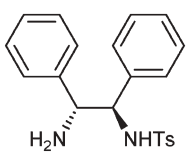
Asymmetric transfer hydrogenation of imines and iminiums catalyzed by a water-soluble catalyst in water†‡

Jiashou Wu,[ab] Fei Wang,[a] Yaping Ma,[a] Xin Cui,[a] Linfeng Cun,[a] Jin Zhu,*[a] Jingen Deng*[a] and Bangliang Yu[a]

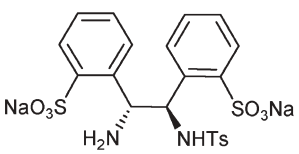
Received (in Cambridge, UK) 12th January 2006, Accepted 6th March 2006
First published as an Advance Article on the web 16th March 2006
DOI: 10.1039/b600496b

The first asymmetric transfer hydrogenation of cyclic imines and iminiums in water was successfully performed in high yields and enantioselectivities with sodium formate as the hydrogen source and CTAB as an additive catalyzed by a water-soluble and recyclable ruthenium(II) complex of the ligand (*R,R*)-2.

Optically active amines are highly important building blocks for biologically active molecules and numerous completely different methods have emerged for the preparation of enantiopure amines in the past few years.[1] On the other hand, as a consequence of the increasing demand for environmentally friendly methods, the use of water in complex-catalyzed reactions is of great interest because of safety, simpler product separation and the possibility of recycling.[2] The catalytic asymmetric hydrogenation of imines is a powerful way to obtain enantiopure amines[1] and particularly, transfer hydrogenation of imines with diamine (**1**) metallic complexes reported initially by Noyori *et al.*[3a] provides great promise for the asymmetric synthesis of chiral amines.[3,4] Despite the progress made in the asymmetric transfer hydrogenation of prochiral ketones in water,[5,6] to the best of our knowledge, no work on asymmetric transfer hydrogenation of imines[7] and iminiums[8,9] in aqueous media has been reported up to now. Here we report for the first time an asymmetric transfer hydrogenation of cyclic imines and iminiums in water catalyzed by a water-soluble Ru^{II}-catalyst.



(*R,R*)-**1**



(*R,R*)-**2**

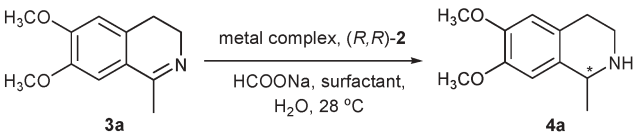
Recently, we reported the transfer hydrogenation of prochiral ketones in water with excellent catalytic activity and high enantioselectivity catalyzed by the Ru^{II} complex of easily accessible water-soluble chiral *o,o′*-disulfonated *N*-tosyl-1,2-diphenylethylene diamine, (*R,R*-)**2**.[6] Encouraged by these results, we tried the transfer hydrogenation of imine **3a** in water with a complex of $[RuCl_2(p\text{-cymene})]_2$ and (*R,R*)-**2**. Although Noyori *et al.* have reported that the asymmetric transfer hydrogenation of imines is not suitable in protic solvents, such as alcohols,[3a] to our surprise, high activity and enantioselectivity were obtained for the transfer hydrogenation of **3a** in aqueous media. Table 1 shows the results of the asymmetric transfer hydrogenation of imine **3a** by employing HCO_2Na as the hydrogen source in water with a variety of metal complexes of (*R,R*)-**2** in the presence of surfactants. Catalyzed by a complex of $[RuCl_2(p\text{-cymene})]_2$ and the ligand (*R,R*)-**2**, imine **3a** was reduced to (*S*)-salsolidine **4a** (Scheme 1) in 89% isolated yield with 90% enantiomeric excess (ee) after 10 h in water (Table 1, entry 1). It is reported that catalytic activity and enantioselectivity can be greatly enhanced by the addition of surfactants in water.[10] When sodium dodecyl sulfate (SDS) was added, both yield and enantioselectivity decreased (entry 2).[10b] The addition of poly(ethylene glycol) mono [4-(1,1,3,3-tetramethylbutylphenyl) ether (Triton X-100) enhanced yield but lowered enantioselectivity (entry 3). Although the addition of cetylpyridium bromide (CPB) increased enantioselectivity to 92% ee, only 68% isolated yield was afforded after 10 h (entry 4). A significant enhancement both in ee value and yield was observed when 3-(*N,N*-dimethyldodecylammonio)propanesulfonate

Table 1 Asymmetric transfer hydrogenation of **3a** in water[a]

Entry	Metal complex	Surfactant	*t*/h	Yield (%)[b]	Ee (%)[c,d]
1	$[RuCl_2(p\text{-cymene})]_2$	—	10	89	90
2	$[RuCl_2(p\text{-cymene})]_2$	SDS	10	79	86
3	$[RuCl_2(p\text{-cymene})]_2$	Triton X-100	10	98	86
4	$[RuCl_2(p\text{-cymene})]_2$	CPB	10	68	92
5	$[RuCl_2(p\text{-cymene})]_2$	DDAPS	10	96	93
6	$[RuCl_2(p\text{-cymene})]_2$	CTAB	10	97	95
7[e]	$[RuCl_2(p\text{-cymene})]_2$	CTAB	10	85	94
8[f]	$[RuCl_2(p\text{-cymene})]_2$	CTAB	10	93	92
9[g]	$[RuCl_2(p\text{-cymene})]_2$	CTAB	6	97	92
10	$[RuCl_2(p\text{-cymene})]_2$	TBAB	10	99	91
11	$[RuCl_2(benzene)]_2$	CTAB	11	98	87
12	$[RuCl_2(mesitylene)]_2$	CTAB	48	90	94
13	$[RuCl_2(4\text{-}tert\text{-butyltoluene})]_2$	CTAB	48	41	96
14	$[Cp^*RhCl_2]_2$	CTAB	20	96	95
15	$[Cp^*IrCl_2]_2$	CTAB	24	88	92

[a] Unless otherwise noted, the reaction was carried out in water at 28 °C for 10 h with 50 mol% surfactant and S/C = 100. [b] Isolated yield. [c] The ee was determined by HPLC analysis with a Daicel Chiralcel OD column. [d] **4a** was determined to be the (*S*)-form by comparing the sign of rotation of the isolated product to the literature data.[3a] [e] With 100 mol% CTAB. [f] With 10 mol% CTAB. [g] At 40 °C.

[a]*Key Laboratory of Asymmetric & Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China. E-mail: jgdeng@cioc.ac.cn; Fax: +86 28 8522 3978*
[b]*Graduate School of Chinese Academy of Sciences, Beijing, China*
† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for intermediates and transfer hydrogenation products. See DOI: 10.1039/b600496b
‡ Dedicated to Professor Yaozhong Jiang on the occasion of his 70th Birthday.



Scheme 1 Asymmetric transfer hydrogenation of imine **3a** in water.

(DDAPS) and cetyltrimethylammonium bromide (CTAB) were added respectively (entries 5 and 6). CTAB gave the best results with 97% isolated yield and 95% ee, which is comparable to the result reported by Noyori *et al.* in a homogeneous system.[3a] A decrease in both yield and enantioselectivity was observed when the amount of CTAB added was reduced to 10 mol% (relative to substrate) or increased to 100 mol% (entries 7 and 8). As the reaction temperature was elevated from 28 °C to 40 °C, the reactivity increased but at the price of enantioselectivity (entry 9 *vs.* entry 6). It is noted that when tetrabutylammonium bromide (TBAB), a phase-transfer catalyst, was added instead of CTAB, a comparable yield but lower enantioselectivity was obtained (entry 10). These results indicate that the formation of micelles and the electrical charge on a micelle are important to achieve high enantioselectivity.[10b] Attempts to further enhance the catalytic activity and enantioselectivity with other Ru^{II} complexes, such as $[RuCl_2(benzene)]_2$, $[RuCl_2(mesitylene)]_2$ and $[RuCl_2(tert\text{-butyl-4-methylbenzene})]_2$, as well as other types of metal complexes, such as $[Cp^*RhCl_2]_2$ and $[Cp^*IrCl_2]_2$, as catalyst precursors in water failed (entries 11–15). In contrary to what Mao and Baker reported,[3b] lower catalytic activity was observed when $[Cp^*RhCl_2]_2$ was used as catalyst precursor although the enantioselectivity (95% ee) remained (entry 14 *vs.* entry 6). Interestingly, a high pH value was observed in the reaction medium and changed from 10.6 to 9.5 at the end of the reaction (entry 1).[10b,11a] The reactivity (97%) and enantioselectivity (95% ee) remained when one equivalent of HCO_2H was added to the reaction mixture (pH 7.0–8.1). However, a decrease of reactivity (82%) and enantioselectivity (93% ee) was observed when HCO_2Na–HCO_2H (2 : 1 molar ratio, pH 4.6–7.2) was used as the hydrogen source during the reaction.[11b] No product was obtained by employing HCOOH as the hydrogen donor.

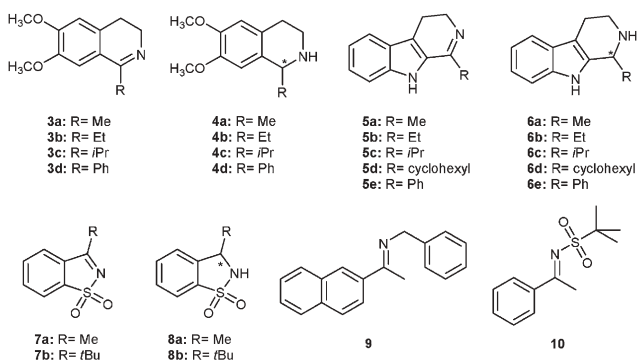
The effectiveness of the present catalytic system was demonstrated by the asymmetric transfer hydrogenation of a variety of cyclic imines in aqueous media under the optimization condition with high yields and excellent enantioselectivities as shown in Table 2. The 1-substituent of the 3,4-dihydroisoquinolines (**3**) obviously affected the reactivities of transfer hydrogenation in water, but high enantioselectivities (92% and 90% ee for **3b** and **3c**, respectively) were obtained (entries 2 and 3), which are comparable with those obtained in the homogeneous system.[3b] Interestingly, the present catalytic system was proven to be a powerful tool for the preparation of enantiopure tetrahydro-β-carboline alkaloids.[4d,f] In all cases, excellent enantioselectivities (98% to 99% ee) were achieved for asymmetric transfer hydrogenation of the dihydro-β-carbolines (**5**), which were higher than those obtained under Noyori's conditions (entry 4 and entries 8–11).[3a,4d,f] It is noticeable that the excellent enantioselectivities remained even when the reaction of **5a** was carried out with a substrate : catalyst (S/C) ratio as high as 500 and 1000 (entries 5–7).[3a] *N*-Sulfonylimines **7a** and **7b** were also smoothly reduced to the corresponding (*R*)-sultams with comparable enantioselectivities

Table 2 Asymmetric transfer hydrogenation of imines and iminiums[a]

Entry	Substrate	S/C	*t*/h	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	**3a**	100	10	97	95	*S*
2	**3b**	100	25	68	92	*S*
3	**3c**	100	25	90	90	*S*
4	**5a**	100	8	97	99	*S*
5	**5a**	200	14	99	99	*S*
6	**5a**	500	38	98	99	*S*
7	**5a**	1000	90	55	99	*S*
8	**5b**	100	20	94	99	(−)
9[e]	**5c**	100	30	92	99	(−)
10	**5d**	100	25	96	98	(−)
11[e]	**5e**	100	48	83	99	*S*
12	**7a**	100	6	97	65	*R*
13	**7b**	100	10	95	94	*R*
14	**11d**	100	12	94	95	(+)
15[f]	**11d**	100	18	98	98	(+)
16[g]	**11d**	100	18	95	50	(+)
17[h]	**11d**	100	21	85	95	(+)
18	**11a**	100	18	86	90	*S*[i]
19[f]	**11a**	100	18	85	90	*S*[i]
20[g]	**11a**	100	18	80	75	*S*[i]

[a] All reactions were carried out in 1.5 mL of water at 28 °C with 50 mol% CTAB and (*R,R*)-**2**/$[RuCl_2(p\text{-cymene})]_2$ = 2.2. [b] Isolated yield. [c] Determined by HPLC analysis with a Daicel Chiralcel OD column. [d] Determined by comparing the sign of rotation of the isolated product to the literatue data. [e] With 3 mL of water and 100 mol% CTAB. [f] The (*R,R*)-**1**-RuCl(*p*-cymene) complex (Noyori catalyst) was used in water with 50 mol% CTAB. [g] HCO_2H–Et_3N (5 : 2) was used as the hydrogen source with Noyori catalyst in CH_3CN. [h] In water without any additives. [i] Determined on the basis of the configuration of **4a** obtained *via* the hydrogenation of **12a**.

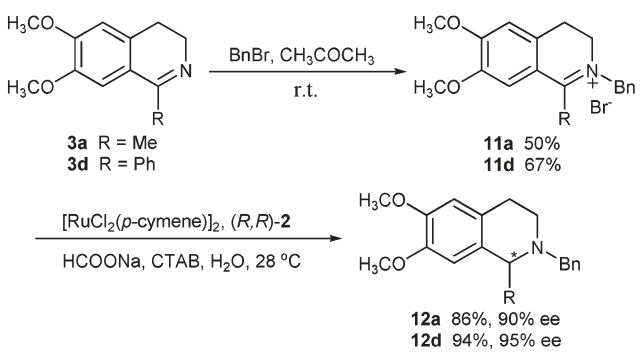
obtained with a formic acid–triethylamine azeotropic mixture as the hydrogen source (entries 12 and 13).[3b,4a] Furthermore, **7b** was applied to test catalyst recycling because of the high activity (entry 13) and low coordinative potential of the product **8b**.[12] Upon completion of the reaction, **8b** was extracted with a mixture of ethyl ether and *n*-hexane (v/v, 1 : 1) three times and one equivalent of formic acid was added into the aqueous phase to regenerate sodium formate. The water-soluble catalyst can be reused for at least three cycles with enantioselectivity remaining. In four consecutive runs, the following enantioselectivities were observed 94%, 94%, 94%, and 93% with 97%, 95%, 96%, and 85% yields, respectively. ICP analysis showed that less than 0.09 mol% of ruthenium of the water-soluble catalyst had been extracted into the organic phase. Unfortunately, attempts at transfer hydrogenation of acyclic imines **9** and **10** in water resulted in complete decomposition for imine **9** and no reaction with imine **10** as a substrate.



Under the present catalytic system, imine **3d** was proven to be totally inactive and no product was isolated even after 72 h.

However, high reactivity of **3d** had been observed with formic acid–triethylamine azeotrope as the hydrogen source,[3a,3b] which may be due to the formation of the protonated iminium ion to enhance the reactivity.[9,13] Because the higher solubility of iminium in water is also speculated, iminium **11d** was synthesized by benzylation of **3d** in 67% yield (Scheme 2) and smoothly reduced to **12d** in water with 94% yield and high enantioselectivity (95% ee) which were superior to those in organic solvent (entry 14).[3a,3b] Interestingly, the transfer hydrogenation of **11d** with the Noyori catalyst gave excellent enantioselectivity (98% ee) and high yield (98%) in water but poor enantioselectivity (50% ee) with formic acid–triethylamine azeotrope as the hydrogen source (entry 15 *vs.* entry 16). Similarly, iminium **11a** was prepared *via* benzylation of **3a** in 50% yield and hydrogenated in water to give **12a** with 90% ee which was comparable to that of **3a** (entry 18 *vs.* entry 1). The same result (90% ee) was achieved by using the Noyori catalyst in water (entry 19), and a similarly poor enantioselectivity (75% ee) was obtained under Noyori conditions (entry 20).[3a] Furthermore, the configuration of **12a** was verified to be the (*S*)-form *via* hydrogenation of **12a** on 10% Pd/C to obtain (*S*)-**4a** in 70% yield and 90% ee, and this implies that the transfer hydrogenation of imine **3a** and iminium **11a** in water may proceed by the same mechanism. Moreover, an ionic[9] and a stepwise reduction[14] mechanism can be proposed for the transfer hydrogenation of iminium **11a** because no hydrogen bonding formed between the iminium cation of **11a** and the NH_2 group of the ruthenium(II)–amide complexes.[13]

In summary, we have performed for the first time the catalytic asymmetric transfer hydrogenation of cyclic imines and iminiums in water by using sodium formate as the hydrogen source and CTAB as an additive with a water-soluble ruthenium(II) complex of the ligand (*R,R*)-**2**, which was shown to be a recyclable catalyst in aqueous reaction. A green approach for the synthesis of natural and unnatural isoquinoline and β-carboline alkaloids, which may have fascinating biological and psychotropic properties,[15] were successfully achieved with excellent enantioselectivities (up to 99% ee) under the present catalytic system.[4] It is noticeable that, in most of cases, the enantioselectivities in water were superior to those obtained with formic acid–triethylamine azeotrope as the hydrogen source in organic solvent.[3,4] The reactivity of imines can be promoted *via* the formation of iminiums and high enantioselectivities (>90% ee) were obtained in the aqueous transfer hydrogenation of iminiums, to the best of our knowledge, which is the best results in the catalytically asymmetric hydrogenation of *tetra*-alkyl-substituted C=N cations.[8,9] Further application of the iminium strategy to asymmetric transfer hydrogenation of isoquinolines is in progress.



Scheme 2 Synthesis and asymmetric transfer hydrogenation of iminiums.

We thank the financial support by the National Natural Science Foundation of China (No. 20025205, 203900507 and 20472981).

Notes and references

1 (*a*) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069–1094; (*b*) J. M. Brunel, *Recent Res. Dev. Org. Chem.*, 2003, **7**, 155–190; (*c*) C. J. Cobley and J. P. Henschke, *Adv. Synth. Catal.*, 2003, **345**, 195–201.
2 For comprehensive reviews on asymmetric catalysis in aqueous media see: (*a*) B. Cornils, *J. Mol. Catal. A: Chem.*, 1999, **143**, 1–10; (*b*) T. Dwars and G. Oehme, *Adv. Synth. Catal.*, 2002, **344**, 239–260; (*c*) D. Sinou, *Adv. Synth. Catal.*, 2002, **344**, 221–237; (*d*) S. Kobayashi and K. Manabe, *Acc. Chem. Res.*, 2002, **35**, 209–217; (*e*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751–2772.
3 (*a*) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916–4917; (*b*) J. 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. Fernández and J. M. Lassaletta, *Adv. Synth. Catal.*, 2005, **347**, 1917–1920.
4 (*a*) K. H. Ahn, C. Ham, S.-K. Kim and C.-W. Cho, *J. Org. Chem.*, 1997, **62**, 7047–7048; (*b*) E. Vedejs, P. Trapencieris and E. Suna, *J. Org. Chem.*, 1999, **64**, 6724–6729; (*c*) G. J. Meuzelaar, M. C. A. van Vliet, L. Maat and R. A. Sheldon, *Eur. J. Org. Chem.*, 1999, 2315–2321; (*d*) L. F. Tietze, Y. Zhou and E. Töpken, *Eur. J. Org. Chem.*, 2000, 2247–2252; (*e*) L. F. Tietze, N. Rackelmann and G. Sekar, *Angew. Chem., Int. Ed.*, 2003, **42**, 4254–4257; (*f*) P. Roszkowski, K. Wojtasiewicz, A. Leniewski, J. K. Maurin, T. Lis and Z. Czarnocki, *J. Mol. Catal. A: Chem.*, 2005, **232**, 143–149.
5 For recent examples on asymmetric transfer hydrogenation of ketones in water, see: (*a*) X. Wu, X. Li, W. Hems, F. King and J. Xiao, *Org. Biomol. Chem.*, 2004, **2**, 1818–1821; (*b*) A. Schlatter, M. K. Kundu and W.-D. Woggon, *Angew. Chem., Int. Ed.*, 2004, **43**, 6731–6734; (*c*) J. Canivet, G. Labat, H. Stoeckli-Evans and G. Süss-Fink, *Eur. J. Inorg. Chem.*, 2005, 4493–4500; (*d*) X. Wu, D. Vinci, T. Ikariya and J. Xiao, *Chem. Commun.*, 2005, 4447–4449.
6 Y. P. Ma, H. Liu, X. Cui, J. Zhu and J. G. Deng, *Org. Lett.*, 2003, **5**, 2103–2106.
7 For asymmetric hydrogenation of imines in an aqueous–organic two-phase solvent system, see: (*a*) Y. Amrani, L. Lecomte and D. Sinou, *Organometallics*, 1989, **8**, 542–547; (*b*) J. Bakos, Á Orosz, B. Heil, M. Laghmari, P. Lhoste and D. Sinou, *J. Chem. Soc., Chem. Commun.*, 1991, 1684–1685; (*c*) C. Lensink and J. G. de Vries, *Tetrahedron: Asymmetry*, 1992, **3**, 235–238; (*d*) C. Lensink, E. Rijnberg and J. G. de Vries, *J. Mol. Catal. A: Chem.*, 1997, **116**, 199–207.
8 For recent examples of asymmetric hydrogenation of iminiums in organic solvent, see: (*a*) J. Szawkalo, A. Zawadzka, K. Wojtasiewicz, A. Leniewski, J. Drabowicz and Z. Czarnocki, *Tetrahedron: Asymmetry*, 2005, **16**, 3619–3621; (*b*) G. D. Williams, C. E. Wade and M. Wills, *Chem. Commun.*, 2005, 4735–4737.
9 M. P. Magee and J. R. Norton, *J. Am. Chem. Soc.*, 2001, **123**, 1778–1779.
10 (*a*) H. Y. Rhyoo, H.-J. Park, W. H. Suh and Y. K. Chung, *Tetrahedron Lett.*, 2002, **43**, 269–272; (*b*) F. Wang, H. Liu, L. Cun, J. Zhu, J. Deng and Y. Jiang, *J. Org. Chem.*, 2005, **70**, 9424–9429.
11 For pH-dependent transfer hydrogenation of ketones, also see: (*a*) S. Ogo, T. Abura and Y. Watanabe, *Organometallics*, 2002, **21**, 2964–2969; (*b*) X. Wu, X. Li, F. King and J. Xiao, *Angew. Chem., Int. Ed.*, 2005, **44**, 3407–3411.
12 C. P. Casey, G. A. Bikzhanova, Q. Cui and I. A. Guzei, *J. Am. Chem. Soc.*, 2005, **127**, 14062–14071.
13 (*a*) R. Noyori, M. Yamakawa and S. Hashiguchi, *J. Org. Chem.*, 2001, **66**, 7931–7944; (*b*) C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi and M. Kavana, *J. Am. Chem. Soc.*, 2001, **123**, 1090–1100; (*c*) S. E. Clapham, A. Hadzovic and R. H. Morris, *Coord. Chem. Rev.*, 2004, **248**, 2201–2237.
14 D. Xue, Y.-C. Chen, X. Cui, Q.-W. Wang, J. Zhu and J.-G. Deng, *J. Org. Chem.*, 2005, **70**, 3584–3591.
15 (*a*) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341–3370; (*b*) T. S. Kaufman, *Synthesis*, 2005, **3**, 339–360; (*c*) M. D. Rozwadowska, *Heterocycles*, 1994, **39**, 903–931; (*d*) T. S. Kaufman, *Tetrahedron: Asymmetry*, 2004, **15**, 1203–1237.

