ORGANIC LETTERS

2003
Vol. 5, No. 12
2103−2106

Asymmetric Transfer Hydrogenation of Prochiral Ketones in Aqueous Media with New Water-Soluble Chiral Vicinal Diamine as Ligand

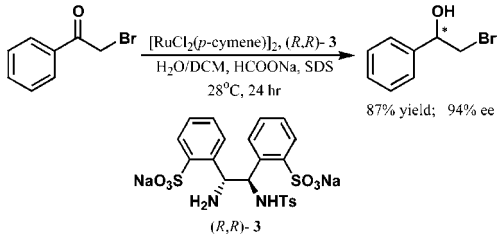
Yaping Ma, Hui Liu, Li Chen, Xin Cui, Jin Zhu, and Jingen Deng*

Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, the Chinese Academy of Sciences, Chengdu 610041, China

jgdeng@cioc.ac.cn

Received March 24, 2003

ABSTRACT



An easily accessible water-soluble chiral *o*-sulfonated 1,2-diphenylethlenediamine 2 and its mono-*N*-tosylated derivative 3 were synthesized for the first time. The ruthenium-complex-catalyzed reduction of prochiral ketones in aqueous media has been examined by using 3 as ligand and sodium formate as the source of hydrogen. The asymmetric transfer hydrogenation of *ω*-bromo acetophenones was achieved, in which only formate displacement occurred when formic acid/triethylamine azeotrope was used as the hydrogen donor.

As a consequence of the increasing demand for atom economy and environmentally friendly methods, the water-soluble ligands and their metal complexes are of great interest in application to catalytic synthesis because of simpler product separation and the possibility of recycling. It is not necessary to use vigorous drying of solvents and substrates in such reactions in aqueous media; unique reactivity and selectivity are often observed in aqueous reactions.[1] Chiral vicinal diamine and its derivatives have been emerged as medicinal agents, in particular in chemotherapy.[2] Their use in organic synthesis has also increased considerably recently, especially in the field of catalytic asymmetric synthesis.[3] The related water-soluble diamine derivatives are of great interest to us. Recently, Bujoli and co-workers developed a water-soluble version of *N*,*N*-dimethyl-1,2-diphenylethane-1,2-diamine by introduction of phosphonic acid moieties on the para position of the aromatic rings via a multistep process.[4] Here, we report an easily accessible water-soluble chiral *o*-sulfonated 1,2-diphenylethlenediamine (DPEN) **2** by direct sulfonation[5] of the chiral DPEN, which is available in our

(1) For reviews on organic synthesis in aqueous media, see: (a) Cornils, B. *J. Mol. Cata. A: Chem.* **1999**, *143*, 1−10. (b) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524−1544. (c) Joó, F. *Acc. Chem. Res.* **2002**, *35*, 738−745. (d) Dwars, T.; Oehme, G. *Adv. Synth. Catal.* **2002**, *344*, 239−260. (e) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533−538. (f) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209−217. (g) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751−2772. (h) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221−237.

(2) For reviews on medicinal agents incorporating a vicinal diamine unit, see: Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug. Res.* **1989**, *33*, 135−149.

(3) (a) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. For a recent example of catalytic asymmetric synthesis, see: (b) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640−5641.

(4) Maillet, C.; Praveen, T.; Janvier, P.; Minguet, S.; Evain, M.; Saluzzo, C.; Tommasino, M. L.; Bujoli, B. *J. Org. Chem.* **2002**, *67*, 8191−8196.

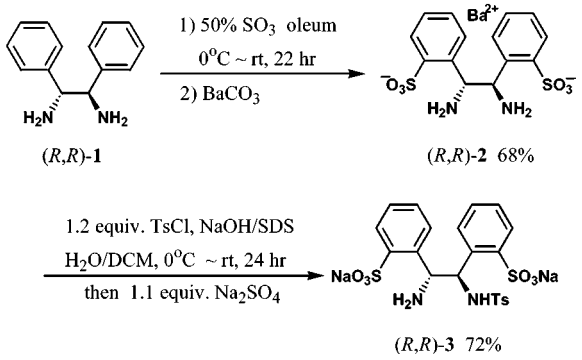
(5) For some examples of tris(*m*-sulfonatophenyl)phosphine associated to rhodium for biphasic aqueous hydroformylation or hydrogenation, see: (a) Kuntz, E. Rhône-Poulenc Recherche FR Patent 2.314.910, 1975. Kuntz, E. G. *Chem. Technol.* **1987**, 570−575. (b) Grosselin, J. M.; Mercier, C.; Grass, F. *Organometallics* **1991**, *10*, 2126−2133.

10.1021/ol0345125 CCC: $25.00
Published on Web 05/10/2003

laboratory on the kilogram scale. Preliminary experiments were then run for the application of this water-soluble ligand on the enantioselective transfer hydrogenation of prochiral ketones by its mono-*N*-tosylated derivative **3**. The enantioselective transfer hydrogenation of prochiral ketones has been achieved using a range of catalysts.[6] Among the best catalysts for these reactions are ruthenium complexes using chiral mono-*N*-tosylated vicinal diamine as ligand; developed by Noyori[7] and Knochel.[8] We also studied dendritic Noyori catalysts for asymmetric transfer hydrogenation of prochiral ketones,[9] which afforded good recyclable activity and enantioselectivity.[9a] But there are still some environmental problems existing in these homogeneous and heterogeneous systems. The water-soluble chiral ruthenium-complex-catalyzed reduction of prochiral ketones in aqueous media may provide the green practice. Recently, Chung[10a−c] and Ogo[10d] reported transfer hydrogenation of ketones with HCO_2Na as a hydrogen donor promoted by the chiral and achiral water-soluble Ru(II) complexes, respectively. Also, Williams[11] reported the asymmetric transfer hydrogenation of ketones in aqueous media with 2-propanol as a hydrogen donor.

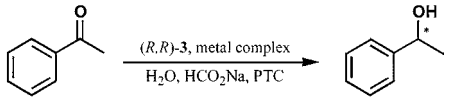
The chiral water-soluble ligand (*R,R*)-**2** was prepared by direct sulfonation as shown in Scheme 1. ^1H NMR, ^{13}C NMR, and IR analyses showed that only *o*-sulfonated product was provided.[12] Subsequently, the mono-*N*-tosylated derivative (*R,R*)-**3** was obtained by tosylation, and we initially tested the ruthenium-catalyzed transfer hydrogenation of acetophenone in aqueous media employing HCO_2Na[10] as the source of hydrogen.

Scheme 1



The water-soluble ruthenium catalyst was prepared by reacting $[RuCl_2(p\text{-cymene})]_2$ with (*R,R*)-**3** at 40 °C for 1 h in aqueous media in the concentration of 0.01 M, and a purple Ru(II) complex was only observed in aqueous phase after biphasic separation. (*R*)-Phenethyl alcohol with high conversion and enantioselectivity (Table 1) was obtained in the transfer hydrogenation of acetophenone without any organic solvent after 24 h at 40 °C with this water-soluble catalyst system, in which the best ratio of (*R,R*)-**3** and $[RuCl_2(p\text{-cymene})]_2$ is 2.2:1. Both SDS and 15-crown-5 as phase-transfer catalysts (PTC) gave >99% conversion and good enantioselectivity (95% and 93% ee, entries 1 and 2). However, poor conversion and lower enantioselectivity were observed without any PTC or surfactants (entry 3). Although asymmetric reduction of acetophenone with S/C = 200 proceeded to give chiral alcohol in 95% yield with 93% ee by prolonging reaction time to 48 h (entries 4 and 5), an increase in the ratio of S/C to 1000 caused a significant

Table 1. Asymmetric Transfer Hydrogenation of Acetophenone in Aqueous Media[a]



entry	metal complexes[b]	HCO_2Na (equiv)	convn[c] (%)	ee[c] (%)	config[d]
1	$[RuCl_2(p\text{-Cy})]_2$	5	>99	95	*R*
2[e]	$[RuCl_2(p\text{-Cy})]_2$	5	>99	93	*R*
3[f]	$[RuCl_2(p\text{-Cy})]_2$	5	34	89	*R*
4[g]	$[RuCl_2(p\text{-Cy})]_2$	5	61	94	*R*
5[g,h]	$[RuCl_2(p\text{-Cy})]_2$	5	95	93	*R*
6[i]	$[RuCl_2(p\text{-Cy})]_2$	5	<1	ND	
7	$[RuCl_2(p\text{-Cy})]_2$	2	47	90	*R*
8	$[RuCl_2(p\text{-Cy})]_2$	10	>99 (75)[j]	94 (94)[j]	*R*
9	$[RuCl_2(p\text{-Cy})]_2$	HCO_2NH_4 (5)	3	7	*R*
10	$[RuCl_2(p\text{-Cy})]_2$	HCO_2NH_4 (10)	5	29	*R*
11[k]	$[RuCl_2(p\text{-Cy})]_2$	5	17	94	*R*
12	$[RuCl_2(PhH)]_2$	5	66	71	*R*
13	$[Cp^*IrCl_2]_2$	5	10	58	*R*
14	$[Cp^*RhCl_2]_2$	5	92	84	*R*

[a] Unless otherwise noted, the reaction was carried out in organic solvent free system at 40 °C for 24 h with 4 mol % SDS and S/C = 100. [b] Cy = cymene. [c] The conversion and ee were determined by GLC on a CP-Cyclodex B-236 M column. [d] Configuration was determined by the sign of rotation of the isolated product. [e] 15-Crown-5 was added as phase-transfer catalyst. [f] The reaction was conducted without PTC or surfactant. [g] S/C = 200. [h] The reaction time is 48 h. [i] S/C = 1000. [j] The data in parentheses was obtained from the second recycling. [k] The reaction was carried out at 28 °C.

(6) For reviews on asymmetric transfer hydrogenation, see: (a) Palmer, M. J.; Wills, M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 2045−2061. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (c) Zassinovich, G. Mestroni, G.; Gladiali. S. *Chem. Rev.* **1992**, *92*, 1051−1069.

(7) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. (b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Soc. Soc.* **1997**, *119*, 8738−8739.

(8) Püntener, K.; Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8165−8168.

(9) (a) Chen, Y. C.; Wu, T. F.; Deng, J. G.; Liu, H.; Jiang, Y. Z.; Choi, M. C. K.; Chan, A. S. C. *Chem. Commun.* **2001**, 1488−1489. (b) Chen, Y. C.; Wu, T. F.; Deng, J. G.; Liu, H.; Cui, X.; Zhu, J.; Jiang, Y. Z.; Choi, M. C. K.; Chan, A. S. C. *J. Org. Chem.* **2002**, *67*, 5301−5306.

(10) (a) Rhyoo, H. Y.; Yoon, Y. A.; Park, H. J.; Chung, Y. K. *Tetrahedron Lett.* **2001**, *42*, 5045−5048. (b) Rhyoo, H. Y.; Park, H. J.; Chung, Y. K. *Chem. Commun.* **2001**, 2064−2065. (c) Rhyoo, H. Y.; Park, H. J.; Suh, W. H.; Chung, Y. K. *Tetrahedron Lett.* **2002**, *43*, 269−272. (d) Ogo, S.; Abura, T.; Watanabe, Y. *Organometallics* **2002**, *21*, 2964−2969.

(11) (a) Bubert, C.; Blacker, J.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Thorpe, T.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4037−4039. (b) Thorpe, T.; Blacker, J.; Brown, S. M.; Bubert, C.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4041−4043.

(12) See the Supporting Information.

decrease in the reactivity (24 h, <1%, entry 6). Compared with the results of different hydrogen sources of HCO_2Na and HCO_2NH_4, we found that HCO_2Na worked effectively (entries 1, 2, and 8 vs 9 and 10). When the amount of HCO_2Na was reduced from 10 to 5 equiv (with respect to acetophenone), the identical conversion and enantioselectivity were obtained (entries 1 vs 8), but a remarkable decrease of the conversion (47%) was observed with 2 equiv of HCO_2Na (entry 7). As the temperature was lowered from 40 to 28 °C, the conversion decreased greatly but without loss of enantioselectivity (entry 11). Other types of metal complexes were tested as catalyst precursors and exhibited only moderate enantioselectivities (entries 12−14). It is noticeable that the ee value completely maintained with slight loss of activity was observed in the reuse of the catalyst (entry 8).[12] As comparison, acetophenone was reduced with (*R*,*R*)-TsDPEN−Ru(II) as a catalyst under these optimization conditions,[13a] and we noticed a small decrease of enantioselectivity (92% ee vs 95% ee, entry 1) but higher activity (TOF, 9.1 vs 5.0 h^{-1}).[13b]

Moreover, a variety of aromatic ketones (**4**−**13**) can be converted to the corresponding chiral alcohols in organic solvent free system under the optimization conditions as shown in Figure 1.[13a] The ring-substituted acetophenones

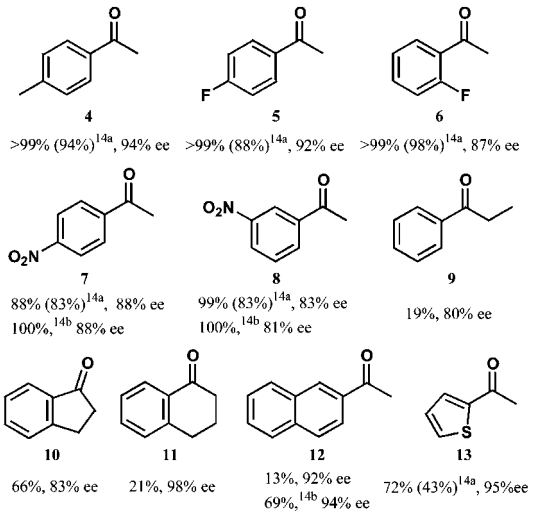


Figure 1. Asymmetric transfer hydrogenation of the aromatic ketones.

4−**8** were reduced with more than 99% conversion except 4′-nitroacetophenone **7** (88%).[14a] The electron-withdrawing groups, especially on the meta or ortho position in the acetophenones decrease the enantiomeric purities (92%, 87%, 88%, and 83% ee for **5**, **6**, **7**, and **8**, respectively), but these results were quite comparable to those in the homogeneous transfer hydrogenation with TsDPEN as ligand.[6] Good to excellent enantioselectivities were observed in the reduction of propiophenone **9**, cyclic substrates **10** and **11**, and 2′-acetonaphthone **12** (80% to 98% ee), and the poor conversion may be due to the poor solubility of these ketones in aqueous media. In the reaction of heteroatom aromatic ketone **13**, chiral alcohol was obtained in high enantioselectivity (95% ee) with moderate conversion (72%). The conversion can be improved by liquid−liquid biphasic condition (DCM/H_2O) for the solid substrates **7**, **8**, and **12** but without loss of enantiomeric purity.[14b]

To our surprise, the asymmetric transfer hydrogenation of *ω*-bromoacetophenone **14a** in aqueous media with sodium formate as the source of hydrogen proceeded to give the expected chiral 2-bromo-1-phenylethanol **15a** (Table 2, entry 1), which is contrary to the result in homogeneous system with formic acid/triethylamine azeotrope as the hydrogen donor due to the formate displacement reaction (entry 4, Scheme 2).[15] When a biphasic system was employed, an epoxide product in the same enantiomeric purity accompanied **15a** (entry 2). This epoxide can be controlled by conducting the reaction at 28 °C with higher yields of **15a** (entry 3). In DCM/H_2O biphasic conditions, **15a** was obtained as the major product without the formation of **17a** even with TsDPEN−Ru(II) as a catalyst, and this result showed that the chemoselectivity can be changed by the biphasic system (entry 5).[15] The electron-withdrawing substrate **14b** and electron-donating substrate **14c** were applied to test the reaction scope, and the optically active **15b** and **15c** were obtained in moderate yields and good enantioselectivities (entries 6 and 7). However, only formate

Table 2. Asymmetric Transfer Hydrogenation of *ω*-Bromo Acetophenones[a]

		product				
		15		**16**		**17**
		yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)	yield[b] (%)
1[d]	**14a**	57	92	trace	ND	*e*
2[f,g]	**14a**	46	93	32	93	
3[f]	**14a**	87	94	trace	ND	
4[h,i]	**14a**	*e*		*e*		75
5[f,h]	**14a**	75	94	trace	ND	
6[f]	**14b**	58	84			
7[f,j]	**14c**	47	92[k]			

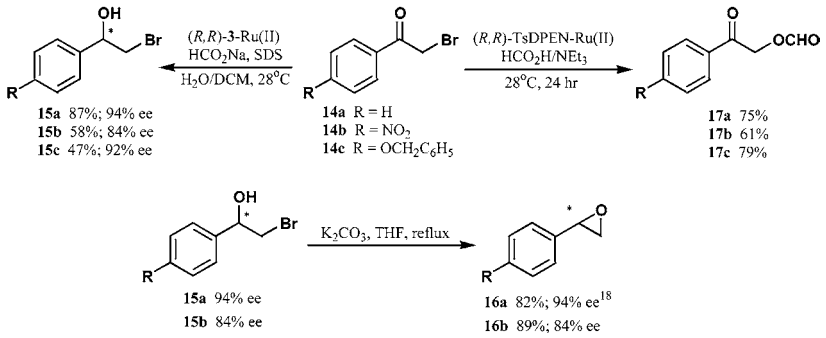
[a] Unless otherwise noted, the reaction was conducted with S/C = 100 and (*R*,*R*)-**3**/$[RuCl_2(p\text{-cymene})]_2$ = 2.2 at 28 °C for 24 h. [b] Isolated yield. [c] Ee was determined by GLC on CP-Cyclodex B-236 M column. [d] Organic solvent free, at 40 °C. [e] No product was detected by ^1H NMR analysis. [f] Biphasic system, DCM/H_2O (v/v = 1:1). [g] At 40 °C. [h] (*R*,*R*)-TsDPEN − $[RuCl_2(p\text{-cymene})]_2$ as catalyst. [i] Neat HCO_2H/NEt_3 as hydrogen source.[15] [j] 48 h. [k] Ee was determined by HPLC on OD column.

(13) (a) Optimization conditions: (*R*,*R*)-**3** and $[RuCl_2(p\text{-cymene})]_2$ (2.2:1) were incubated at 40 °C for 1 h before the substrate (S/C = 100/1), 4 mol % SDS, and 5 equiv of HCO_2Na were added and the reaction was carried out under vigorously stirring in organic solvent free system at 40 °C for 24 h. (b) Average turnover frequency calculated over the 11 h reaction time.

(14) (a) The data in parentheses are the isolated yields. (b) The data were obtained in DCM/H_2O biphasic system.

(15) Cross, D. J.; Kenny, J. A.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1801−1086.

Scheme 2



displacement products **17b** and **17c** formed with the formic acid/triethylamine azeotrope as the hydrogen donor in homogeneous system (Scheme 2).

Because optically active styrene oxides are the key intermediates for the synthesis of various β-adrenergic receptor agonists.[16,17] The resulting 2-bromo-1-phenyl ethanols **15a**,**b** were transformed to the corresponding epoxides **16a**,**b** in good yields without any loss of enantiomeric purity under basic conditions (Scheme 2).[17,18]

In summary, we have developed a novel water-soluble chiral vicinal diamine **2** and synthesized its mono-*N*-tosylated derivative **3** for the first time. The ruthenium complex of **3** was examined for the catalytic asymmetric transfer hydrogenation of prochiral ketones with sodium formate as the source of hydrogen in aqueous media, and high reactivity and enantioselectivity were achieved for most of prochiral aromatic ketones in organic solvent free system. It is noticeable that the asymmetric transfer hydrogenation of ω-bromo acetophenones was achieved, in which the formate displacement reaction occurred while employing formic acid/triethylamine azeotrope as the hydrogen donor in a homogeneous system. This will provide an alternative way for the synthesis of β-adrenergic receptor agonists.[16−18] The further application of this new water-soluble chiral vicinal diamine **3** on a variety of asymmetric reactions and the recyclability of the chiral catalysts in aqueous media are under investigation.

Acknowledgment. We are grateful for the financial support of the National Natural Science Foundation of China.

Supporting Information Available: Experimental procedure for the synthesis and characterization of (*R*,*R*)-**2** and (*R*,*R*)-**3** and the analytical data for chiral aromatic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0345125

(16) Wilkinson, H. S.; Tanoury, G. J.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **2002**, *6*, 146−148.

(17) For the transformation of 2-bromo-1-(4′-benzyloxyphenyl)ethanol **15c** into its corresponding oxetanes **16c**, see: Goswami, J.; Bezbaruah, R. L.; Goswami, A.; Borthakur, N. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3343−3348.

(18) Very recently Izawa and Ikariya reported a practical method for the synthesis of optically active styrene oxides from the asymmetric transfer hydrogenation of ω-chloro acetophenones with HCO_2H/Et_3N containing Cp*RhCl[(*R*,*R*)-Tsdpen] and the sequential treatment with NaOH in one pot procedure, see: Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373−4376.