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Thermomorphic System with Non-Fluorous Phase-Tagged Ru(BINAP) Catalyst: Facile Liquid/Solid Catalyst Separation and Application in Asymmetric Hydrogenation

Yi-Yong Huang,[†,‡] Yan-Mei He,[†] Hai-Feng Zhou,[†] Lei Wu,[†]
Bao-Lin Li,[†] and Qing-Hua Fan*,[†]

Laboratory of Chemical Biology, Institute of Chemistry,
Chinese Academy of Sciences, Beijing 100080, P. R. China,
and Graduate School of Chinese Academy of Sciences,
Beijing 100080, P. R. China

fanqh@iccas.ac.cn

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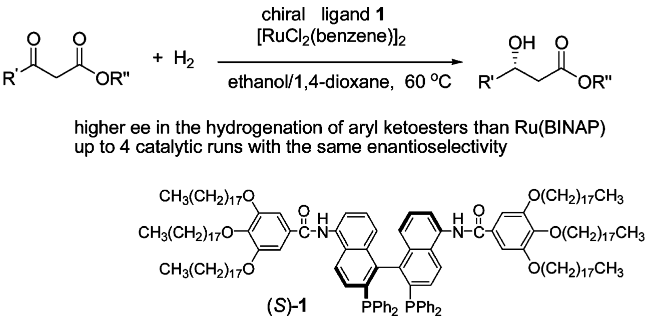

higher ee in the hydrogenation of aryl ketoesters than Ru(BINAP)
up to 4 catalytic runs with the same enantioselectivity

The thermomorphic BINAP derivative **1** tagged with long alkyl chains was prepared from (*S*)-5,5′-diamino BINAP and applied to Ru-catalyzed asymmetric hydrogenation of β-ketoesters under homogeneous conditions in 3:1 (v/v) ethanol/1,4-dioxane at 60 °C with high enantioselectivity (up to 98% ee). Results indicated that the Ru(**1**) catalyst was easily recovered by simple cooling and precipitation and could be used for at least four cycles without any loss of enantioselectivity.

Homogeneous asymmetric catalysis is one of the most important developments in modern synthetic and pharmaceutical chemistry over the past several decades. Many chiral catalysts are known to exhibit high activity and enantioselectivity.[1] However, the high cost of both these chiral ligands and transition metals as well as the regulatory issues associated with trace metal contaminants in the products have restricted their industrial applications. The heterogenization of homogeneous catalysts provides a possible approach to catalyst separation and recycling.[2] Different approaches to the immobilization of homogeneous chiral catalysts have recently been reviewed.[3] These included the immobilization of homogeneous chiral catalysts either by anchoring the catalyst onto organic or inorganic supports via covalent or noncovalent attachment or by using a liquid/liquid two-phase system. In most cases, however, the activity and enantioselectivity of the immobilized catalysts are usually lower than those of the parent homogeneous system as a result of mass transfer limitations.

Fluorous biphasic catalysis (FBC), since the pioneering work of Horváth was reported, has provided an elegant solution to the separation of the catalysts from the products and their reuse.[3i,4,5] One of the unique features of this strategy is that the thermomorphic two phases become homogeneous during the reaction when being heated and then could be readily separated by cooling the reaction mixtures. Although FBC combines the advantages of homogeneous catalysis and heterogeneous catalysis, the large-scale use of perfluorocarbon solvents has some drawbacks: high cost and environmental persistence. In response to these limitations, several research groups have introduced some new methodologies. Recently, Gladysz's group[6] and Yamamoto's group[7] independently introduced the solubility-based thermomorphic properties of heavy fluorous catalysts in nonpolar organic solvent as a new strategy to perform homogeneous fluorous catalysis without fluorous solvent. Jessop and co-workers described a new method for FBC, in which the fluorous solvent was replaced by fluorinated silica, and the fluorous catalyst was dissolved in organic solvent by the presence of CO_2 pressure and could be recovered after the reaction by release of the CO_2 pressure.[8] In addition, Bergbreiter and others developed some novel thermomorphic systems consisting of nonfluorous polymer-supported catalysts via

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[†] Chinese Academy of Sciences.

[‡] Graduate School of Chinese Academy of Sciences.

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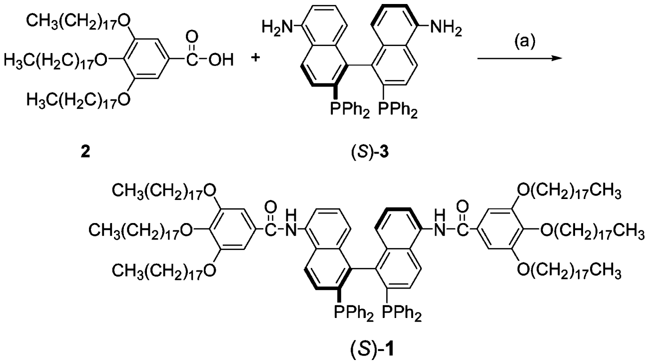
properly choosing of organic solvent mixtures.[9] These thermomorphic catalysts performed homogeneous catalytic reactions and could be easily recovered by simple cooling or heating. However, all these new approaches, to the best of our knowledge, have not been applied for asymmetric catalysis.

In this paper, we report the first example of a thermomorphic system for asymmetric hydrogenation and liquid/solid separation of the chiral catalyst.[10] Our strategy employed alkyl "ponytails" instead of the expensive fluorous ones as the "phase-tags" of the immobilized chiral catalyst. This nonfluorous phase tagged Ru(BINAP) catalyst shows temperature-dependent solubility in 1,4-dioxane/ethanol mixtures. This new system was applied for the asymmetric catalytic hydrogenation of β-ketoesters and exhibited both the advantages of very simple catalyst recycling by liquid/solid-phase separation and high enantioselectivity due to its homogeneous manner at high temperature.

BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] was chosen as a model ligand for this study because it has proven to be an excellent ligand for homogeneous catalysis in various asymmetric hydrogenation reactions.[1a,11] Considering that BINAP itself could not be easily attached onto an organic support via covalent chemical bond, 5,5′-diamino-BINAP **3** was first synthesized according to a literature procedure.[12] The method used to prepare the alkyl chain-tagged BINAP ligand **1** was similar to that of dendritic BINAP described in our previous reports.[13] Condensation reaction of 3,4,5-trioctadecyloxybenzoic acid **2**[14] with **3** in the presence of triphenyl phosphite, pyridine, and calcium chloride in *N*-methyl-2-pyrrolidone (NMP) at 120 °C gave **1** in 70% yield (Scheme 1). The ligand was purified by flash chromatography under N_2 atmosphere and characterized by ^{1}H, ^{13}C, and ^{31}P NMR, MALDI TOF mass spectrometry, and element analysis. All results were in full agreement with the designed structure.

SCHEME 1. Synthesis of the Alkyl Chain-Tagged BINAP Ligand[a]



[a] Reagents and conditions: (a) $(PhO)_3P$, pyridine, $CaCl_2$, NMP, 120 °C, 6 h.

The solubility of the alkyl chain-tagged BINAP was investigated by screening of several commonly used organic solvents. It was found that ligand **1** was soluble in solvents of low to moderate polarity such as hexane, dichloromethane, chloroform, toluene, and THF at room temperature. In contrast, much lower solubility was observed in higher polar solvents such as methanol, ethanol, DMF, and 1,4-dioxane at ambient temperature. It is noteworthy that a significant increase of solubility in DMF or 1,4-dioxane at high temperature was observed. For example, 100 mg of **1** was dissolved in 8 mL of 1,4-dioxane at 60 °C, while more than 96% of **1** was precipitated when the mixture was cooled to 0 °C. Most importantly, in the solvent mixture of 1,4-dioxane and ethanol (1:3, v/v), which was chosen as the reaction solvent for the thermomorphic catalytic system studied below, much lower solubility was observed at low temperature (in this case, 98% of **1** could be precipitated after being cooled). This significantly large temperature-dependent solubility of ligand **1** in ethanol and 1,4-dioxane should allow the efficient recycling of the catalyst by simple cooling.

We chose asymmetric hydrogenation of β-ketoesters as a model reaction for evaluation of this thermomorphic catalytic system.[15,16] This is due to the following facts: (a) the reduced products are useful building blocks for the synthesis of biologically active compounds and natural products; (b) Ru(BINAP)-type complexes have proved to be excellent catalysts for this asymmetric transformation; (c) such reactions are usually carried out at high temperature.

The alkyl chain-tagged Ru(BINAP) catalyst Ru(II) was prepared in situ by the reaction of ligand **1** with $[RuCl_2(benzene)]_2$ in DMF at 100 °C for 20 min.[17] To choose the proper solvent system, which meets the requirements of the thermomorphic biphase catalysis, we first studied the solubility of the Ru complex in the mixture of ethanol and 1,4-dioxane. Ru[(*S*)-**1**] complex (3.6 mg) was dissolved in 0.5 mL of 1,4-dioxane at 60 °C, and then the poor solvent, ethanol, was added dropwise into the solution. The complex was dissolved until the volume of the ethanol was up to 2 mL. Thus, a homogeneous catalysis could be achieved over a range of 20−100% (v/v) of 1,4-dioxane in the mixture solvent at this temperature. Upon

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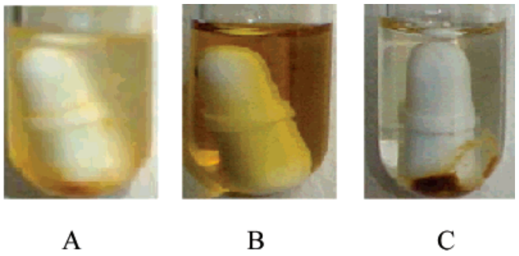
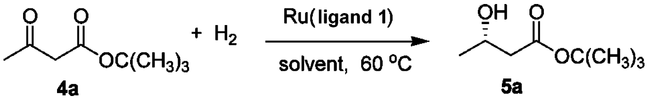


FIGURE 1. Photographs of the alkyl phase-tagged Ru(BINAP) catalyst in ethanol/1,4-dioxane (3:1) solvent at different temperatures: (A) catalyst suspension (before heating); (B) homogeneous solution when heating at 60 °C; and (C) catalyst precipitation after cooling to 0 °C and centrifuging.

TABLE 1. Solvent Effect on Asymmetric Hydrogenation of β-Ketoester 4a Catalyzed by Ru(1)[a]



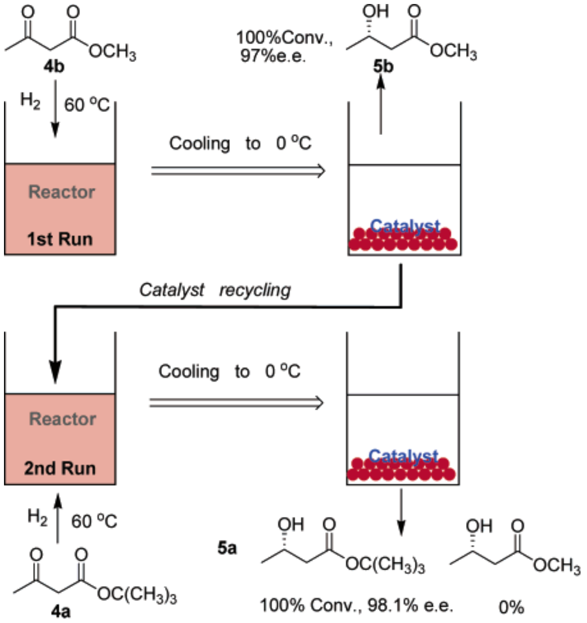
entry	solvent	conv[b] (%)	ee[b] (%)
1	CH_2Cl_2	100 (>98)[c]	93.5
2	toluene	0	0
3	THF	12	33.0
4	1,4-dioxane	22	57.0
5	ethanol	93 (81)[c]	96.0
6	ethanol/1,4-dioxane (1:1, v/v)	100 (>98)[c]	96.5
7	ethanol/1,4-dioxane (3:1, v/v)	100 (>98)[c]	97.0
8[d]	ethanol	100 (>98)[c]	96.9

[a] All reactions were carried out with a substrate concentration of 0.12 M ($v = 2$ mL) under 40 atm of H_2 at 60 °C for 24 h with 0.5 mol % catalyst loading. [b] ee values and conversions were determined by GC on a Chirasil-Dex CP 7502 (30 m × 0.25 mm) column. [c] Selectivity for **5a** based on GC analysis is shown in parentheses. [d] Catalyst Ru(BINAP) was used instead of Ru(**1**).

cooling to 0 °C, it was found that ruthenium complex stayed mainly in the solid phase of this thermomorphic system (Figure 1). The amount of the metal catalyst dissolved in the solvent mixtures with different ratios was determined by using ICP-MS. It was found that the ruthenium concentrations in solvent of 1:1, 2:1, and 3:1 ethanol/1,4-dioxane (2 mL volume in total) are 2.28 (96.2% recovery), 1.96 (96.7 recoevery), and 0.87 (98.6% recoevery) ppm, respectively. In the case of increasing the amount of ethanol in the solvent mixture, slightly lower catalyst solubility was observed.

To investigate the solvent effect, *tert*-butyl acetoacetate **4a** was chosen as the standard substrate for the asymmetric hydrogenation. As shown in Table 1, the reaction proceeded smoothly in dichloromethane with high enantioselectivity and 100% conversion (entry 1). In contrast, no activity was observed in toluene. When the moderate polarity solvents such as THF and 1,4-dioxane were used, low activities and low to moderate enantioselectivities were obtained (entries 3 and 4). These results are similar to those obtained by Ru(BINAP) reported by Vankelecom.[15c] Performing the reaction in ethanol, which has proven to be a good solvent for this type reaction, resulted in high enantioselectivity and 93% conversion, albeit much lower selectivity as compared to the Ru(BINAP) catalyst (81% vs > 98% as shown in entry 5 and entry 8). The insolubility of the catalyst in ethanol leaded to low activity, and the acetal formation as the byproduct was observed.[15c] It is noteworthy that the thermomorphic catalytic system consisting of solvent mixture of ethanol and 1,4-dioxane gave the highest enantioselectivity and 100% conversion (entry 7). The ratio of two solvents showed almost no effects on the catalyst performance (entries 6 and 7). Therefore, we chose 3:1 ethanol and 1,4-dioxane as the optimizing solvent system for the later experiments.

SCHEME 2. Illustration of Sequenced Asymmetric Hydrogenation of β-Ketoesters 4b and 4a by the Thermomorphic System with Ru(1) in Solvent Mixture of Ethanol/1,4-Dioxane and Catalyst Recycling via Liquid/Solid-Phase Separation Showing the Complete Separation of the Product in the First Run



We then turned our attention to investigating the facile recovery of the alkyl chain-tagged Ru(BINAP) catalyst from the reaction mixtures. As illustrated in Scheme 2, the unique feature of this strategy was that the catalytic reaction was carried out in a homogeneous manner, and the reaction mixture would be separated into two phases (liquid/solid) by simple cooling after the reaction. In the presence of 0.1 mol % of Ru(**1**), the hydrogenation of **4b** was first carried out under 40 atm H_2 pressure at 60 °C for 24 h. Upon cooling to 0 °C and release of H_2, the catalyst was precipitated and isolated by centrifugation or filtration as in the usual solid-supported catalytic reaction. The first run reaction gave **5b** with 100% conversion and 97% ee, which was significantly higher that that of Ru catalyst derived from fluorous phase-tagged BINAP derivative (up to 80% ee).[5k] The recovered catalyst was then used for the hydrogenation of **4a** under otherwise identical reaction conditions. In the second run reaction, 100% conversion and 98% ee were achieved without detecting any **5b** (Scheme 2). It was thus demonstrated that the reaction product could be completely separated from the solid catalyst phase. In contrast, in the case of liquid/liquid biphasic catalysis, a few products from the previous run did remain in the catalyst-containing phase of the next run.[9,13b]

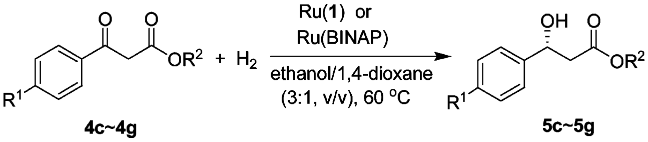
Next, the recycling of catalyst Ru(**1**) was studied in the asymmetric hydrogenation of **4a** and **4b**, respectively. As shown in Table 2, catalyst Ru(**1**) could be used for at least four cycles in both cases without any loss of enantioselectivity. To study the activity of the recycled catalyst, we measured the TOF of each catalytic run at 1 h reaction time. The results (Table 2) indicated that the activity decreased slightly for the first three runs but began to drop sharply at the fourth run. This loss of

TABLE 2. Recycle of the Catalyst for Asymmetric Hydrogenation of β-Ketoesters 4a and 4b[a]

	4a		**4b**	
run	conv[b,c] (%)	ee[b] (%)	conv[b] (%)	ee[b] (%)
1	100 (92)	96.9	100	97.8
2	100 (85)	96.5	100	98.6
3	100 (70)	94.9	100	98.2
4	93 (25)	96.0	83	97.3

[a] All reactions were carried out with substrate concentration of 0.06 M (1.5 mL of ethanol and 0.5 mL of 1,4-dioxane) under 40 atm of H_2 at 60 °C for 10 h with 1 mol % catalyst loading. [b] ee values and conversions were determined by GC on a Chirasil-Dex CP 7502 (30 m × 0.25 mm) column. [c] Average TOF at lower than 100% conversion (after 1 h reaction) is shown in parentheses.

TABLE 3. Asymmetric Hydrogenation of Various β-Aryl Ketoesters Catalyzed by Ru(1)[a]



entry	substrate (R^1/R^2)	ee (%)
1	**4c** (H/Me)	92.9 (87.3)[b,d]
2	**4d** (H/Et)	91.1 (86.3)[c,d]
3	**4e** (Cl/Me)	89.6 (86.6)[c,d]
4	**4f** (F/Me)	87.3 (85.7)[c,d]
5	**4g** (MeO/Me)	83.7 (82.5)[c,d]

[a] All reactions were carried out with a substrate concentration of 0.12 M (1.5 mL of ethanol and 0.5 mL of 1,4-dioxane) under 40 atm of H_2 at 60 °C for 24 h with 0.5 mol % catalyst loading. All reactions have >99% conversion except for entry 5 (60% conversion). [b] The ee value was determined by GC on a Chiraldex G-TA CA 73035 (50 m × 0.25 mm) column. [c] The ee values were determined by GC on a Chirasil-Dex CP 7502 (30 m × 0.25 mm) column. [d] Data in parentheses was obtained from Ru(BINAP) catalyst.

activity may not reflect the intrinsic instability of the thermomorphic Ru(**1**) catalyst. The catalyst recycling and reused experiments were conducted without rigorous exclusion of air. Thus, a few of the oxygen-sensitive ruthenium hydride species could be oxidized, which may contribute to the loss of activity of the recycled catalyst. On the other hand, after isolation of the catalyst, the filtrate of **5a** in 2 mL of ethanol/1,4-dioxane was further employed for the catalytic hydrogenation of **4b** under the same experimental conditions. In this case, no product of **5b** was observed at all. In addition, the ICP-MS spectroscopic analysis of the filtrate indicated that about 1.78% of Ru catalyst has leached into the organic product. These results indicated that the catalytically active ruthenium species could be effectively recovered under this biphasic condition.

Having established the facile catalyst recycling of this thermomorphic catalytic system, we next examined a variety of β-aryl ketoesters. As shown in Table 3, all substrates were successfully hydrogenated with high ee values and complete conversions except for **4g** (60% conversion) by using 0.5 mol % of Ru catalyst derived from ligand **1** at 60 °C. It should be emphasized that the level of enantiocontrol for all β-aryl ketoesters was higher than those obtained from the parent homogeneous Ru(BINAP) catalyst. For example, **4c** was reduced to **5c** with 92.9% ee by Ru(**1**) but 87.3% ee by Ru(BINAP) (entry 1). This enantioselectivity enhancement was probably due to the steric effect of the 5,5′-substituents on BINAP, and a similar but much more remarkable substituent effect was observed in the case of 4,4′-substited BINAP derivatives.[15e]

In summary, a new BINAP derivative bearing alkyl ponytails was synthesized and proven to be a highly effective ligand for Ru-catalyzed hydrogenation of β−ketoesters in the mixture of ethanol/1,4-dioxane. This nonfluorous phase-tagged catalyst could be easily recovered by simple cooling and reused without any loss of enantioselectivity. Since light alcohols have been found to be the best solvents for most asymmetric hydrogenation reactions, this system can be extended to other chiral phosphine-containing catalysts. Thus, this strategy will lead to a general method for separating products from homogeneous catalysts and recovering the chiral catalysts by simple liquid/solid-phase separation.

Experimental Section

General Procedure for the Asymmetric Hydrogenation of β-Ketoesters and the Catalyst Recycling. In a glovebox, to a mixture of $[RuCl_2(benzene)]_2$ (3.0 mg, 0.006 mmol) in 2 mL of freshly distilled and degassed DMF was added ligand (*S*)-**1** (33.0 mg, 0.0135 mmol). The mixture was stirred at 100 °C for 20 min, and DMF was removed under vacuum to give the Ru catalyst. Then an autoclave containing a glass tube was charged with Ru(**1**) (3.6 mg, 1.2×10^{-3} mmol), β-ketoester (0.24 mmol) and 2 mL of ethanol/1,4-dioxane (3:1, v/v) under N_2 atmosphere. The autoclave was closed and finally pressurized with hydrogen to 40 atm. After being stirred at 60 °C for a certain time, the autoclave was cooled to room temperature and the H_2 was carefully released. The tube in the autoclave was taken out in the glovebox and sealed. The reaction mixtures were further cooled to 0 °C, and the precipitated catalyst was isolated by centrifuging and washed with ethanol one time. The solution was sucked out with a syringe and used for product analysis. The recovered catalyst could be reused just as in the first run. The enantiomeric purity of the product was determined by GC on a Chirasil-Dex CP 7502 column.

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Supporting Information Available: General experimental information, BINAP ligand synthesis details, and characterization data of the ligand and the reduced products. This material is available free of charge via the Internet at http://pubs.acs.org.

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