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A practical process to chiral ferrocenyl alcohols via asymmetric transfer hydrogenation catalyzed with a PEG-bound Ru catalyst in water and its application in preparing Ugi's amine

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ABSTRACT

Chiral ligand (*S*,*S*)-PEG-BsDPEN has been found to be efficient for the asymmetric transfer hydrogenation of various ferrocenyl ketones. With sodium formate as a hydrogen donor, PEG 2000 and water as the reacting media, the catalyst system could be recycled several times. This procedure could be scaled up to a 100 mmol or more in a common round flask which is easy to perform in ordinary laboratories. The preparation of Ugi's amine with the ferrocenyl alcohol was also investigated.

1. Introduction

Chiral ferrocenyl ligands have been successfully applied in a variety of asymmetric catalytic reactions. Hayashi et al. prepared a series of chiral ferrocenylphosphine ligands starting from chiral α-dimethyl aminoethylferrocene and successfully used these ligands in asymmetric hydrosilylation, hydrogenation, and Grignard cross coupling reactions.[1] Ito et al. reported the preparation of chiral diphosphine ligands possessing both central and planar chiral elements on biferrocene backbone.[2] Togni et al. developed a series of highly effective bisphosphanes such as Josiphos and chiral tridentate phosphines. They successfully applied these chiral ligands in the industrial production of chiral compounds, Pd-catalyzed allylic alkylation, and hydroamination of activated olefins.[3] Knochel et al. prepared a number of ferrocenyl ligands with two phosphanyl substituents and C_2-symmetrical ferrocenyl diamino diphosphines (diamino FERRIPHOS ligands) for asymmetric hydrogenation and Pd(0)-catalyzed allylic substitution reactions, rhodium-catalyzed enantioselective reduction of methyl α-acetamidoacrylates, with excellent results.[4] Spindler described a series of diphosphines (the Walphos ligand family, based on the phenylferrocenylethyl backbone) and used them in the rhodium- or ruthenium-catalyzed asymmetric hydrogenation of olefins and ketones with enantioselectivities of up to 95% and 97%, respectively. A 2-isopropylcinnamic acid derivative of industrial interest was hydrogenated with turnover numbers of >5000 in 95% ee.[5] Boaz et al. reported the preparation of phosphinoferrocenylaminophosphines and the application of them in the rhodium-catalyzed asymmetric hydrogenation.[6] Recently, in an attempt to broaden the scope of chiral ferrocenyl ligands, we prepared a series of new chiral phosphine–phosphinites, phosphine–phosphoramidites, phosphine–phosphites, and fluorinated phosphinoferrocenylaminophosphines based on the ferrocene framework. Good to excellent ee values (up to 99.7% ee) and nearly quantitative yields were obtained in the Rh-catalyzed asymmetric hydrogenation of enamides and α-dehydroamino acid derivatives.[7]

Although chiral ferrocenyl alcohols are the key intermediates for the synthesis of various chiral ligands, there were limited reports on the preparation of these useful compounds via asymmetric catalysis so far. Ding et al. reported the asymmetric hydrogenation of ferrocenyl ketones catalyzed by a Ru(II) catalyst with achiral monodentate phosphine and chiral 1,2-diphenylethylenediamine ligand, up to 87% yield with 87% ee was obtained.[8] Hayashi et al. reported the first example of asymmetric nucleophilic addition of dialkylzinc to ferrocenecarboxaldehyde[9a] and Molina et al. described the synthesis of 8-*N*,*N*-bis(ferrocenylmethyl)aminomenthol and its application in the enantioselective addition of diethylzinc to aldehydes.[9b] Chan et al. used [((*R*)-xylyl-P-Phos)$RuCl_2$((*R*,*R*)-DPEN)] as the precatalyst for the hydrogenation of acetyl ferrocene, which provided excellent yields and ees in optimal conditions.[10] Matsumura reported the asymmetric reduction of ferrocenyl ketones by Cl_3SiH with a catalyst derived from L-proline.[11] Recently, Rodrigues described their studies on the asymmetric transfer hydrogenation (ATH) of ferrocenyl ketones with HCOOH/Et_3N azeotrope as the hydrogen donor and Ru/TsDPEN as the catalyst.[12] Under optimal conditions, high ee values (up to 98% ee) were obtained but with moderate isolated yield (69%).

Generally, isopropyl alcohol and the HCOOH/Et_3N azeotrope were commonly used as the hydrogen donor and reaction media in asymmetric transfer hydrogenation. Xiao et al. employed water as the solvent and HCOONa as the hydrogen donor in this reaction.[13] They found that the reaction rates could be accelerated in water with Ru-TsDPEN as the catalyst and with a slight decrease

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in enantioselectivities. Recently, we developed a new chiral ligand PEG-BsDPEN which is practical for the Ru-catalyzed asymmetric transfer hydrogenation of aromatic ketones in water.[14] With this background, it is possible to develop a method to prepare chiral ferrocenyl alcohols in water for improving the yields and the recyclability of the catalyst so that the associated chiral ligands can be made on a large scale and used in ordinary laboratories. Herein we report our preparation of chiral ferrocenyl alcohols via an asymmetric transfer hydrogenation catalyzed with PEG-bound Ru catalyst in water and its application in the preparation of chiral Ugi's amine.

2. Results and discussion

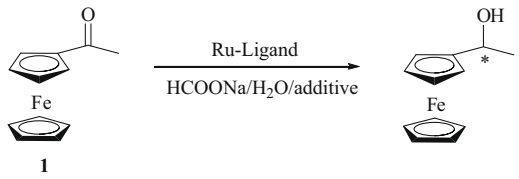
We began our study of the asymmetric transfer hydrogenation of ferrocenyl ketones with water as the reaction media for the development of a practical protocol. We first used Ru-TsDPEN as a catalyst for the asymmetric transfer hydrogenation of ferrocenyl ketone **1** with HCOONa as the hydrogen donor. After the reaction proceeded for 24 h at ambient temperature, only trace products were obtained. The yield rose to 67% (with 95% ee) when the reaction temperature was increased to 40 °C. It could be concluded that the solubility of ferrocenyl ketone **1** in water resulted in the poor yield of the product. For improving the solubility of the substrate and catalyst in water, we added dichloromethane or PEG to the reaction system and found that both of them were favorable to the improvement of yields and ee values (Table 1, entry 4–7, 98% yield with 96% ee for dichloromethane, 96% yield with 97% ee for PEG 400, 94% yield with 98% ee for PEG 750, and 95% yield with 97% ee for PEG 2000, respectively).

We then screened other catalysts such as Ru-TsCYPN and Ru-PEGBsDPEN (Scheme 1) for the reaction with PEG 2000 as the additive. Both catalysts gave very good results under the optimal conditions (Table 1, entry 8–9, 90% yield with 93% ee for Ru-TsCYPN and 94% yield with 98% ee for Ru-PEGBsDPEN as the catalyst, respectively).

The ATH reaction of other ferrocenyl ketones with HCOONa as the hydrogen donor and Ru-PEGBsDPEN as the catalyst was also performed and the results are listed in Table 2. All ferrocenyl ketones could be reduced under the optimal reaction conditions with good yields and ees.

The use of expensive noble metal and chiral ligands is important for the recycling of catalysts to the asymmetric hydrogen transfer. Although the Ru-TsDPEN catalyst could be recycled in the asymmetric hydrogen transfer of typical aromatic ketones by adding surfactant or PEG to the reaction system,[15] there were problems in carrying out the recycling of the catalyst for acetyl ferrocene as the substrate. The secondary alcohols derived from this ketone could not be extracted with non-polar solvents such as hexane, which many researchers have used for other ketones. Polar solvents, such as ether, could effectively extract the products, but the catalyst Ru-TsDPEN was also lost in the process. On the other hand, the solubility of PEG 2000 in ether is very low but the catalyst Ru-PEGBsDPEN dissolved in the aqueous solution of PEG 2000 well. Keeping these characteristics of catalyst, substrate and additive in mind, we carried out the asymmetric transfer

Table 1
Various conditions for the asymmetric transfer hydrogenation[a]

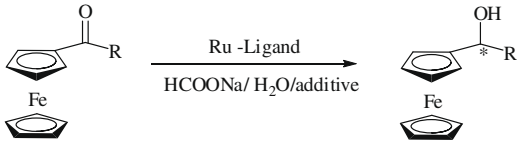


1

Entry	Catalyst	Temperature	Additive	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	TsDPEN	rt	None	Trace	—	
2	TsDPEN	40	None	67	95	(*S*)
3	TsDPEN	60	None	74	95	(*S*)
4	TsDPEN	40	CH_2Cl_2	98	96	(*S*)
5[e]	TsDPEN	40	Peg400	96	97	(*S*)
6[e]	TsDPEN	40	Peg750	94	98	(*S*)
7[e]	TsDPEN	40	Peg2000	95	97	(*S*)
8[e]	cyTsDPEN	40	Peg2000	90	93	(*S*)
9[e]	PEG-BsDPEN	40	Peg2000	94	98	(*S*)

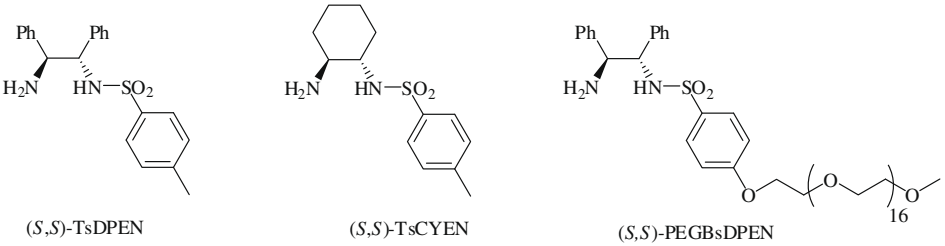
[a] The reaction was carried out for 24 h (S/C = 100/1).
[b] Isolated yields were obtained by flash chromatography.
[c] The enantiomeric excess was determined by HPLC on a chiralcel AS-H column.
[d] The absolute configuration was assigned on the basis of signs of specific rotation.[12].
[e] PEG/H_2O = 1/1(w/w).

Table 2
The ATH reaction of other ferrocenyl ketones[a]



Entry	R	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	CH_2Cl	95	98	(*S*)
2	Ph	97	93	(*R*)
3	2-MeOPh	90	97	—
4	1-Napthyl	94	98	—
5	2-Napthyl	94	90	—

[a] The reaction was carried out for 24 h (S/C = 100/1).
[b] Isolated yields were obtained by flash chromatography.
[c] The enantiomeric excess was determined by HPLC on a chiralcel AS-H column.
[d] The absolute configuration was assigned on the basis of signs of specific rotation.[10,12]



Scheme 1. Chiral ligands used for asymmetric transfer hydrogenation of ferrocenyl ketone.

hydrogenation of acetyl ferrocene with Ru-PEGBsDPEN as the catalyst and PEG2000-H_2O as the reaction media. The results indicated that the catalyst-PEG2000 system indeed could be well separated from the product chiral ferrocenyl alcohol **2**. Table 3 summarizes the results of the recycling of the catalyst and the results indicate that good chemical yields were obtained even on the fourth runs, and the enantioselectivity was consistent over all the five runs.

We also scaled-up this protocol to a 100 mmol (22.8-g level) in a common round flask and gratifyingly found the resulting alcohol reaching the same level of yield and ee (95% yield with 98% ee). This indicated that this strategy provided an easy and practical method for preparing chiral ferrocenyl alcohol without high pressure hydrogen in ordinary laboratories.

The preparation of *N*,*N*-dimethyl-l-ferrocenylethylamine (Ugi's amine) using chiral ferrocenyl alcohol **1** as starting material is shown in Scheme 2.

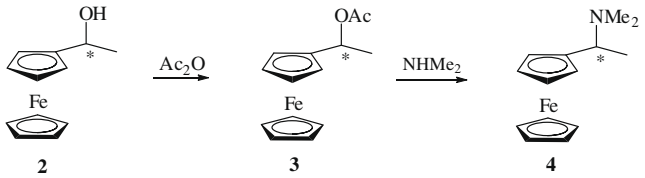
Usually, the preparation of Ugi's amine and its analogs has been carried out in organic solvents such as ethanol or methanol, and a high concentration of amine (up to 50%) had to be used in the amination of the acetate of ferrocenyl alcohols to produce the corresponding chiral amine.[1c] As an alternative method when such a high concentration of dimethylamine is very convenient, we tried to carry out the reaction with a 33% dimethylamine aqueous solution in ethanol. However, we failed to obtain satisfactory chemical yields at such a low concentration of dimethylamine. Considering that PEG has been successfully used as a reaction medium and additive in a variety of organic reactions, we carried out the reaction in the presence of PEG as additive. When polyethyleneglycol-2000 (PEG 2000) was used as an additive, the reactant could effectively react in aqueous medium with a low concentration of dimethylamine.

3. Conclusion

In conclusion, we have developed an efficient process for the preparation of chiral ferrocenyl alcohols which were the key intermediates for the preparation of various chiral ligands. With Ru-PEGBsDPEN as the catalyst, the reaction could be carried out in a common round flask using PEG 2000 and water as the reaction medium. Comparing with HCOOH/Et_3N azeotrope as the hydrogen donor and Ru-TsDPEN as the catalyst, the chemical yields were improved from 69% to more than 90% and the catalyst system could be used up to five times. The 100 mmol (or more) reaction scale makes this strategy especially suitable for ordinary laboratories.

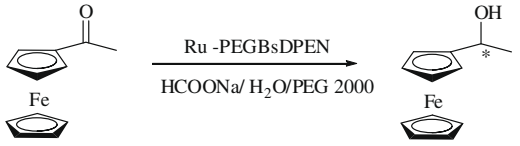
4. Experimental

The NMR spectra were recorded with TMS as the internal standard on a Varian 300 spectrometer. Coupling constants were given in Hz. Enantiomeric excess was determined by HPLC on Chiralcel AS-H columns. Optical rotations were determined on a Perkin Elmer 341 polarimeter. MS spectra were recorded on an Agilent LC-MS 6120 with ESI or APCI. All the asymmetric transfer hydrogenation and the catalyst recycling were performed under an argon atmosphere. The reactions were monitored by thin layer chromatography coated with silica gel.



Scheme 2. Preparation of Ugi's amine.

Table 3
Catalyst recycling of asymmetric transfer hydrogenation of acetyl ferrocene[a]



Entry	Time (d)	Yield[b] (%)	ee[c] (%)
1	1	94	97
2	1	92	97
3	2	94	97
4	2	83	96
5	2	75	95

[a] The reaction was carried out at 40 °C (S/C = 100/1).
[b] Isolated yields were obtained by flash chromatography.
[c] The enantiomeric excess was determined by HPLC on a chiralcel AS-H column.

4.1. General procedure for the asymmetric transfer hydrogenation of ferrocenyl ketones

Under an argon atmosphere, $[RuCl_2(p\text{-cymeme})]_2$ (3.1 mg, 0.005 mmol) and PEGBsDPEN (16.1 mg, 0.012 mmol) in degassed H_2O (1 mL) were stirred at 40 °C for 1 h to form the Ru-PEGBsDPEN catalyst. After the yellow catalyst solution was cooled to room temperature, a mixture of acetyl ferrocene (228.0 mg, 1 mmol), HCOONa (340 mg, 5 mmol), and PEG2000 (1 g) was added. Diethyl ether was added to the mixture after the mixture had been stirred at 40 °C for 24 h under argon. The ether solution was separated and then the solvent was removed under reduced pressure. The residue was purified by flash column on silica (EtOAc/hexane 1:10) to afford the product and the ee value was determined by HPLC analysis on a chiralcel AS-H column. The aqueous solution of PEG 2000 and the catalyst were added to the substrate and HCOOH for the next recycle.

4.1.1. (*S*)-(+)-1-Ferrocenylethanol 1

Yellow solid, 94% yield, 98% ee (determined by Daicel Chiralpack AS column, hexane/*i*-PrOH 90/10, 0.5 mL/min, 14.5 min (major), 15.7 min (minor); $[\alpha]_D^{20} = +28$ (*c* 1.33, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): 4.56 (m, 1H), 4.17–4.28 (m, 9H), 1.85 (d, 1H), 1.45 (d, 3H); ^{13}C NMR ($CDCl_3$): 94.6, 68.2, 67.9, 67.8, 66.1, 66.0, 65.4, 23.8; MS (ESI) *m/z* (%): 230.3.

4.1.2. Preparation of (*S*)-l-Ferrocenylethyl acetate[17]

A solution of 47.5 ml (504 mmol) of Ac_2O and a catalytic amount of DMAP were added to a stirred solution of 23 g (100 mmol) of (*S*)-l-ferrocenylethanol in 185 ml of freshly distilled triethylamine. After stirring for 17 h at room temperature, the orange solution was partitioned between water and EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The oily residue obtained after solvent evaporation was used for the next step without further purification.

4.1.3. Preparation of (*S*)-*N*,*N*-dimethyl-1-ferrocenylethylamine

To the (*S*)-l-Ferrocenylethyl acetate, 48 mL (320 mmol) of aqueous 33% dimethylamine and 20 mL of PEG were added. After the mixture was stirred at room temperature for 3 days, ethyl acetate (30 mL) was added and the organic layer was separated.

The organic layer was extracted with 10% phosphoric acid. The aqueous solution of phosphoric acid was made alkaline (pH 9) by adding 3 M sodium hydroxide and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography to give 22 g of the pure product (85.6% isolated yield). ^{1}HNMR (300 MHz, $CDCl_3$), 1.54 (d, 3H), 2.18 (s, 6H), 3.47 (m, 1H), 4.12 (s, 5H), 4.17–4.20 (m, 4H) ppm. The enantiomeric excess of the *N*,*N*-dimethyl-l-ferrocenylethylamine (97% ee) was determined by ^{1}H NMR spectroscopy using (*S*)-mandelic acid as a chiral protonating agent.[16]

The solutions of crude Ugi's amine (97% ee) obtained above and 12.9 g of (*R*)-(+)-tartaric acid, each in 50 ml of methanol, are mixed at 55 °C and seeded. After slow cooling, 31.5 g of the tartrate of (*S*)-**4** is obtained, which is set free to 19.8 g (90% yield, >99% ee) of (*S*)-**4**.

Acknowledgments

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References

1. (a) Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, A. A. *J. Am. Chem. Soc.* **1976**, *98*, 3718; (b) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138; (c) Ohno, A.; Yamane, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 2495; (d) Han, J. W.; Tokunaga, N.; Hayashi, T. *Helv. Chim. Acta* **2002**, *85*, 3848.
2. Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 593.
3. (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062; (b) Barbaro, P.; Togni, A. *Organometallic* **1995**, *14*, 3570; (c) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30.
4. (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3112; (b) Almena Perea, J. J.; Borner, A.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 8073; (c) Lotz, M.; Ireland, T.; Almena Pera, J. J.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1839; (d) Lotz, M.; Kramer, G.; Knochel, P. *Chem. Commun.* **2002**, 2546.
5. Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.
6. Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421.
7. (a) Li, X.; Jia, X.; Xu, L.; Kok, S. H. L.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1904; (b) Jia, X.; Li, X.; Lam, W. S.; Kok, S. H. L.; Xu, L.; Lu, G.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2273.
8. Jing, Q.; Zhang, X.; Sun, J.; Ding, K. *Adv. Synth. Catal.* **2005**, *347*, 1193.
9. (a) Matsumoto, Y.; Ohno, A.; Lu, S.; Hayashi, T.; Oguni, N.; Hayashi, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1763; (b) Vilaplana, M. J.; Molina, P.; Arques, A.; Andres, C.; Pedrosa, R. *Tetrahedron: Asymmetry* **2002**, *13*, 5.
10. Lam, W.; Kok, S. H. L.; Yeung, T. T. L. A.; Wu, J.; Cheung, H. Y. b.; Lam, F. L.; Yeung, C. H.; Chan, A. S. C. *Adv. Synth. Catal.* **2006**, *348*, 370.
11. Matsumura, Y.; Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O. *Org. Lett.* **2006**, *8*, 3789.
12. Ursini, C. V.; Mazzeo, F.; Rodrigues, J. A. R. *Tetrahedron: Asymmetry* **2006**, *17*, 3335.
13. Wu, X.; Li, X.; Xiao, J. *Org. Biomol. Chem.* **2004**, *2*, 1818–1821.
14. (a) Liu, J.; Zhou, Y.; Wu, Y.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2008**, *19*, 832; (b) Liu, J.; Zhou, D.; Jia, X.; Huang, L.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2008**, *19*, 1824.
15. Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *5*, 2103.
16. Kataeva, N. A.; Grishin, Yu. K.; Dunina, V. V. *Russ. Chem. Bull.* **2001**, *50*, 1323.
17. (a) Gokel, G.; Marquarding, D.; Ugi, I. *J. Org. Chem.* **1972**, *37*, 3052; (b) Woltersdorf, M.; Kranich, R.; Schmalz, H.-G. *Tetrahedron* **1997**, *53*, 7219.