Rhodium catalyzed pH Dependent Asymmetric Transfer Hydrogenation of Imines in Water with Formic acid-Triethylamine as Hydrogen Donor

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Abstract: Rhodium catalyzed 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 6-10 min reaction time. In comparison with the common azeotropic F–T system, the reduction with 1.1/1 F/T is faster.

Keywords: asymmetric transfer hydrogenation, rhodium, water.

1. Introduction

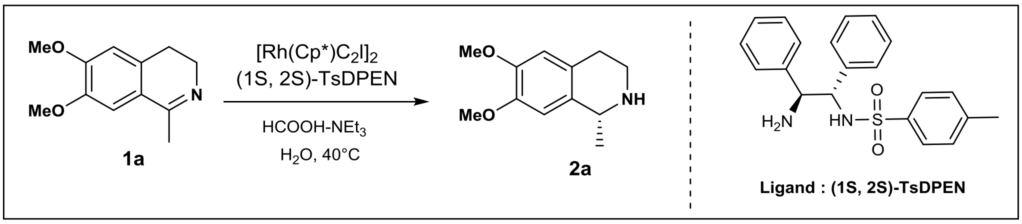
Enantiomerically enriched active amines are significant synthetic precursors for biologically active molecules in medical, pharmaceutical, agricultural sciences, flavor, and fragrance industries [1]. The choice of reaction medium and H donor is important in achieving an ATH reaction with high efficiency. 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 [2, 3]. Herein we wish to report our results on the ATH of imines in water with F/T as the H donor. Role of pH was investigated by varying the F/T ratio in ATH of imines with water and it was found that ATH of imine is pH dependent.

2. Experimental

Round bottom flask containing a magnetic stirring bar, and [Rh(Cp*)Cl2]2(1.55 mg, 0.0025 mmol)and (1S, 2S)-TsDPEN (2.75 mg, 0.007 5mmol) in distilled water (1 ml) was stirred for 1 h at 40°C to generate the pre-catalyst. To the above pre-catalyst solution imine substrate (0.5 mmol), 1.1 F/T(formic acid-triethylamine) mixture 1ml was added into precatalyst solution. The reaction mixture was stirred at 40°C for the time indicated, then cooled to room temperature and basified with 0.5 M Na_2CO_3 solution and extracted with DCM (3 ml x 2). Organic phase was dried over Na2SO4 and solvent was removed under reduced pressure. Conversion was determined by GC and enantioselectivity was determined by Chiral HPLC

3. Results and discussion

ATH of **1a** was investigated using rhodium catalyst and (1R,2R)-N-*p*-Tosyl-1,2-diphenylethylenediamine (TsDPEN) as a ligand by varying ratios of F/T (formic acid/ triethylamine) in water (Scheme 1).



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

Reaction was investigated at different F/T ratio (0.5 to 5.0) with H_2O as solvent. ATH of imines was found to be strongly pH dependent with water as solvent. Figure 1 shows the graph of turnover frequency (TOF) and enantioselectivity versus initial pH of the F/T−H_2O mixture. The F/T ratio is shown to affect both the reduction rate and enantioselectivity for ATH reaction, with the optimum F/T ratio being 1.1 in the ATH of imines with the Rh-(1S,2S)-TsDPEN catalyst. 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.

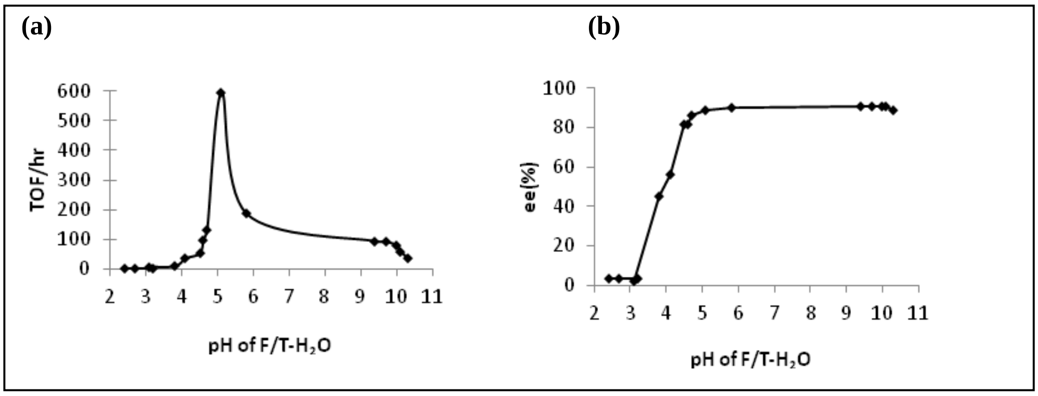


Figure 1. (a)TOF against initial pH; (b) ee against initial pH of F/T solution for ATH of imine **1a:**0.5 mmol, Rh-TsDPEN: 0.005 mmol, F/T: 1 ml, H_2O: 1 ml, Temp: 40°C

The higher rates at pH values greater than 4 could be due to the increased concentration of $HCOO^-$. At pH >4, HCOOH (pKa= 3.6) exists predominately as $HCOO^-$, which is essential for the formation of the rhodium formato complex as per the mechanism of ATH reaction. Use of methanol as a cosolvent enhanced reduction activity of imines. Variety of imine substrates have been reduced with 1.1F/T mixture as reductant, affording high yields (94−96%) and good to excellent enantioselectivities (89−98%).

4. Conclusions

We have developed a simple protocol for efficient ATH of imines in water with F/T as the H-donor and Rh-(1S, 2S)-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.

References

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