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Dual Functionalities of Hydrogen-Bonding Self-Assembled Catalysts in Chelation-Assisted Hydroacylation

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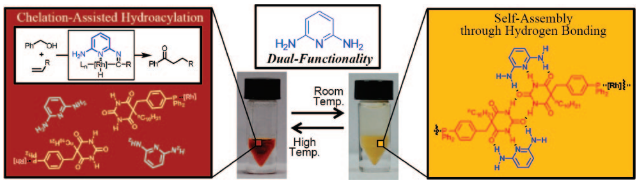

A recyclable catalyst for chelation-assisted hydroacylation of an olefin with primary alcohol was developed using hydrogen-bonding self-assembled catalysts consisting of 2,6-diaminopyridine and barbiturate phosphine−rhodium(I) complex. Upon heating, these two catalysts act as homogeneous catalysts due to cleavage of the hydrogen bond, and these associate to form supramolecular assemblies via hydrogen bonding that can be separated from immiscible product phase upon cooling after the reaction.

Transition-metal-catalyzed activation of C−H bonds is considered to be a good method for generating new C−C bonds in organic synthesis.[1] In particular, hydroacylation is a powerful tool for the direct synthesis of ketones from aldehyde and alkene in an atom-economical way.[2] We have developed an efficient chelation-assisted hydroacylation using a cocatalyst system consisting of a rhodium complex and 2-amino-3-picoline, which facilitates the C−H bond activation and suppresses decarbonylation.[3,4] This protocol was further applied to the use of primary alcohol instead of aldehyde.[3,5]

The recovery and reuse of transition metal catalysts have recently attracted much attention in organometallic chemistry.[6] Various methods using supports such as hyperbranched polymers,[7] dendrimers,[8] and hybrid materials[9] or tagging the catalyst to the solid or soluble supports[10] have been developed. In our first attempt to recycle hydroacylation catalysts, we demonstrated the reuse of a rhodium complex by employing polystyrene-based phosphine in which the catalytic reaction showed low reactivity compared with the corresponding homogeneous catalytic reaction.[11] Covalently bonded solid-supported catalysts often suffer from low efficiency because of reduced homogeneity during the reaction. Here we wish to report a new recyclable self-assembling organic catalyst capable of reversibly binding with the metal−phosphine ligand.

Hydrogen bonding is useful here since the adducts show reversible temperature-dependent dissociation on heating. On the basis of this phenomenon, we have developed a hydrogen-bond-controlled system for the recycling catalysts. For example, a hydrogen-bonding mixed solvent system, consisting of 4,4′-dipyridyl and phenol, was devised for recovery of organic and organometallic catalysts.[3,12] Another interesting system is a supported recyclable catalyst system consisting of a barbiturate bearing a phosphine ligand (BA-PPh$_2$, **1a**) with Rh(I), one connecting a 2-aminopyridin-4-yl group (BA-2-AP, **1b**), and 5-hexyl-2,4,6-triaminopyrimidine (TP, **2a**) as a polymeric hydrogen-bonding mediator for hydroacylation as shown in Scheme 1.[3,13] However, it was unexpectedly found that, even without organic catalyst BA-2-AP (**1b**), hydroacylation of 1-alkene with benzyl alcohol could be achieved in the presence

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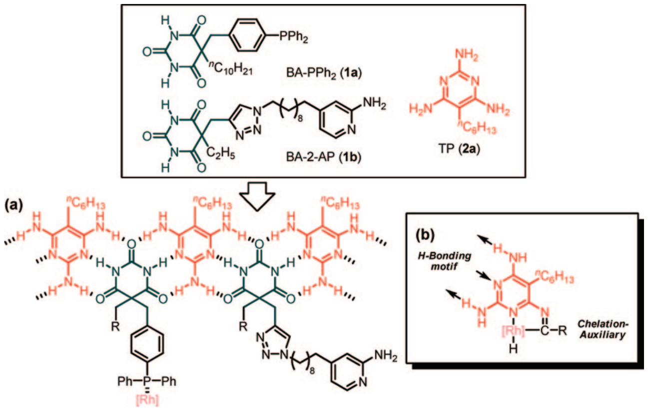
SCHEME 1. **(a) Self-Assembly of TP (2a) with BA-PPh$_2$ (1a) and BA-2-AP (1b) and (b) Chelation-Assisted C−H Bond Cleavage by TP**



SCHEME 2. **(a) Hydrogen-Bonding Interaction of BA-PPh$_2$ (1a) with bis-DAP (2b) and (b) Two Possible Hydrogen-Bonding Modes of Interaction between BA-PPh$_2$ (1a) and DAP (2c)**

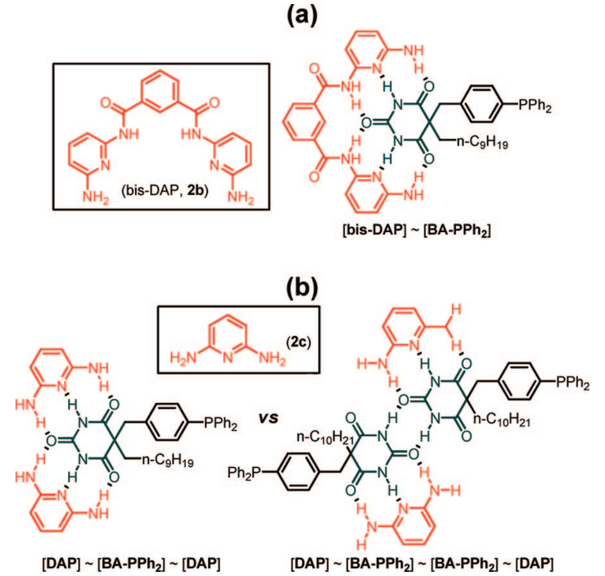
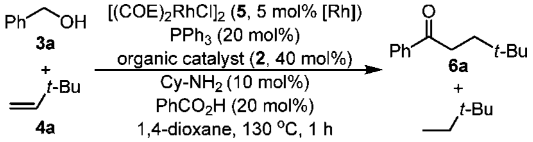
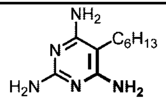
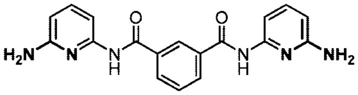
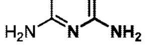
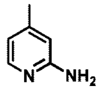


TABLE 1. **Isolated Yield (GC Yield) of Chelation-Assisted Hydroacylation Using Different Organic Catalyst 2**



Entry	Organic catalyst (2)	Isolated yield (%)[a]
1	 (2a)	28(35)
2	 (2b)	27(35)
3	 (2c)	72(79)
4		83(88)

[a] GC yields are given in parentheses.

of **1a** and **2a** to give a small amount of product.[14] It can be speculated that **2a** has dual functionalities: hydrogen-bonding mediator with barbiturate **1a-Rh** and chelation assistant auxiliary for hydroacylation.

On the basis of the above result, catalytic activities of some potential organic catalysts with dual functionalities, such as *N*^{1},*N*^{3}-bis(6-aminopyridin-2-yl)isophthalamide[15] (bis-DAP, **2b**) and 2,6-diaminopyridine (DAP, **2c**) were tested for hydroacylation (Table 1). Since the 2,6-diaminopyridine (DAP) unit interacts with barbiturate via three hydrogen bonds, the expected hydrogen bonding network of each DAP derivative and barbiturate are illustrated in Scheme 2.

The catalytic activities of these DAP derivatives as well as TP (**2a**) for hydroacylation were compared with that of 2-amino-4-picoline (Table 1). Benzyl alcohol (**3a**) was treated with 3,3-dimethyl-1-butene (**4a**) at 130 °C for 1 h in the presence of Rh(I)/PPh$_3$ catalyst and **2a** to give 4,4-dimethyl-1-phenylpentan-1-one (**6a**) in a 28% isolated yield (entry 1). When the identical reaction was carried out with bis-DAP (**2b**), product **6a** was isolated in a 27% yield. However, with DAP (**2c**), a 72% isolated yield of **6a** was obtained. This result is comparable to that of 2-amino-4-picoline. As a result, **2c** was chosen as a chelation-assisted recyclable catalyst for hydroacylation.

As stated earlier, two possible modes of hydrogen-bonding self-assemblies from **1a** and **2c** are shown in Scheme 2b. Although the structural arrangement of [DAP]−[BA-PPh$_2$]−[DAP] (1/2 ratio of **1a**/**2c**) seems to be reasonable, that of [DAP]−[BA-PPh$_2$]−[BA-PPh$_2$]−[DAP] (1/1 ratio) is also possible based on the single-crystal X-ray structural analysis of the similar type of 2,6-diaminopyridine−platinum(II) barbiturate complex previously reported.[16] For the clear structural determination in solution, the interaction of BA-PPh$_2$ (**1a**) with DAP (**2c**) was studied by ^{1}H NMR spectroscopy in CDCl$_3$. Hydrogen bonding between **1a** and **2c** was evidenced by marked downfield shifts in the signal corresponding to the N−H of **2c**. The Job plot determined by ^{1}H NMR experiments revealed that a 1:1 complex such as [DAP]−[BA-PPh$_2$]−[BA-PPh$_2$]−[DAP] might be formed between **1a** and **2c** (Figure 1a; see Supporting Information). Moreover, the resulting organometallic complexes may be highly cross-linked by coordinating Rh(I) to phosphines,[17] which results in the formation of insoluble hydrogen-bonding assemblies (Figure 1b).

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(14) Reaction of benzyl alcohol (**3a**) and 3,3-dimethyl-1-butene (**4a**) was carried out in the presence of [(COE)$_2$RhCl]$_2$ (**5**, 5 mol %), BA-PPh$_2$ (**1a**, 40 mol %), TP (**2a**, 40 mol %), cyclohexylamine (10 mol %), and benzoic acid (20 mol %) in 1,4-dioxane at 130 °C to afford **6a** in a 24% GC yield after 1 h.

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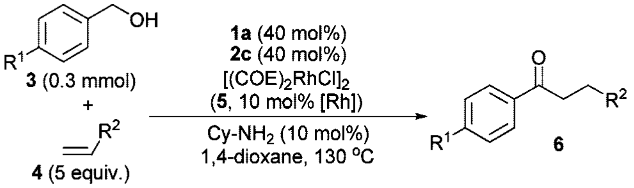
TABLE 2. **Recycle of Catalysts 1a-Rh and 2c for Hydroacylation of 4 with 3**[a]



entry	R^1 (**3**)	R^2 (**4**)	ketone (**6**)	rxn time (h)	isolated yield of product (%) 1	2	3	4	5	6
1	H (**3a**)	^{t}C$_4$H$_9$ (**4a**)	**6a**	6	78	83	86	76	76	77
2	**3a**	^{n}C$_4$H$_9$ (**4b**)	**6b**	6	70	84	84	78	75	80
3	CF$_3$ (**3b**)	**4a**	**6c**	6	83	89	81	77	77	82
4	MeO (**3c**)	**4a**	**6d**	3	77	71	81	78	72	78

[a] At 1st and 4th runs, 25 mol % of benzoic acid was added, and cyclohexylamine was added in every run.

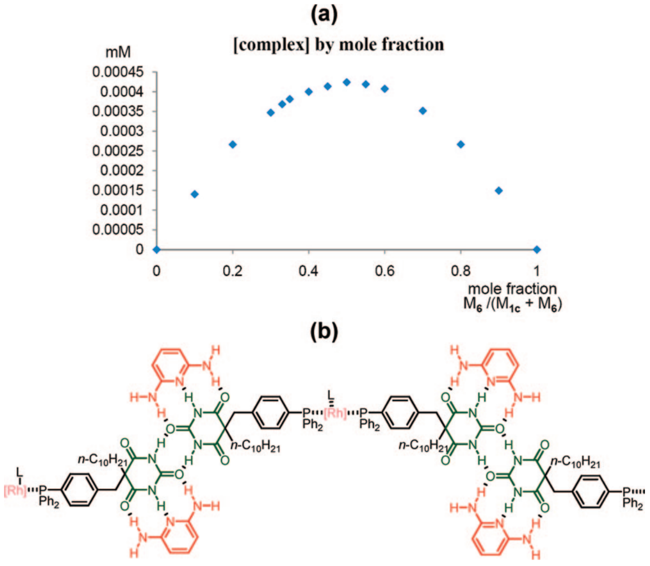


FIGURE 1. (a) Job plot between **1a** and **2c** (determined by ^{1}H NMR spectroscopy in CDCl$_3$ and (b) expected structure of the resulting supramolecular assembly after addition of rhodium complex.

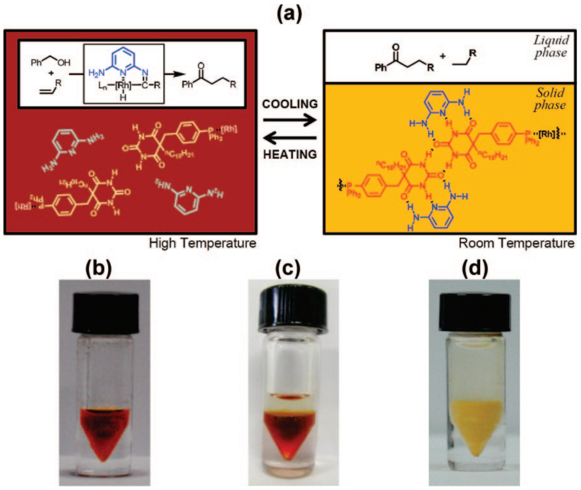


FIGURE 2. (a) Schematic illustration of the recycling organometallic and organic catalysts, **1a-Rh** with **2c** for hydroacylation. (b) Homogeneous phase consisting of **1a-Rh**, **2c**, **3a**, **4a**, benzoic acid, and Cy-NH$_2$ in 1,4-dioxane at high temperature (130 °C). (c) Separation of reaction mixture (liquid/liquid) from Figure 2b after cooling to room temperature (25 °C). (d) Supramolecular solid obtained upon addition of *n*-pentane to the sample shown in Figure 2c for decanting the product.

This self-assembly system of BA-PPh$_2$ (**1a**) and DAP (**2c**) was applied to the reaction of benzyl alcohol (**3a**) with 3,3-dimethyl-1-butene (**4a**) in the presence of [(COE)$_2$RhCl]$_2$ (**5**, 10 mol % [Rh]), cyclohexylamine (Cy-NH$_2$, 10 mol %), and benzoic acid (25 mol %)[18] at 130 °C for 6 h in 1,4-dioxane (Figure 2a). The ratio of **1a** and **2c** was adjusted to 1:1 to form a supramolecular hydrogen-bonding complex. During the reaction at high temperature, the system was homogeneous because a hydrogen-bonding network cannot be established (Figure 2b), but it was heterogenized at room temperature to form two phases after the reaction due to the formation of a hydrogen-bonding network (Figure 2c). After the addition of *n*-pentane, a lower phase was precipitated to form a yellow solid. It was found that barbiturate **1a-Rh** remained in the lower solid phase assembled with **2c**, while the product **6a** was separated from the self-assembled mixture of **1a-Rh** and **2c** by decanting the upper layer and washing the lower layer with *n*-pentane (Figure 2d).

The remaining barbiturate **1a-Rh** and DAP (**2c**) were recycled for the next reaction with addition of substrates and solvent. This process was repeated up to the sixth catalytic reaction, and the yield of product **6a** was sustained (Table 2, entry 1). Other alcohols **3** and olefins **4** were applied to this reaction, affording the corresponding ketones with good to moderate yields for the repeated use of catalysts without loss of the reactivity (entries 2−4). In particular, 4-methoxybenzyl alcohol (**3c**) showed better reactivity than the other substrates since the reaction time could be reduced from 6 to 3 h (entry 4).

To confirm whether product ketones were completely separated from the lower solid catalyst mixtures, the reactions were performed using different substrates in every cycle (Table 3). It was found that only a trace amount of ketone in the previous run remained in the next run. The first reaction was carried out using **3b** and **4a** to give **6c** in an 80% isolated yield (88% GC yield) due to its reduced reactivity compared with that of **3a** and **3c**. The separated barbiturates **1a-Rh** and **2c** were reused for the next reaction of **3a** and **4b** to afford **6b** in a 91% isolated yield (100% GC yield) while detecting less than 1% of **6c**. In the third run using **3c** and **4a**, a 92% isolated yield of **6d** and **6b** was obtained with a ratio of 99:1.

In conclusion, a novel recyclable organic catalyst system for chelation-assisted hydroacylation of an olefin with primary alcohol was developed using 2,6-diaminopyridine (DAP, **2c**)

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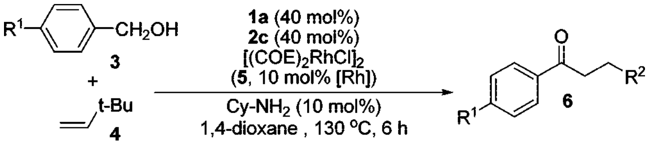
[18] CyNH$_2$ and benzoic acid are additives for accelerating the hydroacylation reaction.

TABLE 3. Hydroacylation with Different Substrates Showing Complete Separation of the Product in Each Run[a]



run	reactants (**3**, **4**)	isolated yield (%)
1	$R^1 = CF_3$ (**3b**), $R^2 = {}^tC_4H_9$ (**4a**)	80 (**6c**)
2	$R^1 = H$ (**3a**), $R^2 = {}^nC_4H_9$ (**4b**)	91 (**6b**:**6c** = 99:1)
3	$R^1 = MeO$ (**3c**), $R^2 = {}^tC_4H_9$ (**4a**)	92 (**6d**:**6b** = 99:1)

[a] At first run, 25 mol % of benzoic acid was added, and cyclohexylamine was added in every run.

as a chelation auxiliary catalyst and barbiturate bearing phosphine-Rh (**1a-Rh**) as a self-assembling partner. The self-assembly of DAP and BA-PPh_2 expressed one of two functionalities (catalysis and hydrogen-bonding self-assembly support) depending on the applied thermal condition. During the reaction at high temperature, the system is homogeneous and shows good catalytic activity. After the reaction, the system is heterogenized at room temperature to form two immiscible phases for the facile recovery of catalysts. We are currently investigating further applications of this recycling catalysis protocol for other catalytic reactions.

Experimental Section

A screw-capped pressure vial (1 mL) was charged with 32.4 mg (0.3 mmol) of benzyl alcohol (**3a**), 126 mg (1.5 mmol) of 3,3-dimethyl-1-butene (**4a**), 10.8 mg (0.015 mmol) of $[(COE)_2RhCl]_2$ (**5**), 65.0 mg (0.12 mmol) of barbiturate **1a**, 14.7 mg (0.12 mmol) of 2,6-diaminopyridine (**2c**), 3 mg (0.03 mmol) of cyclohexylamine, 9.0 mg (0.0075 mmol) of benzoic acid, and 50 mg of 1,4-dioxane in a dry box. The reaction mixture was stirred for 6 h in an oil bath that was preheated at 130 °C. After cooling to room temperature, *n*-pentane (1 mL) was added to the reaction mixture, which was stirred and centrifuged. The upper *n*-pentane layer was decanted using a pipet. This process was repeated three times. The solvent in combined solution was evaporated, and the resulting residue was purified by column chromatography (SiO_2, *n*-hexane) to give 44.5 mg (78% yield) of **6a**. To the remaining solid layer were added 32.4 mg (0.3 mmol) of benzyl alcohol (**3a**), 126 mg (1.5 mmol) of 3,3-dimethyl-1-butene (**4a**), 3 mg (0.03 mmol) of cyclohexylamine, and 50 mg of 1,4-dioxane for the next reaction. The reaction procedure was repeated, and the results are shown in entry 1, Table 2.

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Supporting Information Available: Experimental details of Job plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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