Ruthenium-catalysed efficient asymmetric transfer hydrogenation of aromatic ketones using cinchona alkaloids as chiral ligands

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Cinchona alkaloid derivatives were applied in asymmetric transfer hydrogenation of aromatic ketones in a ruthenium catalytic system using *i*-PrOH as the hydrogen source. A series of aromatic ketones could be transfer-hydrogenated to the corresponding alcohols with good to excellent conversion and enantioselectivity. The best results were achieved using 9-amino(9-deoxy) epiquinidine as the ligand; the enantioselectivity with acetophenone and 2'-(trifluoromethyl)acetophenone could reach 90% ee.

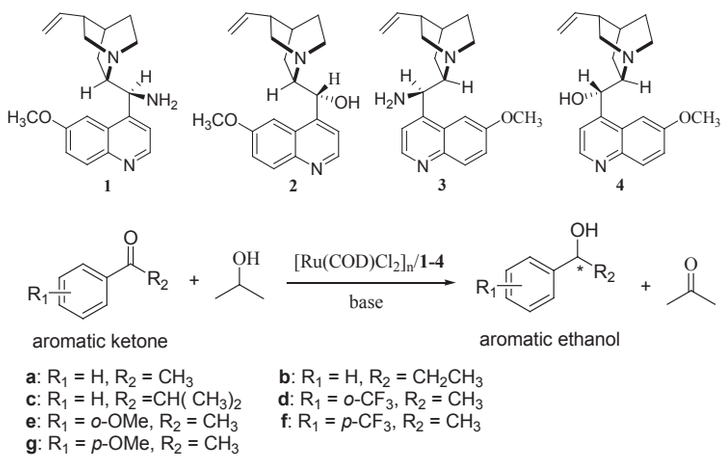
Keywords: cinchona alkaloid, asymmetric transfer hydrogenation, ruthenium, aromatic ketone

Cinchona alkaloids and their derivatives have been widely used as versatile chiral catalysts, ligands, column packing, and chiral shift reagents.[1] The asymmetric transfer hydrogenation of aromatic ketones has attracted much attention, since the transfer hydrogenation products are key intermediates and advanced materials in the manufacture of pharmaceuticals and organic synthesis.[2,3] In view of the low cost of the reducing agent and operational simplicity, a metal-catalysed transfer hydrogenation reaction using *i*-PrOH as a hydrogen source appears to be a safe and attractive supplement to catalytic hydrogenation with hydrogen. In the last decade, some chiral diamine ligands and chiral N,P ligands have been used to coordinate with metals such as Ru, Rh and Ir in enantioselective transfer hydrogenation of aromatic ketones.[4–8] Noyori and co-workers developed highly efficient chiral TsDPEN-base ruthenium or iridium catalysts for the asymmetric transfer hydrogenation of aromatic ketones to chiral alcohols with excellent enantiomeric purity.[4] Since the asymmetric transfer hydrogenation of aromatic ketones has great significance in homogeneous enantioselective industrial processes, the development of new easily obtained and stable catalysts that provide high activity and enantioselectivity remains a scientific challenge. As part of our ongoing research in the field of reduction of aromatic ketones,[9–13] reported here are the results of our studies on ruthenium catalysed asymmetric transfer hydrogenation of aromatic ketones using cinchona alkaloids **1–4** as chiral ligands. The combination with cinchona alkaloid derivatives and ruthenium has proven to be highly efficient and enantioselective.[8]

Result and discussion

The Ru(II) catalyst was generated *in situ* by mixing cinchona alkaloids **1–4** with $[Ru(COD)Cl_2]_n$ (cinchona alkaloid : Ru = 1 : 1) in *i*-PrOH at room temperature under argon. Transfer hydrogenation occurred when base and aromatic ketones were added to the above catalyst solution. Initial studies were performed using acetophenone **a** as a model substrate under different conditions (Scheme 1). For the transfer hydrogenation reaction of the acetophenone **a**, the absolute configuration of the product was highly dependent upon both the C8-position and C9-position configuration in the chiral ligands. The results are summarised in Table 1. 9-Amino(9-deoxy)epiquinine **1** and 9-amino(9-deoxy)epiquinidine **3**, acting as diastereomeric pairs, led to the products with different absolute configurations. Other chiral ligands, such as quinine **2** and quinidine **4** were tested, and the amine group in the 9-position of the ligand is essential.

The amount of catalyst had an important influence on the reaction. As in Table 2, when 1% catalyst was used, the reaction did not occur at 0 °C. The transfer hydrogenation conversion was influenced by an increase of the amount of catalyst, a lowering of the reaction temperature and by the reaction time. When the ratio of catalyst increased from 1 to 10%, the enantioselectivity increased as the ratio of catalyst increased (entries 1–5). Extension of the ratio of catalyst from 10 to 30% resulted in a slight erosion of the asymmetric induction (entries 5–7). The effect of temperature on the enantioselectivity



a: R_1 = H, R_2 = CH_3 **b**: R_1 = H, R_2 = CH_2CH_3
c: R_1 = H, R_2 = $CH(CH_3)_2$ **d**: R_1 = *o*-CF_3, R_2 = CH_3
e: R_1 = *o*-OMe, R_2 = CH_3 **f**: R_1 = *p*-CF_3, R_2 = CH_3
g: R_1 = *p*-OMe, R_2 = CH_3

Scheme 1 Cinchona alkaloids used and the asymmetric transfer hydrogenation of aromatic ketones.

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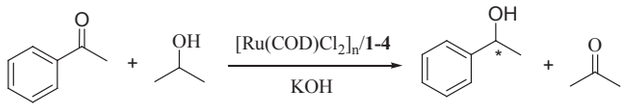
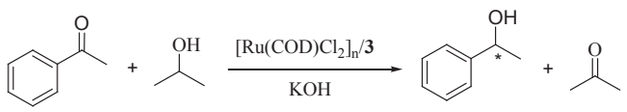
Table 1 Influence of Ru(II)–**1–4** complexes on the catalytic transfer hydrogenation of acetophenone[a]



Ligands	Yield/%	ee/%	Configuration[b]
1	95	36	*R*
2	0	–	–
3	93	75	*S*
4	0	–	–

[a]Reactions were carried out using a 0.1 M solution of acetophenone (1 mmol) in *i*-PrOH, acetophenone : Ru : ligand : KOH = 100 : 5 : 5 : 10, 35 °C, 48 h.
[b]Determined by sign of rotation.

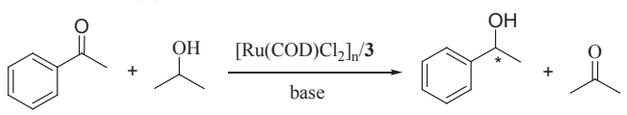
Table 2 Influence of the ratio of catalyst to substrate and temperature on the transfer hydrogenation of acetophenone catalysed by Ru(II)–**3** complex



Entry	Catalyst /%	Temperature /°C	Time /h	Yield /%	ee /%	Configuration
1	1	0	48	0	0	–
2	3	20	48	60	68	*S*
3	5	0–20	96	81	81	*S*
4	10	0–20	48	72	84	*S*
5	10	0	96	83	90	*S*
6	20	0	96	90	88	*S*
7	30	0	48	70	85	*S*

The reaction conditions are the same as in Table 1 (ligand **3**) except for the amount of catalyst, the reaction temperature and the reaction time.

Table 3 Influence of the base on the transfer hydrogenation of acetophenone catalysed by Ru(II)–**3** complex[a]



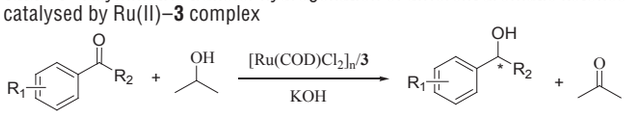
Entry	Base	Base : Ru /mol	Yield /%	ee /(%)	Configuration
1	LiOH	2 : 1	57	78	*S*
2	NaOH	2 : 1	72	85	*S*
3	KOH	2 : 1	83	90	*S*
4	KOH	0 : 1	0	–	–
5	KOH	1 : 1	27	70	*S*
6	KOH	4 : 1	89	85	*S*
7	KOH	8 : 1	80	82	*S*

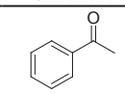
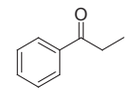
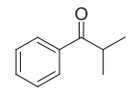
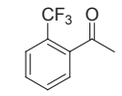
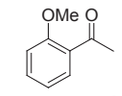
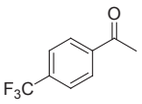
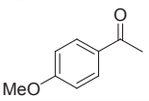
[a]Reactions were carried out using a 0.1 M solution of acetophenone (1 mmol) in *i*-PrOH, acetophenone : Ru : ligand = 100 : 10 : 10, 0 °C, 96 h.

of the reaction transfer hydrogenation was significant. The enantioselectivity increased constantly as the temperature was lowered, although the rate of reaction was reduced (entries 4 *versus* 5). The best enantiomeric excess (90% ee) was achieved at 0 °C with 10% catalyst (entry 5).

As in previous reports, the base could activate the asymmetric transfer hydrogenation catalyst markedly.[4–8] We have studied the effect of base additives on the reduction of acetophenone (Table 3). Ru(II)–**3** complex was inactive without the base (entry 4). When alkali metal hydroxides LiOH, NaOH and KOH were tested in the transfer hydrogenation of acetophenone, both the activity and the enantioselectivity decreased in the order of KOH > NaOH > LiOH (entries 1–3). When the molar ratio of KOH : Ru was lower, the yield and enantioselectivity decreased dramatically (entries 4 and 5). On the other hand, when we sequentially increased the amount of base, the yield and enantioselectivity went down slightly (entries 6 and 7).

Table 4 Asymmetric transfer hydrogenation of different aromatic ketones catalysed by Ru(II)–**3** complex



Entry	Substrate	Yield/%	ee/%	Configuration[a]
1		83	90	*S*
2		98	86	*S*
3		24	66	*S*
4		96	90	*S*
5		56	87	*S*
6		97	72	*S*
7		70	63	*S*

The reaction conditions are the same as in Table 3 (Ru : Base = 1 : 2).
[a]Determined by sign of rotation.

Some representative examples are listed in Table 4 for the asymmetric transfer hydrogenation of aromatic ketones catalysed by the Ru(II)–**3** complex under the optimised conditions. In general, good to excellent conversions and enantioselectivities were achieved. The conversion and enantioselectivity of the reaction was affected by the steric and electronic properties of the substrates. The enantioselectivity decreased by increasing the bulkiness of the alkyl group from methyl or primary alkyl to isopropyl (entries 1–3). Substitution at the phenyl ring of acetophenone with an electron-drawing group gave yields and enantioselectivity that were higher than those with electron-donating groups (entries 4 and 6 *versus* 5 and 7). It was found that when the substituent is in the *para* position of acetophenone, the degree of the enantioselection was obviously decreased in comparison to the *ortho*-substituted counterparts (entries 6 and 7 *versus* 4 and 5). Meanwhile, the degree of the activity of a *para*-substituted acetophenone was increased in comparison to an *ortho*-substituted counterpart because of the steric bulk (entries 6 and 7 *versus* 4 and 5). The highest enantiomatic excesses were obtained in the hydrogenation of acetophenone (entry 1) and 2'-(trifluoromethyl)acetophenone (entry 4).

In conclusion, we have demonstrated that the combination of $[Ru(COD)Cl_2]_n$ and cinchona alkaloid derivatives results in the formation of efficient catalysts for asymmetric transfer hydrogenation of aromatic ketones. For a variety of aromatic ketones, moderate to excellent enantioselectivity are observed. The work reported here succeeded in the creation of a new

catalyst for the highly enantioselective transfer hydrogenation of aromatic ketones. Additional work is ongoing.

Experimental

Quinine and quinidine were purchased from Acros Organics. Cinchona alkaloid derivatives were synthesised according to the procedures reported by Brunner *et al*.[14,15] Di-isopropyl azodicarboxylate was purchased from Fluka. Hydrazoic acid-benzene (3.6%) was prepared starting from sodium azide and sulfuric acid in our laboratory. All other reagents were purchased from Kelong Chemical Reagent Co. Inc. Acetophenone was distilled prior to use. Tetrahydrofuran was freshly distilled under nitrogen from a deep-blue solution of sodium-benzophenone. *iso*-Propanol was treated with sodium and degassed. Other chemicals were used as received. ^{1}H NMR was performed in $CDCl_3$ and recorded on a Varian INOVA 400 MHz spectrometer, and ^{1}H NMR spectra were collected at 400.0 MHz using a 10,000 Hz spectral width, a relaxation delay of 1.0 s, and Me_4Si (0.0 ppm) as the internal reference. Products were analysed by GC (hydrogen as carrier gas) with an FID detector and 30 m × 0.25 mm × 0.15μm β-DEX120 capillary column. All optical rotations ($[\alpha]^{25}_D$) were measured on a Perkin-Elmer 341 polarimeter. Optical rotations were measured at the wavelength of the sodium D-line (589.3 nm) at a temperature of 25 °C.

9-Amino(9-deoxy)epiquinine (**1**): A well stirred mixture of quinine **2** (3.24 g, 10 mmol) and triphenylphosphine (3.15 g, 12 mmol) in absolute THF (50 mL) was cooled to 0 °C, and hydrazoic acid-benzene (3.6%, 12 mmol) was added. Then, DIAD (di-isopropyl azodicarboxylate; 2.16 mL, 11 mmol) in absolute THF (10 mL) was added slowly. The mixture was heated to 50 °C and a yellow transparent solution was obtained. The reaction was stirred for 3 h at 50 °C. Then triphenylphosphine (2.62 g, 10 mmol) in absolute THF (10 mL) was added in one portion and the solution was stirred at 40 °C until gas evolution ceased. Water (2 mL) was added and the solution was stirred overnight. Solvents were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and poured into 2 M hydrochloric acid (1 : 1, 100 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 30 mL). Then 2 M NaOH was added until pH > 10. The mixture was extracted with diethyl ether (3 × 60 mL) and the combined organic phase was washed with saturated Na_2CO_3 aqueous solution (3 × 60 mL) and dried with Na_2CO_3. The solvent was removed and the product **1** was obtained following purification on silica gel (eluent : Et_2O–MeOH–Et_3N = 10 : 1 : 0.3), slightly yellow oil, yield 51%. $[\alpha]^{25}_D$ +80.1 (*c* 1.0 in $CHCl_3$) [lit.[14], $[\alpha]^{25}_D$ +80 (*c* 1.1 in $CHCl_3$)]. IR: ν_{max} (KBr)/cm^{-1} 3384, 3290, 2940, 2860, 1630, 1605, 1517. ^{1}H NMR (400 M, $CDCl_3$), δ 0.81 (m, 1H), 1.27–1.62 (m, 4H), 2.08 (m, 2H), 2.29 (m, 1H), 2.77 (m, 2H), 3.02–3.34 (m, 3H), 3.97 (s, 3H), 4.60 (d, *J* = 10.1 Hz, 1H), 4.97 (m, 2H), 5.79 (m, 1H), 7.36–8.09 (m, 4H), 8.77 (d, *J* = 4.2 Hz, 1H). MS: *m*/*z* 323 (M^+).

9-Amino(9-deoxy)epiquinidine (**3**) was synthesised by a similar procedure, and isolated as a slightly yellow oil, yield 45%. $[\alpha]^{25}_D$ +69.6 (*c* 2.5 in $CHCl_3$) [lit.[15], yield 46%. $[\alpha]^{22}_D$ = +69 (*c* 2.51 in $CHCl_3$)]. IR: ν_{max} (KBr)/cm^{-1} 3375, 3290, 2940, 2850, 1635, 1600, 1518. ^{1}H NMR (400 M, $CDCl_3$), δ 0.95 (m, 1H), 1.15–1.22 (m, 1H), 1.46–1.56(m, 3H), 2.16 (m, 2H), 2.28 (m, 1H), 2.79–3.21 (m, 5H), 3.97 (s, 3H), 4.67 (d, *J* = 9.9 Hz, 1H), 5.09 (m, 2H), 5.85 (m, 1H), 7.35–8.19 (m, 4H), 8.75 (d, *J* = 4.5 Hz, 1H). MS: *m*/*z* 323 (M^+).

Asymmetric transfer hydrogenation reaction; general procedure

Cinchona alkaloid was added to $[Ru(COD)Cl_2]_n$ in dry degassed *i*-PrOH (10 mL) and stirred at room temperature for 30 min under argon. The base was added and the reaction mixture was stirred for another 30 min. The aromatic ketone was then added in one portion (0.1 M) and the reduction was conducted at the given temperature for the time indicated. After completion of the reaction, the resulting solution was neutralised, and then extracted with Et_2O. The organic phase was dried over $MgSO_4$ and the conversion and enantiomeric excess were determined by GC analysis according to the literature.[4,16–18]

(S)-(−)-1-Phenylethanol: Table 4, entry 1; 83% yield, 90% ee (*S*), $[\alpha]^{25}_D$ = −45.0 (*c* 1.0, CH_2Cl_2) [lit.[4], $[\alpha]^{23}_D$ = −50.0 (*c* 1.0, CH_2Cl_2)]. ^{1}H NMR (400 M, $CDCl_3$), δ 1.40–1.55 (m, 3H), 1.90 (s, 1H), 4.95 (d, *J* = 6.3 Hz, 1H), 7.20–7.65 (m, 5H). GC β-DEX120 capillary column, column temperature: 115 °C, t (*R*) = 12.7 min, t (*S*) = 13.5 min.

(S)-(−)-1-Phenyl-1-propanol: Table 4, entry 2; 98% yield, 86% ee (*S*), $[\alpha]^{25}_D$ = −30.5 (*c* 5.0, EtOH) [lit.[4], $[\alpha]^{23}_D$ = −34.0 (*c* 5.03, EtOH)]. ^{1}H NMR (400 M, $CDCl_3$), δ 1.15–1.25 (m, 3H), 1.69 (s, 1H), 1.72–1.92 (m, 2H), 4.61 (d, *J* = 4.5 Hz, 1H), 7.20–7.56 (m, 5H). GC β-DEX120 capillary column, column temperature: 115 °C, t (*R*) = 14.5 min, t (*S*) = 15.9 min.

(S)-(−)-2-Methyl-1-phenyl-1-propanol: Table 4, entry 3; 24% yield, 66% ee (*S*), $[\alpha]^{25}_D$ = −33.0 (*c* 0.5, Et_2O) [lit.[16], $[\alpha]^{23}_D$ = −45.7 (*c* 0.0623, Et_2O)]. ^{1}H NMR (400 M, $CDCl_3$), δ 0.89–1.10 (m, 3H), 1.20–1.35 (m, 3H), 1.86–1.96 (m, 2H), 4.32–4.40 (m, 1H), 7.29–7.46 (m, 5H). GC β-DEX120 capillary column, column temperature: 115 °C, t (*R*) = 18.6 min, t (*S*) = 19.8 min.

(S)-(−)-1-o-Trifluoromethylphenylethanol: Table 4, entry 4; 96% yield, 90% ee (*S*), $[\alpha]^{25}_D$ = −36.0 (*c* 0.7, MeOH) [lit.[17,18], $[\alpha]^{20}_D$ = −35.4 (*c* 0.70, MeOH)]. ^{1}H NMR (400 M, $CDCl_3$), δ 1.49–1.55 (m, 3H), 1.99 (s, 1H), 5.25 (d, *J* = 6.1 Hz, 1H), 7.36–7.81 (m, 4H). GC β-DEX120 capillary column, column temperature: 115 °C, t (*R*) = 21.6 min, t (*S*) = 22.5 min.

(S)-(−)-1-o-Methoxyphenylethanol: Table 4, entry 5; 56% yield, 87% ee (*S*), $[\alpha]^{25}_D$ = −29.6 (*c* 1.0, MeOH) [lit.[4], $[\alpha]^{23}_D$ = −32.7 (*c* 1.0, MeOH)]. ^{1}H NMR (400 M, $CDCl_3$), δ 1.50 (m, 3H), 2.19 (s, 1H), 3.87 (s, 3H), 5.10 (m, 1H), 6.96–7.34 (m, 4H). GC β-DEX120 capillary column, column temperature: 120 °C, t (*R*) = 24.7 min, t (*S*) = 26.4 min.

(S)-(−)-1-p-Trifluoromethylphenylethanol: Table 4, entry 6; 97% yield, 72% ee (*S*), $[\alpha]^{25}_D$ = −12.9 (*c* 0.1, MeOH) [lit.[16], $[\alpha]^{23}_D$ = −10.8 (*c* 0.0578, MeOH)]. ^{1}H NMR (400 M, $CDCl_3$), δ 1.51 (m, 3H), 2.10 (s, 1H), 4.96 (m, 1H), 7.36–7.54 (m, 4H). GC β-DEX120 capillary column, column temperature: 115 °C, t (*R*) = 20.7 min, t (*S*) = 22.4 min.

(S)-(−)-1-p-Methoxyphenylethanol: Table 4, entry 7; 70% yield, 63% ee (*S*), $[\alpha]^{25}_D$ = −33.9 (*c* 1.0, $CHCl_3$) [lit.[4], $[\alpha]^{23}_D$ = −51.9 (c 1.04, $CHCl_3$)]. ^{1}H NMR (400 M, $CDCl_3$), δ 1.49 (m, 3H), 1.85 (s, 1H), 3.89 (s, 3H), 4.95 (m, 1H), 6.86–7.34 (m, 4H). GC β-DEX120 capillary column, column temperature: 120 °C, t (*R*) = 26.6 min, t (*S*) = 28.2 min.

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