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Novel recoverable catalysts for asymmetric transfer hydrogenation

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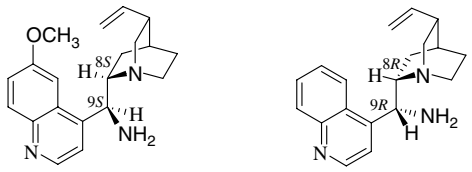
Abstract—9-Amino(9-deoxy)epiquinine and 9-amino(9-deoxy)epicinchonine were applied in asymmetric transfer hydrogenation of aromatic ketones in both iridium and rhodium catalytic systems using *i*-propanol as the hydrogen source. Good to excellent conversions and enantioselectivities were observed with a variety of aromatic ketones. Moreover, the Ir complex and Rh complex of 9-amino(9-deoxy)cinchonine were recovered in high yields with dilute hydrochloric acid. The enantioselectivity of 1-phenylethanol was nearly maintained after six cycles.

Homogeneous catalytic asymmetric transfer hydrogenation has become one of the most important developments in chemistry.[1] In view of the low cost of reducing agent and operational simplicity, this reaction provides an efficient method for the preparation of optically active secondary alcohols from carbonyl compounds.[2] However, its application in industry is greatly limited, partly due to the problems of separation and recycling of the often expensive or toxic catalysts.[3] To overcome these drawbacks, Tu and co-workers[4] have immobilized chiral Ru–TsDPEN onto amorphous silica gel and mesoporous silicas, which could be recovered in multiple consecutive catalytic runs with the completely maintained enantioselectivity. Lin and co-workers[5] have designed novel magnetite nanoparticle-supported chiral Ru complexes with phosphonic acid-substituted BINAP [Ru(BINAP–PO_3H_2)(DPEN)Cl_2], which can be recycled by magnetic decantation. Dyson[6] and Ohta[7] have, respectively, attached imidazolium units to TsDPEN, and tried to recycle them in ionic liquid. Deng and co-workers[8] have synthesized a series of dendritic ligands based on Noyori-Ikariya's TsDPEN ligands and recovered them successfully through solvent precipitation. Sinou and co-workers[9] have reported salen type ligands, perfluorinated diamines, which were recycled in the 'Fluorous Biphasic Systems (FBSs)'. All these reports have their highlights in recycling of ligands or catalysts. However, it is still a great challenge for us to develop a simpler, more practical, recoverable and environment-friendly catalytic system in homogeneous catalytic asymmetric transfer hydrogenation.

Herein, we report our discovery of catalytic performance of 9-amino(9-deoxy)epiquinine **1a** and 9-amino-(9-deoxy)epicinchonine **1b** (Scheme 1) in asymmetric transfer hydrogenation. Moreover, a simple approach to recover the catalysts from the reaction mixture by dilute hydrochloric acid is described.

Chiral ligands **1a** and **1b** were synthesized from natural products, quinine and cinchonine, according to the procedure of Brunner et al.[10] These chiral ligands associated with $[Rh(COD)Cl]_2$ or $[Ir(COD)Cl]_2$ were used in the asymmetric reduction of aromatic ketones (Scheme 2) with *i*-propanol as the hydrogen source and KOH as basic co-catalyst. First, the Rh(I) or Ir(I) catalyst was generated in situ by stirring **1a** and **1b** with $[Rh(COD)Cl]_2$ or $[Ir(COD)Cl]_2$ (2:1) in *i*-propanol at room temperature



1a **1b**

Scheme 1. Chiral ligands **1a** and **1b** derived from natural *Cinchona* alkaloids.

Keywords: Asymmetric transfer hydrogenation; *Cinchona* alkaloids; Aromatic ketones.
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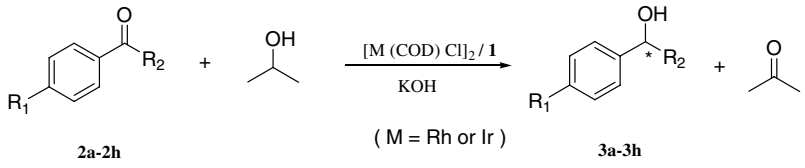

2a-2h 3a-3h

2a R_1=H R_2=CH_3 **2e** R_1=Cl R_2=CH_3
2b R_1=H R_2=CH_2CH_3 **2f** R_1=CF_3 R_2=CH_3
2c R_1=H R_2=$CH_2CH_2CH_3$ **2g** R_1=OCH_3 R_2=CH_3
2d R_1=H R_2=$CH(CH_3)_2$ **2h** R_1=CH_3 R_2=CH_3

Scheme 2. Asymmetric transfer hydrogenation of ketones.

under argon for 0.5 h. Transfer hydrogenation occurred when KOH and ketones were added to the above catalyst solution at −20 °C. A variety of aromatic ketones were tested in the catalytic system using different ligands and catalytic precursor.[11] In general, good to excellent chemical yields and enantioselectivities were achieved (Table 1).

As we can see, the absolute configuration of the product was highly dependent upon the C8-position and C9-position configuration in the chiral ligands. **1a** and **1b** led to the products with opposite absolute configurations. **1a**, with the additional methoxy group, giving only slightly lower ees than **1b** (Table 1, entries 1, 2 vs 3, 4). Different metal center also led to different enantio excess value. Ir catalyst was slightly superior to Rh catalyst (entry 2 vs 1, entry 4 vs 3).

Moreover, influence of the steric and electronic properties of the substrates on conversion and enantioselectivity were also investigated. Those acetophenones with an electron-donation group on the phenyl ring gave yields and ees similar to those obtained with acetophenone (Table 1, entries 10, 11 vs 4). Introduction of an electron-drawing group, however, led to lower ees (entries 8 and 9). Interestingly, the bulk of the R_2 group in the ketones did not demonstrate a dramatic influence on enantioselectivities (entries 5, 6 and 7 vs 4). Furthermore, *iso*-butylphenone, among the most notorious substrates in asymmetric transfer hydrogenation, was converted to the corresponding optically active alcohol in 97% ee and 90% yield (entry 7), presenting a significant improvement on the result in previous literature.

Sharpless[12] has reported one simple approach to recover the *Cinchona* alkaloids ligands in asymmetric dihydroxylation by extracting reaction mixture with dilute sulfuric acid. This enlightens us to recover 9-amino-*Cinchona* alkaloids by using the good solubility of their hydrochloride in water. First attempt to recycle the ligand was performed in the Rh catalyst of **1b** catalyzed asymmetric transfer hydrogenation of acetophenone. When the reduction reaction was ceased, 1 mol L^{-1} hydrochloric acid and diethyl ether (1:1) were added and the reaction mixture was stirred for 10 min. The alcohol product and unreacted material of transfer hydrogenation reaction were extracted into organic phase, whereas the hydrochloride of **1b** remained in the water phase. In order to obtain the free amine ligand, we slowly added saturated Na_2CO_3 solution to adjust the aqueous phase to pH ~ 10 and extracted the water phase with CH_2Cl_2. Surprisingly, we found that the desired free ligand **1b**, a light yellow oil, was not obtained, however, the Rh complex of **1b**, a fine yellow solid, has been recovered directly. We tested it with another transfer hydrogenation of acetophenone without any purification. Excitingly, the enantioselectivity and the chemical yield of 1-phenylethanol were almost maintained. Encouraged by these results, we then synthesized the complex instead of in situ in the asymmetric transfer hydrogenation of acetophenone. The complex can be synthesized readily by stirring $[Rh(COD)Cl]_2$ and **1b** in CH_2Cl_2 and it precipi-

Table 1. Asymmetric transfer hydrogenation of different ketones[a]

Entry	Ketone	Ligand	Catalyst precursor	Time (h)	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	**2a**	**1a**	$[Rh(COD)Cl]_2$	48	85	90	*R*
2	**2a**	**1a**	$[Ir(COD)Cl]_2$	48	87	94	*R*
3	**2a**	**1b**	$[Rh(COD)Cl]_2$	48	83	93	*S*
4	**2a**	**1b**	$[Ir(COD)Cl]_2$	48	86	95	*S*
5	**2b**	**1b**	$[Ir(COD)Cl]_2$	48	70	94	*S*
6	**2c**	**1b**	$[Ir(COD)Cl]_2$	24	70	96	*S*
7	**2d**	**1b**	$[Ir(COD)Cl]_2$	48	90	97	*S*
8	**2e**	**1b**	$[Ir(COD)Cl]_2$	48	50	72	*S*
9	**2f**	**1b**	$[Ir(COD)Cl]_2$	30	90	77	*S*
10	**2g**	**1b**	$[Ir(COD)Cl]_2$	40	85	97	*S*
11	**2h**	**1b**	$[Ir(COD)Cl]_2$	48	85	95	*S*

[a] Conditions: reactions were carried out using a 0.05 mol L^{-1} solution of ketone (1 mmol) in *i*-propanol; ketone/M/ligand/KOH = 100:10:10:20.
[b] Isolated yields.
[c] Determined by chiral CP-Cyclodex B-236 M column and chiral HPLC.
[d] Configurations were assigned by comparison with the sign of the specific rotation of the known compounds.

Table 2. Reuse of catalyst in asymmetric transfer hydrogenation of acetophenone[a]

Run	Rh/**1b** catalyst			Ir/**1b** catalyst		
	product		Recovered yield of catalyst (%)	product		Recovered yield of catalyst (%)
	Yield[b] (%)	ee[c] (%)		Yield[b] (%)	ee[c] (%)	
1	81	94	91	87	95	93
2	78	93	93	83	95	90
3	77	92	92	82	94	92
4	75	91	91	79	93	91
5	70	93	95	80	94	94
6	72	93	93	75	95	93

[a] Conditions: reactions were carried out using a 0.05 mol L^{-1} solution of acetophenone (1 mmol) in *i*-propanol; ketone/M/ligand/KOH = 100:10:10:20, reaction time is 48 h.
[b] Isolated yields.
[c] Determined by chiral CP-Cyclodex B-236 M column and chiral HPLC.

tated with hexane.[13] When using the complex in the asymmetric transfer hydrogenation, high enantioselectivity was obtained (94% ee) as expected. With similar procedure, Ir complex of **1b** was also formed[14] and tested in the asymmetric transfer hydrogenation of acetophenone, resulting in 87% yield of 1-phenylethanol, and ee up to 95%.

We further test the recycled Rh complex of **1b** in asymmetric transfer hydrogenation of acetophenone.[15] We found the enantioselectivities were nearly maintained at 93% in six runs, and 91–95% of catalyst were recovered. We also determined the metal content of the aqueous phase after recycling the complex by using inductively coupled plasma atomic emission spectrometry (ICP-AES). The amount of Rh leaching was 1.7%, 1.5%, 1.4%, 1.1%, 1.5% and 1.2%, respectively, in the six reaction batches (including the workup procedures). By the same way, Ir complex of **1b** was also recovered in the catalytic system. Again, we found the enantioselectivities were nearly maintained at 95% in six runs, and the catalyst recovery yields were verified from 90% to 94% (Table 2). Moreover, the Ir leaching in the six runs was 1.4%, 1.6%, 1.8%, 1.2%, 0.9% and 1.1%, respectively. All the metal leaching was less than 2%, which was in agreement with the nearly maintained enantioselectivities of the catalysts in the recycling reactions.

In summary, we have developed two simple and recyclable homogeneous catalysts for asymmetric transfer hydrogenation of aromatic ketones. Except for osmium-catalyzed Sharpless AD and AA, these are the best enantioselectivities reported using the intact *Cinchona* alkaloids skeleton as ligands in metal-catalyzed asymmetric reactions.[16] Moreover, a simple method to recover both the iridium and rhodium complex of 9-amino(9-deoxy)epicinchonine **1b** were demonstrated. Further study will be focused on investigating their catalytic performance in other asymmetric catalysis system.

Acknowledgements

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11. Typical procedure for asymmetric transfer hydrogenation: 0.05 mmol $[Rh(COD)Cl]_2$ or $[Ir(COD)Cl]_2$ was added to a solution of 0.1 mmol ligand **1a** or **1b** in 20 mL dry degassed *i*-propanol and stirred at room temperature for 30 min under argon. KOH (0.2 mmol) was added and the reaction mixture was stirred for another 10 min. Ketone (1 mmol) was then added in portion (0.05 mol L^{-1}) and the reduction was conducted at −20 °C for the time indicated (monitored by TLC). After completion of the reaction, the resulting solution was neutralized with 1 mol L^{-1} HCl, and then extracted with Et_2O. The organic

phase was dried over $MgSO_4$ and the solvent was evaporated to give the corresponding alcohol, which was purified by flash chromatography on silica gel. The enantiomeric excess was determined by GC or HPLC analysis according to literature.

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13. Rh/9-amino(9-deoxy)cinchonine complex: In 50 mL Schlenk tube, 0.01 mmol 9-amino(9-deoxy)cinchonine was dissolved in 15 mL dry degassed CH_2Cl_2. After 0.005 mmol $[Rh(COD)Cl]_2$ was added, the mixture was stirred at room temperature under nitrogen for 30 min, and a yellow solution was formed. Hexane was added dropwise until the solution turned cloudy. When it was cooled to 0 °C, a yellow solid was precipitated. The precipitate was filtered, and dried under vacuum to afford the Rh/9-amino(9-deoxy)cinchonine complex. Yield 93%. mp (dec.) 210–220 °C. $[\alpha]_D^{25} + 113$ (*c* 0.5, $CHCl_3$). MS (FAB): *m*/*z* (%) 504 ($[M-Cl]^+$, 20), 293 (55), 157 (100), 136 (95), 79 (80). IR (KBr) ν_{max}/cm^{-1}: 3429, 2931, 2872, 1637, 1591, 1458, 1034, 754. ^1H NMR (400 MHz, $CDCl_3$): δ 0.97–1.67 (m, 5H), 2.11 (s, 2H), 2.23–2.65 (m , 9H), 3.04–3.05(m, 5H), 4.41–4.82 (m,5H), 5.04–5.05 (m, 2H), 5.88–5.90 (m, 1H), 7.57–8.37 (m, 5H), 8.90 (d, $J = 5.0$ Hz, 1H).
14. Ir/9-amino(9-deoxy)cinchonine complex was prepared in the same manner of Ref. 13. light orange solid, yield 91%. mp (dec.) 180–190 °C. $[\alpha]_D^{25} + 125$ (*c* 0.5, $CHCl_3$). MS (FAB): *m*/*z* (%) 594 ($[M-Cl]^+$, 10), 293 (45), 157 (85), 136 (65), 79 (100). IR(KBr) ν_{max}/cm^{-1}: 3425, 2935, 2872, 1637, 1593, 1511, 993, 756. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94–1.65 (m, 5H), 2.06 (s, 2H), 2.30–2.69 (m, 9H), 3.05–3.07 (m, 5H), 4.45–4.76 (m, 5H), 5.06–5.07 (m, 2H), 5.85–5.86 (m, 1H), 7.53–8.35 (m, 5H), 8.87 (d, $J = 5.0$ Hz, 1H).
15. Typical procedure for recovering the catalysts in asymmetric transfer hydrogenation of acetophenone: 0.2 mmol catalyst (Rh/9-amino(9-deoxy)cinchonine complex or Ir/9-amino(9-deoxy)cinchonine complex) was added to 40 mL degassed dry *i*-propanol and stirred at room temperature for 30 min under argon. KOH (0.4 mmol) was added and the reaction mixture was stirred for another 10 min. Acetophenone (2 mmol) was then added in portion (0.05 mol L^{-1}) and the reduction was conducted at −20 °C for about 48 h (monitored by TLC). After completion of the reaction, the resulting solution was poured into 50 mL 1 mol L^{-1} HCl and 50 mL Et_2O, and the mixture was stirred for another 10 min. The two phases were separated and the water phase was extracted with Et_2O. Dried over $MgSO_4$, the solvent was evaporated to give the corresponding alcohol, which was purified by flash chromatography on silica gel. The water phase was cooled to 0 °C, and saturated Na_2CO_3 solution was added dropwise to adjust the water phase to pH ≈ 10. CH_2Cl_2 (30 mL) was added to the mixture. After separation, the water phase was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was dried over Na_2CO_3 and the solvent was evaporated to give the corresponding complex, which can be used in the next run without further purification.
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