Organic LETTERS

Letter

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Asymmetric Transfer Hydrogenation of Imines in Water by Varying the Ratio of Formic Acid to Triethylamine

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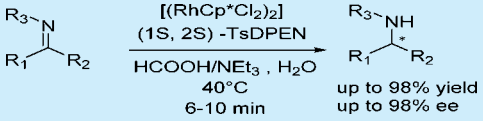
Supporting Information

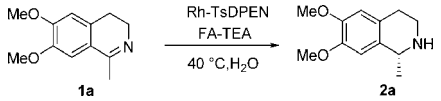
ABSTRACT: Asymmetric transfer hydrogenation (ATH) of imines has been performed with variation in formic acid (F) and triethylamine (T) molar ratios in water. The F/T ratio is shown to affect both the reduction rate and enantioselectivity, with the optimum ratio being 1.1 in the ATH of imines with the Rh-(1*S*,2*S*)-TsDPEN catalyst. Use of methanol as a cosolvent enhanced reduction activity. A variety of imine substrates have been reduced, affording high yields (94−98%) and good to excellent enantioselectivities (89−98%). In comparison with the common azeotropic F−T system, the reduction with 1.1/1 F/T is faster.



Enantiomerically enriched active amines are significant synthetic precursors for biologically active molecules in medical, pharmaceutical, agricultural sciences, flavor, and fragrance industries.[1] Different methods have been utilized for the synthesis of enantiomerically pure amines in the past few years.[2] Asymmetric transfer hydrogenation (ATH) of imines is one of the most popular methods due to its operational simplicity and avoidance of the use of hazardous hydrogen gas and pressure vessels.[3] Various chiral catalysts have been investigated for ATH of imines, but the most outstanding to date are the Ru and Rh complexes with the optically active *N*-toluenesulfonyl-1,2-diphenylethylenediamine (TsDPEN) ligand[4] in organic solvents with a formic acid−triethylamine azeotrope as a H donor.[2−4] The choice of reaction medium and H donor is important in achieving an ATH reaction with high efficiency. The metal catalyzed ATH of imines is mostly performed in an azeotropic mixture of formic acid (HCOOH) and triethylamine (NEt_3) (F−T), with the F/T molar ratio being 5:2 or with HCOONa as the hydrogen source and water as the solvent.[3−5] Recently we have reported a significant enhancement in ATH of imines in water with the use of methanol as a cosolvent.[6] The activity as well as enantioselectivity is very good with an azeotropic F/T and Rh or Ru complex/TsDPEN catalyst system.[2−6] However, it is observed in the literature that the main drawback of ATH in an azeotropic F/T is that some catalytic complexes exhibit sluggish activity and require a longer induction period under acidic conditions.[7] ATH of ketones has been investigated in water using F/T as the hydrogen donor, and the activity as well as enantioselectivity was found to be dependent on the F/T ratio (initial pH of the reaction mixture).[7b,8] To the best of our knowledge there are no reports on the effect of the F/T ratio (initial pH of the reaction mixture) on the activity and enantioselectivity of ATH of imines with water as solvent, and there are very few reports on pH dependent ATH of imines.[10] Herein we wish to report our results on the ATH of imines in water with F/T as the H donor. Variation of the F/T ratio in ATH of imines with water as a solvent was investigated, and it was found that ATH of imine is pH dependent. Significant improvement in imine conversion with excellent enantioselectivity was observed for a wide range of imine derivatives with Rh-(1*S*,2*S*)-TsDPEN catalyst under an optimum F/T ratio in water with a short reaction time.

To initiate this study, we examined the ATH of imine **1a** as a model substrate to amine **2a** as the product (Scheme 1) using

Scheme 1. ATH of Imine 1a by Varying FA−TEA Ratio



CH_2Cl_2 and H_2O as solvents (Table 1). The precatalyst was generated by treating (1*S*,2*S*)-Ts-DPEN (0.0075 mmol) with $[RhCl_2(Cp^*)_2]$ (0.0025 mmol) in water (1 mL) at 40 °C for 1 h,[11] and the reduction was started by introducing the HCOOH−NEt_3 (F/T) azeotrope (1.0 mL ; molar ratio F/T = 2.5/1) and **1a** with a substrate/catalyst (S/C) ratio of 100:1.

Table 1. Comparison of ATH of 1a with 2.5/1 F/T in CH_2Cl_2 and in H_2O[a]

entry	catalyst	f/t ratio	solvent	time (min)	conv (%)[b]	ee (%)[c]
1	Rh-TsDPEN	2.5/1	CH_2Cl_2	10	99	89
2	Rh-TsDPEN	2.5/1	H_2O	60	9	nd[d]
3	Rh-TsDPEN	2.5/1	H_2O	1440	99	2
4	Rh-TsDPEN	5.0/1	H_2O	180	0	nd[d]
5	Rh-TsDPEN	5.0/1	H_2O	300	2	nd[d]

[a]Reaction conditions: **1a**, 0.5 mmol; $[RhCp^*Cl_2]_2$, 0.0025 mmol; (1*S*,2*S*)-TsDPEN, 0.0075 mmol; F/T, 1 mL; H_2O, 1 mL; temp, 40 °C. [b]Determined by GC equipped with HP-1 column. [c]Determined by HPLC equipped with chiral column. [d]Not determined.

Received: March 26, 2015
Published: May 29, 2015

DOI: 10.1021/acs.orglett.5b00889
Org. Lett. 2015, 17, 2878−2881

As reported in the literature,[2a] the reaction proceeded smoothly with CH_2Cl_2 as solvent with F/T (2.5/1) as the H donor and 99% of imine **1a** was converted into (*R*)-**2a** in 10 min with 89% ee (Table 1, entry 1).

To our surprise, with H_2O as solvent, a much slower reaction rate was observed (Table 1, entry 2). Thus, only 9% conversion was observed for the reduction of **1a** at 40 °C in 1 h; the conversion rose to 99% after a prolonged time of 1440 min with a decrease in ee to 2% (Table 1, entry 2). The major difference was that the pH value of the azeotrope−water system was 3 at the beginning of the reaction, while that of the F/T azeotrope (2.5/1)−CH_2Cl_2 (organic solvent) was 5. We have investigated the effect of the initial pH of F/T by systematically varying the molar ratio of F/T in water, and the results are presented below.

The ATH of imine **1a** (0.5 mmol) was performed in water (1 mL) at various initial solution pH values by adjusting the F/T molar ratios in a 0.5 to 5.0 range; the total solution volume was kept constant at 2.0 mL. Figure 1a shows the graph of turnover

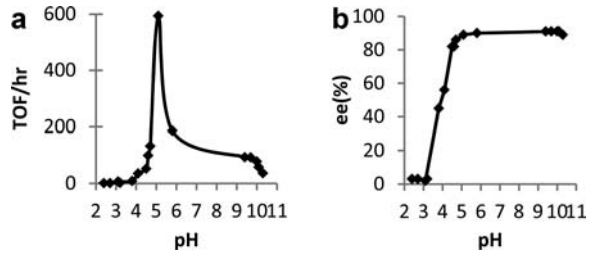


Figure 1. (a) TOF against initial solution pH values; (b) ee against initial solution pH for the reduction of imine **1a** (0.5 mmol) by HCOOH−NEt_3 in water (2 mL total volume) with $[RhCp^*Cl_2]_2$ (0.0025 mmol), (1*S*,2*S*)-TsDPEN (0.0075 mmol) at 40 °C. The initial pH values were determined by varying the HCOOH/NEt_3 molar ratios from 5.0/1.0 to 0.5/1.0.

frequency (TOF) as a function of initial pH of the F/T−water mixture (see Table S1 in Supporting Information (SI) for details), while Figure 1b shows the ee versus initial pH of the F/T−water mixture. The reaction barely took place at low pH values (pH range 2.4−3.1) and slowly accelerated at pH 3.1. At high F/T ratios (F/T ratio 5.0−2.0, pH range 2.4−3.8), the reaction medium was strongly acidic and only 19% conversion was achieved in 24 h. As seen in Table 1 with the ATH of imine **1a** at F/T ratio 5.0 (initial pH 2.4), the reaction did not proceed even after 180 min of reaction time and only 2% conversion was attained at 300 min (Table 1, entries 4−5). The results observed indicate sluggish activity in terms of conversion and ee and a long induction period under acidic conditions. Zhou et al. have observed similar results for ATH of ketones. Activity increased significantly with the increase in initial pH of the F/T solution in the range 4.8−5.6, and the highest TOF value of 594 h^{-1} was observed at pH 5.1. Activity decreased with the further increase in pH of the solution and decreased significantly with the increase in pH beyond 9.4. TOF values varied significantly with the change in initial pH values of F/T mixtures. The observed results confirm the pH dependent ATH of imines in water. The higher rates at pH values greater than 4 could be due to the increased concentration of $HCOO^-$. At pH >4, HCOOH (pK_a = 3.6) exists predominately as $HCOO^-$, which is essential for the formation of the rhodium formato complex as per the mechanism of ATH reaction.

In order to understand the role of pH in detail, ATH of **1a** was investigated by systematically varying the F/T ratio in a range of 1.5 to 0.5, and the results obtained for ATH of **1a** (conversion) after 60 min of reaction time with intermediate sampling are presented in Figure 2. As shown in Figure 2, the

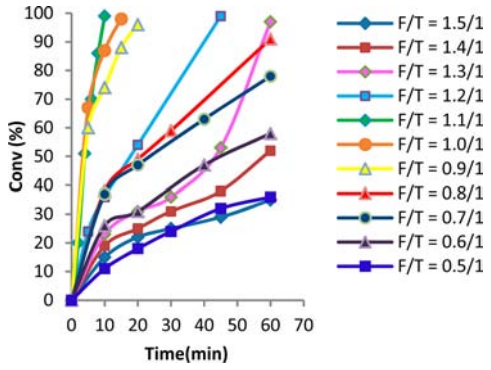


Figure 2. Conversion versus reaction time for ATH of imine **1a** using Rh-TsDPEN in F/T mixtures at different initial F/T ratios at 40 °C. **1a**, 0.5 mmol; F/T, 1 mL; H_2O, 1 mL; $[RhCp^*Cl_2]_2$, 0.0025 mmol; (1*S*,2*S*)-TsDPEN, 0.0075 mmol.

reduction of imine **1a** proceeded slowly at F/T ratio 1.5 to 1.4 (pH range 4.1 to 4.5) and a **1a** conversion of 30−50% was observed in 60 min. The reaction accelerated with the decrease in F/T ratio between 1.3 to 1.1 (pH range 4.6−5.1), and complete conversion of **1a** was obtained in just 10 min at an F/T ratio of 1.1. A remarkable acceleration in rate was observed for ATH of **1a** at F/T ratio 1.1/1 in water compared to those with azeotropic F/T (2.5/1) in water, and the results are presented in Figure 3. With a further decrease in F/T ratio to

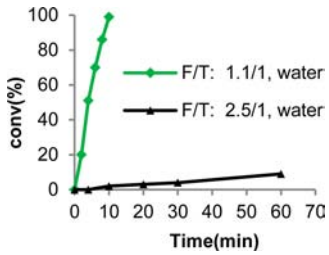


Figure 3. Comparison of ATH of **1a** in 1.1/1 F/T in water and 2.5/1 F/T in water: **1a**, 0.5 mmol; total volume, 2 mL; at 40 °C.

1.0 and 0.9, the pH of the reaction mixture became basic (pH 8.7−9.4) and the reduction slowed and reached completion in 30 and 60 min, respectively. The rate of reduction decreased significantly under strongly basic conditions (F/T, 0.8 to 0.5; pH range 9.7−10.3). Thus, the results of the F/T ratio variation show that ATH of imines proceeded effectively under slightly acidic conditions (pH 5.1).

Enantioselectivities were determined at the end of the reaction, and the results are presented in Figure 1b. The results indicate that at acidic pH (2.4−4.1) ee values were very low (3−56%). As the pH increased, the ee values increased. Thus, for reactions with pH values in a 5.1−10.3 range, ee values were high (82−91%) and remained constant up to pH 10.3. As seen from Figure 1a and b, both the rate of reduction and ee were strongly dependent on the initial pH value and best results were observed at an initial pH of 5.1 (F/T ratio: 1.1/1). Variation in ee with changes in F/T ratio from 1.5:1 to 0.5:1 with time

DOI: 10.1021/acs.orglett.5b00889
Org. Lett. 2015, 17, 2878−2881

sampling is presented in Figure S1 in the SI. The ee was in a range of 54−58% at F/T ratio 1.5 and increased to ∼80% for F/T ratio 1.4:1 and 1.3:1 indicating strong dependence on the initial pH of the reaction mixture. The ee values were in an 84−89% range for experiments with the F/T ratio in a 1.2:1 to 0.5:1 range indicating the ee was not significantly affected by the higher basicity of the reaction mixture. These results with decreased ee values at acidic pH resemble those of aqueous ATH[8,11,12] and F/T variation of ketones in water.[7,8]

The results obtained clearly show that the activity and ee of ATH of imines are pH regulated, similar to ATH of ketones.[10−13]Based on the literature reports[14] and results obtained in the present work, we propose two catalytic cycles likely to operate under acidic and basic conditions, depending on the F/T molar ratios (Scheme S1 and discussion, SI).Under strong acidic conditions the Rh-TsDPEN chelate is broken resulting in lower activity and ee. At pH 5.1 and above, the chelate is intact giving good activity and ee.The best results for ATH of **1a** were obtained at F/T ratio 1.1/1 and pH 5.1, which is a slightly acidic pH. Thus, probably iminium ion formation occurred very efficiently at this pH value. The iminium ion formed might be entering into the catalytic cycle and accepts hydride from Rh-hydride species, forming amine **2a** as the product.

The efficiency of various catalysts was tested with (1*S*,2*S*)-TsDPEN ligands for ATH of imine **1a** with F/T (molar ratio of 1.1/1) in water, and the best results were obtained with the Rh-TsDPEN catalyst (Table S2, SI). In our recently published paper we observed significant enhancement in activity for ATH of imines in water with HCOONa as the hydrogen source with methanol as a cosolvent.[6] Based on these results we tested methanol as a cosolvent for catalyst screening with F/T (molar ratio of 1.1/1) in water (Table 2, entry 2). From the results, the Rh catalyst was found to be the most active catalyst and ATH reaction of **1a** achieved the highest conversion of 99% with 89% ee in a short reaction time of 10 min using the Rh-TsDPEN catalyst and water as solvent (Table 2, entry 1) and 99% conversion was achieved in 6 min with 89% ee with methanol as cosolvent (Table 2, entry 2). The rate of reduction of **1a** was slow for all other catalysts tested as compared to the Rh based catalyst (Table S2, SI) however; activity increased with the use of methanol as a cosolvent for both Ru and Ir catalysts. The enhanced reaction rate with methanol as a cosolvent could be attributed to the fact that cosolvents have H-bond donor and/or acceptor groups for aqueous solubility and a small hydrocarbon region that serves to disrupt the strong H-bond network of pure water, thereby increasing the solubility of reactants/products in the reaction mixture.

Optimum results in terms of both activity and enantioselectivity for ATH of **1a** in the F/T−H_2O/MeOH system were obtained with the Rh-TsDPEN catalyst, and hence a screening of various imine derivatives (Scheme 2) was performed with S/C ratio 200 with the Rh catalyst; the results are presented in Table 2. Imines with alkyl groups on the imino carbon displayed 99% conversions in 6 min (95−98% yields) with ee's of 83−99% (Table 2, entries 3−9). The chain length of the alkyl group had little effect on the enantioselectivity (Table 2, entry 6). The imine **1h** having a bulky phenyl group on the imino carbon required 60 min to achieve 87% conversion with an ee of 5%, and in this case a second aromatic system apparently interferes with selective catalyst binding, resulting in a low ee value (Table 2, entry 10).[2a]

With an aromatic group with more substituents, the activity was very sluggish and only 29% conversion was attained for imine **1i** in 60 min with a 2% ee value (Table 2, entry 11). The investigations were extended to include the reduction of cyclic sulfonamide and *β*-carboline derivatives (Table 2, entries 12−14). Cyclic sulfonamides have been widely used in asymmetric reactions.[16] *β*-Carboline derivative **3a** was obtained in 95% yield with 91% enantioselectivity (Table 2, entry 12), and **3b** was obtained in 92% yield with 97% enantioselectivity (Table 2, entry 13). Cyclic sulfonamide **5** was reduced in 6 min with a 96% yield and 32% ee (Table 2, entry 14). When ATH of imine **7** was performed at F/T ratio 1.1/1, a 96% yield obtained in 15 min with 81% enantioselectivity (Table 2, entry 15). We also performed ATH of **1a** at an S/C ratio of 500 under similar

Scheme 2. ATH of Imines with Rh-TsDPEN in 1.1/1 F/T

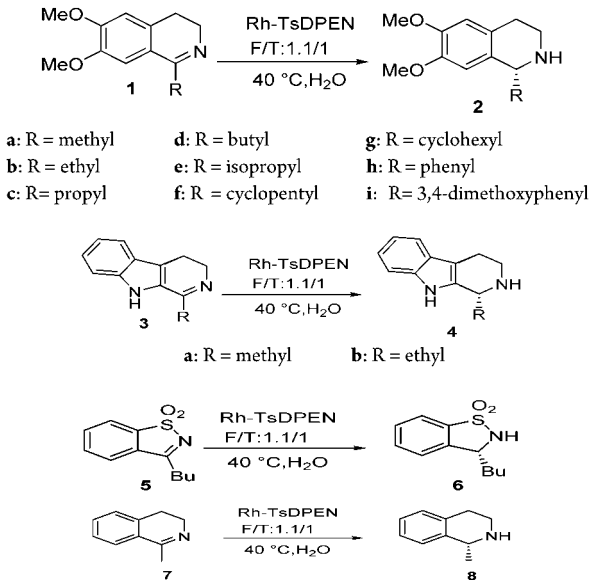


Table 2. ATH of Imines with Rh-TsDPEN in F/T (1.1/1)−H_2O/MeOH[a]

entry	imine	s/c	time (min)	yield (%)	ee (%)[d]
1[b]	**1a**	100	10	99[c]	89
2	**1a**	100	6	99[c]	89
3	**1a**	200	6	98	89
4	**1b**	200	6	95	85
5	**1c**	200	6	95	88
6	**1d**	200	6	96	88
7	**1e**	200	6	98	83
8	**1f**	200	6	97	97
9	**1g**	200	6	98	99
10	**1h**	200	60	87[c]	5
11	**1i**	200	60	29[c]	2
12	**3a**	200	10	95	91
13	**3b**	200	10	92	97
14	**5**	200	6	96	32
15	**7**	200	15	96	81
16	**1a**	500	10	92	88

[a]Reaction conditions: Imine, 1 mmol; $[RhCp^*Cl_2]_2$, 0.0025 mmol; (1*S*,2*S*)-TsDPEN, 0.0075 mmol; F/T (1.1/1) 1 mL; H_2O, 0.5 mL; MeOH, 0.5 mL; at 40 °C. [b]F/T (1.1/1) 1 mL; H_2O, 1 mL. [c]Conversion determined by GC using HP1 column. [d]ee determined by Chiral HPLC.

DOI: 10.1021/acs.orglett.5b00889
Org. Lett. 2015, 17, 2878−2881

conditions, and the reaction proceeded with a 92% yield of **2a** in 10 min with 88% enantioselectivity (Table 2, entry 16). Thus, a 1.1/1 F/T ratio in a water−methanol system with the Rh-TsDPEN catalyst was found to be highly effective for a higher substrate loading.

Thus, we have developed a simple protocol for efficient ATH of imines in water with F/T as the H-donor and a Rh-TsDPEN catalyst system. The reaction was found to be strongly dependent on the initial pH of F/T in water, and the best results were obtained with an F/T molar ratio of 1.1/1. Further enhancement in activity was observed with methanol as a cosolvent. Under such conditions excellent yields (94−98%) and good enantioselectivities (89−98%) were observed in a short reaction time for a variety of imine substrates including β-carboline, cyclic sulfonyl imines, and methoxy substituted cyclic imine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and HPLC traces of products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00889.

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.orglett.5b00889
Org. Lett. 2015, 17, 2878−2881