

A New Solvent System for Recycling Catalysts for Chelation-Assisted Hydroacylation of Olefins with Primary Alcohols

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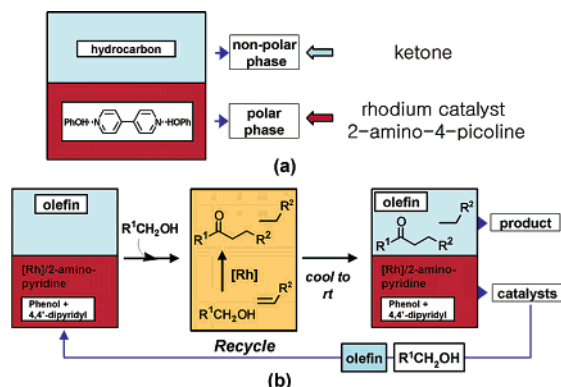
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C–H bond activation by transition metal catalysts is one of the current interests in organic synthesis.¹ Particularly, hydroacylation through aldehydic C–H bond activation provides an efficient synthetic method for preparing ketones.² In the course of our studies on chelation-assisted hydroacylation,³ a one-pot protocol to obtain ketones from primary alcohols and olefins was devised using a cocatalyst system of a rhodium complex and 2-aminopyridine.⁴ Recently, we demonstrated the reuse of a rhodium catalyst in this protocol by using polystyrene-based phosphine.^{4c} However, the polymer-based system exhibited inferior reactivity as compared with the homogeneous catalysis due to heterogeneity. Moreover, 2-aminopyridines, used as a chelation auxiliary,^{3c} should be added at each cycle. Therefore, we have investigated a biphasic system which fulfills the following two requirements: complete homogeneity during the reaction and the easy separation of 2-aminopyridines as well as the transition metal complex after the reaction. There have been various approaches to separate and reuse homogeneous catalysts,⁵ such as aqueous biphasic systems,⁶ fluoruous biphasic systems,⁷ and soluble polymer-based ligands.⁸ However, these methods need to immobilize both 2-aminopyridines and a transition metal complex to polymer or tagging corresponding functional groups. Attempts to use ionic liquids as a reaction medium⁹ failed, presumably due to heterogeneity derived from limited solubility of olefin.¹⁰ Herein described is a new approach to recycle the catalysts for chelation-assisted hydroacylation of olefins with primary alcohols, using a hydrogen-bonding solvent, in which a rhodium complex and 2-aminopyridine are confined after the reaction and thus separated from products for reuse.

In our experiment, a mixed solvent consisting of phenol and 4,4'-dipyridyl, which was known to form a hydrogen-bonding complex,¹¹ was used as a reaction medium. As depicted in Scheme 1a, it forms

Scheme 1. (a) A Biphasic System Using Hydrogen-Bonding Solvent, and (b) a Schematic Diagram of the Recycling of the Catalysts for Chelation-Assisted Hydroacylation with Primary Alcohol



two immiscible phases with hydrocarbon such as alkane or olefin at room temperature. Because a hydrogen-bonding network cannot

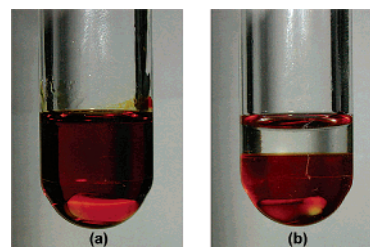


Figure 1. A phase separation of the reaction mixture consisting of benzyl alcohol, 1-decene, [(C₈H₁₄)₂RhCl]₂, 4-PBA, 2-amino-4-picoline, phenol, and 4,4'-dipyridyl. (a) Two phases immersed into one phase upon heating (120 °C), and then (b) separated into two phases at room temperature.

Table 1. Recycling of the Catalysts for Hydroacylation of **2a** with **1a**

$$\text{PhCH}_2\text{OH} \text{ (1a)} + \text{olefin} \text{ (2a)} \xrightarrow[\text{4,4'-dipyridyl, phenol, 150 }^\circ\text{C, 6 h}]{\text{3a (5 mol\%), phosphine (4, 20 mol\%)}} \text{ketone} \text{ (6a)}$$

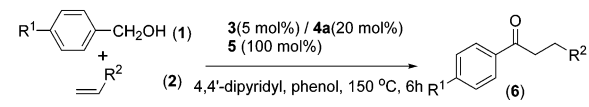
entry	phosphine (4)	additive	isolated yield of 6a (%)						
			1	2	3	4	5	6	7
1	4-PBA (4a)		88	96	92	95	91	93	96
2	PPh ₃ (4b)	PhCO ₂ H (20 mol %)	93	34	28	12			
3 ^a	4a		94	56	61	43	29		

^a The reaction was performed in the absence of phenol.

be established at high temperature, these two phases turned into one phase upon heating as shown in Figure 1a. Thus, a homogeneous catalysis could be achieved during the reaction, and the reaction mixture separated into two phases after the reaction (Figure 1b). In this biphasic system, it was found that 2-aminopyridine and the rhodium complex stayed in the polar phase (phenol and 4,4'-dipyridyl),¹² while the product of hydroacylation, ketone, largely stayed in the nonpolar hydrocarbon. Therefore, the catalysts could be separated from ketone for recycling after the reaction (Scheme 1b).

This solvent system consisting of phenol and 4,4'-dipyridyl was applied to the reaction of benzyl alcohol (**1a**) and 1-hexene (**2a**) in the presence of [(C₈H₁₄)₂RhCl]₂ (**3**, 5 mol %), phosphine (**4**), and 2-amino-4-picoline (**5**, 100 mol %) at 150 °C for 6 h. After the homogeneous reaction, it was cooled to room temperature to form two phases. Heptanophenone (**6a**) was separated from the catalysts by decanting the upper layer and washing the lower layer with *n*-pentane three times. The remaining lower layer containing catalysts was recycled for the next reaction (Table 1).

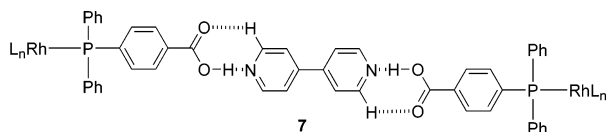
When 4-diphenylphosphinobenzoic acid (**4a**, 4-PBA) was used as an external ligand, the reactivity was retained for repeated uses, giving 88–96% isolated yields (av. 93%) of heptanophenone **6a** (entry 1). In this system, rhodium catalyst was strongly immobilized in the polar phase, which was confirmed by ICP-MS analyses. Only a trace amount (0.088 and 0.16 μg, respectively) of Rh was found in the separated nonpolar phases of cycles 1 and 2, corresponding

Table 2. Recycling of the Catalyst for Hydroacylation of **2** with **1**


entry	R ¹ (1)	R ² (2)	ketone (6)	isolated yield of product (%)							
				1	2	3	4	5	6	7	8
1	H (1a)	<i>t</i> -Bu (2b)	6b	90	87	93	96	97	95	92	93
2	1a	C ₆ H ₁₃ (2c)	6c	85	77	97	95	98	90	83	92
3	1a	C ₈ H ₁₇ (2d)	6d	89	91	86	90	88	94	82	89
4	CF ₃ (1b)	2a	6e	87	92	97	95	89	91	88	87
5	MeO (1c)	2a	6f	92	98	92	96	92	94	91	97
6	1c	2b	6g	94	91	92	96	90	95	91	87

to a leaching of 0.005% and 0.01% of initial Rh (1.63 mg). A chelation auxiliary **5** also stayed mainly in the polar phase even though a very small amount of **5** was found in the nonpolar phase occasionally (2–5% based on the initial amount), which resulted in no significant decrease in the yield of **6a** in the next run.¹³ On the other hand, when the reaction was performed in the presence of triphenylphosphine (**4b**) and benzoic acid,¹⁴ instead of **4a**, the yield of **6a** dropped after the second run (entry 2).

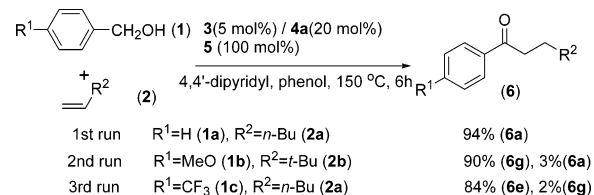
A high affinity of rhodium catalyst to the hydrogen-bonding solvent in the presence of **4a** as a ligand might be ascribed to the existence of acid functionality in **4a**. When the reaction was carried out in the absence of phenol, a solid/liquid phase separation took place by precipitation after the reaction, while a homogeneous catalysis was achieved during the reaction.¹⁵ We assumed that the precipitation might be attributed to a hydrogen-bonding assembly consisting of an Rh(I) complex bearing **4a** and 4,4'-dipyridyl as in **7**.¹⁶ The solid phase could be separated by decanting the liquid, but the reactivity was not retained to result in a gradual decrease in the yield of **6a**, which might be due to the large leaching of 2-amino-4-picoline (entry 3).¹⁷



Other benzyl alcohols (**1**) and olefins (**2**) were applied to the reaction to give the corresponding ketones in good yields for the repeated uses of catalyst (Table 2).

To examine whether ketone was completely separated from the polar phase, the reactions were performed using different substrates in every cycle, and it was found that only a small amount of ketone remained in the polar phase as shown in Scheme 2. The first reaction was carried out using **1a** and **2a** to give **6a** in 94% isolated yield. The separated lower phase was used for the next reaction of 4-methoxybenzyl alcohol (**1b**) and 3,3-dimethyl-1-butene (**2b**) to afford 1-(4-methoxyphenyl) heptanone (**6g**) in 90% yield along with a small amount of **6a**. At the third cycle using 4-(α,α,α -trifluoromethyl)-benzyl alcohol (**1c**) and **2a**, 84% yield of 1-[4-(trifluoromethyl)phenyl]heptan-1-one (**6e**) was obtained as well as 2% of **6g**.

In conclusion, a new method to recycle catalysts for chelation-assisted hydroacylation with primary alcohols was devised using a hydrogen-bonding solvent system consisting of 4,4'-dipyridyl and phenol. During the reaction at high temperature, the system is completely homogeneous so as to give efficient catalytic activity, while it is heterogenized to form two immiscible phases for facile recovery of catalyst. This approach exhibited retention of catalytic activity for repeated uses. Currently, we are investigating the

Scheme 2

application of this protocol to other catalytic reactions and developing more general recycling catalytic systems, because this system cannot be applied to the reaction in which the product is soluble in the polar phase.

Acknowledgment. This work was supported by the National Research Laboratory (NRL) (2000-N-NL-01-C-271) Program administered by the Ministry of Science and Technology and CBMH.

Supporting Information Available: Experimental details and the result of the reaction using ionic liquid (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- When 2-amino-4-picoline was added to a biphasic system of phenol, 4,4'-dipyridyl, and 1-hexene, 2-amino-4-picoline resided largely in the polar phase (phenol and 4,4'-dipyridyl). See Supporting Information.
- Because an excess amount of **5** was used in the reaction, such a small loss of **5** seems not to affect the reactivity.
- It was reported that the addition of benzoic acid improved the reactivity of hydroacylation. See ref 3b.
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- At every cycle, a significant amount of **5** was found in the nonpolar phase (more than 10% of the initial amount of **5**).

JA038071W