

resembles with intermediate **6** in the catalytic cycle (Scheme 2). Although the N–H bond of the catalyst already activates the imine, the methanol solvent molecule may provide additional activation through hydrogen bonding (Scheme 2). This observation is also supported by computational study of transfer hydrogenation in methanol in which it has been shown that methanol as a solvent could lower the thermodynamic free energy of hydrogen transfer and even alter the mechanism.[10]

Conclusions

In summary, we have developed a simple protocol for ATH of imines in homogeneous H_2O–MeOH solvent media with Rh–TsDPEN catalyst system and HCOONa as a hydrogen donor which affords rapid access to highly enantioselective chiral amines. Excellent enantioselectivities and good conversions were achieved for various imine derivatives. The DFT calculations provide insights into the nature of the ATH mechanism and showcase the significance of the role of hydrogen bonding through solvent molecule in improving the activity of the process. This simple and more efficient aqueous-methanolic co-solvent media with Rh–TsDPEN catalyst system provides a valuable alternative to modified water soluble ligands and it also offers several advantages, including mild reaction conditions, operational simplicity.

Notes and references

1 (*a*) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069–1094; (*b*) C. J. Cobley and J. P. Henschke, *Adv. Synth. Catal.*, 2003, **345**, 195–201.

2 (*a*) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916–4917; (*b*) J. M. Mao and D. C. Baker, *Org. Lett.*, 1999, **1**, 841–843; (*c*) G. D. Williams, R. A. Pike, C. E. Wade and M. Wills, *Org. Lett.*, 2003, **5**, 4227–4230; (*d*) A. Ros, A. Magriz, H. Dietrich, M. Ford, R. Fernandez and J. M. Lassaletta, *Adv. Synth. Catal.*, 2005, **347**, 1917–1920.

3 S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562–7563.

4 (*a*) Y. Amrani, L. Lecomte, D. Sinou, J. Bakos, I. Toth and B. Heil, *Organometallics*, 1989, **8**, 542–547; (*b*) J. Bakos, A. Orosz, B. Heil, M. Laghmari, P. Lhoste and D. Sinou, *J. Chem. Soc., Chem. Commun.*, 1991, **23**, 1684–1685; (*c*) C. Lensink and J. G. Devries, *Tetrahedron: Asymmetry*, 1992, **3**, 235–238; (*d*) C. Lensink, E. Rijnberg and J. G. deVries, *J. Mol. Catal. A: Chem.*, 1997, **116**, 199–207; (*e*) P. Roszkowski and Z. Czarnocki, *Mini-Rev. Org. Chem.*, 2007, **4**, 190–200; (*f*) J. Vaclavik, M. Kuzma, J. Prech and P. Kacer, *Organometallics*, 2011, **30**, 4822–4829; (*g*) J. Pechacek, J. Vaclavik, J. Prech, P. Sot, J. Januscak, B. Vilhanova, J. Vavrik, M. Kuzma and P. Kacer, *Tetrahedron: Asymmetry*, 2013, **24**, 233–239; (*h*) J. Vaclavik, P. Sot, B. Vilhanova, J. Pechacek, M. Kuzma and P. Kacer, *Molecules*, 2013, **18**, 6804–6828.

5 (*a*) J. S. Wu, F. Wang, Y. P. Ma, X. C. Cui, L. F. Cun, J. Zhu, J. G. Deng and B. L. Yu, *Chem. Commun.*, 2006, 1766–1768; (*b*) L. Li, J. S. Wu, F. Wang, J. Liao, H. Zhang, C. X. Lian, J. Zhu and J. G. Deng, *Green Chem.*, 2007, **9**, 23–25; (*c*) J. Canivet and G. Suss-Fink, *Green Chem.*, 2007, **9**, 391–397; (*d*) L. Evanno, J. Ormala and P. M. Pihko, *Chem.–Eur. J.*, 2009, **15**, 12963–12967; (*e*) N. Haraguchi, K. Tsuru, Y. Arakawa and S. Itsuno, *Org. Biomol. Chem.*, 2009, **7**, 69–75; (*f*) Y. F. Tang, X. F. Li, C. X. Lian, J. Zhu and J. G. Deng, *Tetrahedron:Asymmetry*, 2011, **22**, 1530–1535; (*g*) L. Wang, Q. Zhou, C. H. Qu, Q. W. Wang, L. F. Cun, J. Zhu and J. G. Deng, *Tetrahedron*, 2013, **69**, 6500–6506; (*h*) H. Sugie, Y. Hashimoto, N. Haraguchi and S. Itsuno, *J. Organomet. Chem.*, 2014, **751**, 711–716.

6 K. Mashima, T. Abe and K. Tani, *Chem. Lett.*, 1998, 1199–1200.

7 X. F. Wu, X. H. Li, A. Zanotti-Gerosa, A. Pettman, J. K. Liu, A. J. Mills and J. L. Xiao, *Chem.–Eur. J.*, 2008, **14**, 2209–2222.

8 N. Fleury-Brégeot, V. de la Fuente, S. Castillón and C. Claver, *ChemCatChem*, 2010, **2**, 1346–1371.

9 S. H. Yalkowsky, *Solubility and Solubilization in Aqueous Media*, American Chemical Society, 1999.

10 J. W. Handgraaf and E. J. Meijer, *J. Am. Chem. Soc.*, 2007, **129**, 3099–3103.

11 A. Pavlova and E. J. Meijer, *ChemPhysChem*, 2012, **13**, 3492–3496.

12 X. Wu, J. Liu, D. Di Tommaso, J. A. Iggo, C. R. A. Catlow, J. Bacsa and J. Xiao, *Chem.–Eur. J.*, 2008, **14**, 7699–7715.

13 Y. S. Jung and R. A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492–5502.

14 P. A. Dub and T. Ikariya, *J. Am. Chem. Soc.*, 2013, **135**, 2604–2619.

15 (*a*) A. H. Ell, J. B. Johnson and J. E. Backvall, *Chem. Commun.*, 2003, 1652–1653; (*b*) C. P. Casey, G. A. Bikzhanova, Q. Cui and I. A. Guzei, *J. Am. Chem. Soc.*, 2005, **127**, 14062–14071; (*c*) J. S. M. Samec, A. H. Ell, J. B. Aberg, T. Privalov, L. Eriksson and J. E. Backvall, *J. Am. Chem. Soc.*, 2006, **128**, 14293–14305; (*d*) T. Privalov, J. S. M. Samec and J. E. Backvall, *Organometallics*, 2007, **26**, 2840–2848.

16 A. J. Blacker, E. Clot, S. B. Duckett, O. Eisenstein, J. Grace, A. Nova, R. N. Perutz, D. J. Taylor and A. C. Whitwood, *Chem. Commun.*, 2009, 6801–6803.

17 A. Nova, D. J. Taylor, A. J. Blacker, S. B. Duckett, R. N. Perutz and O. Eisenstein, *Organometallics*, 2014, **33**, 3433–3442.

18 D. G. Blackmond, M. Ropic and M. Stefinovic, *Org. Process Res. Dev.*, 2006, **10**, 457–463.

19 J. E. D. Martins, G. J. Clarkson and M. Wills, *Org. Lett.*, 2009, **11**, 847–850.

