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Recyclable Self-Assembly-Supported Catalyst for Chelation-Assisted Hydroacylation of an Olefin with a Primary Alcohol

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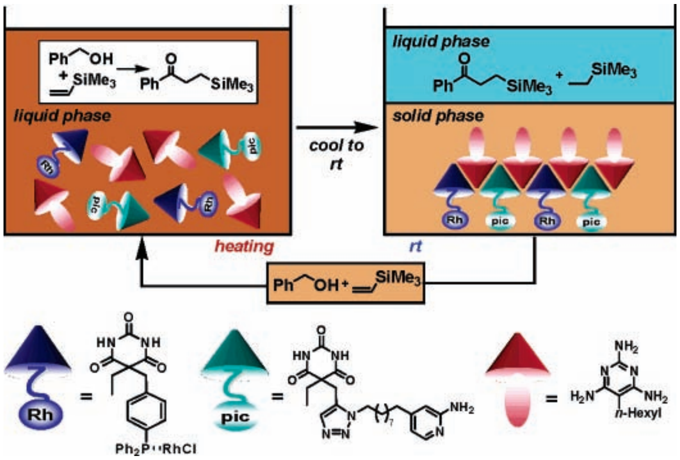
ABSTRACT



A novel recyclable catalyst for chelation-assisted hydroacylation of an olefin with a primary alcohol was developed by utilizing a hydrogen-bonding self-assembly motif consisting of a barbiturate bearing 2-aminopyridin-4-yl group and 5-hexyl-2,4,6-triaminopyrimidine. This was further applied to a mixed catalyst system to recycle both organic and organometallic catalysts.

The activation of C−H bonds by transition metal catalysts is considered to be one of the most efficient methods for producing a new C−C bond in organic synthesis.[1] In particular, hydroacylation through aldehydic C−H bond activation provides a useful method for the direct synthesis of ketone.[2] We have successfully developed an efficient catalytic system for a chelation-assisted hydroacylation using a cocatalyst that consists of a rhodium complex and 2-aminopyridine derivative, which facilitates the C−H bond activation and suppresses decarbonylation: a direct synthesis of ketone from aldehyde and olefin[3] and from primary alcohol and olefin.[4] With this protocol we demonstrated the reuse of a rhodium complex by employing polystyrene-based phosphine,[5] in which the catalytic reaction showed low reactivity compared to the corresponding homogeneous catalytic reaction.[4a] The covalently bonded solid-supported

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[1] (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.

[2] (a) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451. (b) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286.

[3] (a) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200. (b) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (c) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2423.

[4] (a) Jun, C.-H.; Huh, C.-W.; Na, S.-J. *Angew. Chem., Int. Ed.* **1998**, *37*, 145. (b) Jun, C.-H.; Hwang, D.-C. *Polymer* **1998**, *39*, 7143.

[5] Jun, C.-H.; Hong, H.-S.; Huh, C.-W. *Tetrahedron Lett.* **1999**, *40*, 8897.

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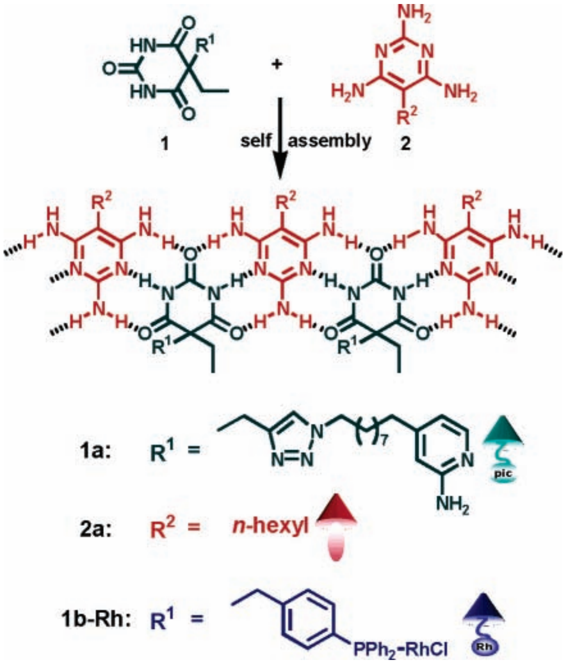
catalysts often suffer from low efficiency because of reduced homogeneity during the reaction. Consequently, various methods using soluble supports have been developed: hyperbranched polymers,[6] dendrimers,[7] and hybrid materials,[8] or tagging of the catalyst to the solid or soluble supports.[9] We have developed a new solvent system consisting of 4,4′-bipyridyl and phenol, for recycling catalysts of chelation-assisted hydroacylation of olefins with primary alcohols.[10] Although this solvent system exhibited a good reactivity and an easy separation of the rhodium catalyst and 2-amino-4-picoline from the product ketone for the recycling catalysis, this catalytic system has the limitation of partial leaching of the organic catalyst, 2-amino-4-picoline. Recently, we developed a recyclable supported catalyst system for recycling a rhodium complex for orthoalkylation using a hydrogen-bonding self-assembly motif consisting of a barbiturate bearing a phosphine ligand and 5-hexyl-2,4,6-triaminopyrimidine.[11] Here, we wish to report a new recyclable self-assembly catalyst system for chelation-assisted hydroacylation of olefin with primary alcohol.

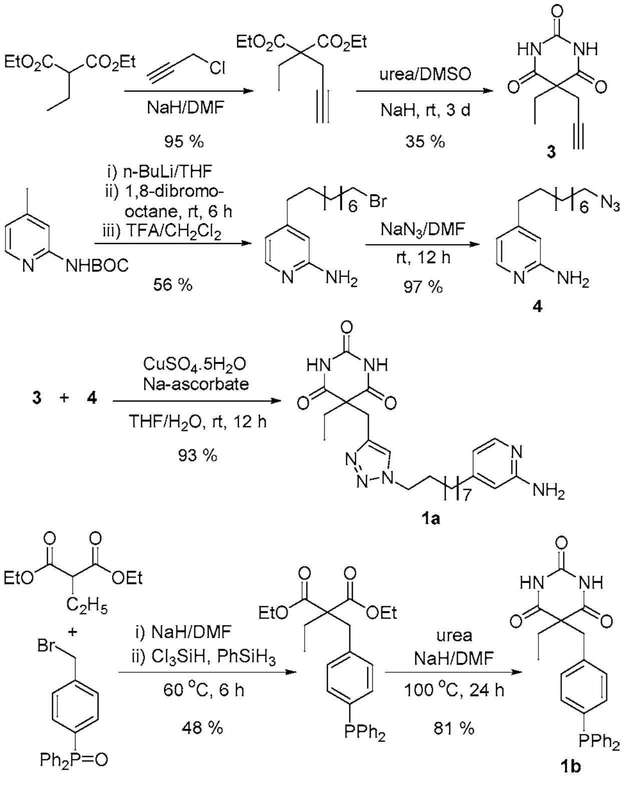
The barbiturate is known to form a supramolecular assembly with 2,4,6-triaminopyrimidine through six hydrogen bondings per molecule.[12] Therefore, we expected that the barbiturate **1a** bearing a 2-aminopyridin-4-yl group as a chelation auxiliary would lead to the formation of a hydrogen-bonding self-assembly with 5-hexyl-2,4,6-triaminopyrimidine (**2a**), which can serve as a support for recycling the organic catalyst (Scheme 1).

The barbiturate **1a** was prepared in several steps (Scheme 2). First, compound **3** bearing a propargyl group was prepared from diethyl ethylmalonate and propargyl chloride. This was followed by a barbiturate formation with urea. 2-Aminopyridine derivative **4**, having an azido group, was also prepared by functionalization of amine-protected 2-amino-4-picoline. Copper(I)-catalyzed [2 + 3] dipolar cycloaddition of **3** and **4** was achieved in the presence of $CuSO_4 \cdot 5H_2O$ and Na-ascorbate to afford **1a** via “click chemistry”.[13] The barbiturate **1b** was also prepared by the literature method[11] with slight modification: a nucleophilic addition of diethyl ethylmalonate on the 4-benzyl bromide group of triphen-

Scheme 1. Barbiturate-Substituted 2-Aminopyridine (**1a**), Triphenylphosphine (**1b**), and Its Interaction with 5-Hexyl-2,4,6-triaminopyrimidine (**2a**)



Scheme 2. Synthesis of **1a** and **1b**



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(6) (a) Bergbreiter, D. E. *Catal. Today* **1998**, *42*, 389. (b) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531. (c) Wentworth, P., Jr.; Janda, K. D. *Chem. Commun.* **1999**, 1917. (d) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc.* **1999**, *122*, 11101. (e) Schlenk, C.; Kleij, A. W.; Frey, H.; van Koten, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3445. (f) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058. (g) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 11105. (h) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345.

(7) Recent review on dendrimers in catalysis: Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1829.

(8) Lindner, E.; Schneller, T.; Auer, F.; Mayer, H. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2154.

(9) (a) Yoshida, J. -i; Itami, K. *Chem. Rev.* **2002**, *102*, 3693. (b) de Groot, D.; de Waal, B. F. M.; Reek, J. N. H.; Schenning, A. P. H. J.; Kamer, P. C. J.; Meijer, E. W.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2001**, *123*, 8453. (c) Chen, R.; Bronger, R. P. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2004**, *126*, 14557. (d) Yang, J.; Ding, S.; Radosz, M.; Shen, Y. *Macromolecules* **2004**, *37*, 1728. (e) Davies, H. M. L.; Walji, A. M.; Nagashima, T. *J. Am. Chem. Soc.* **2004**, *126*, 4271.

(10) Chang, D.-H.; Lee, D.-Y.; Hong, B.-S.; Choi, J.-H.; Jun, C.-H. *J. Am. Chem. Soc.,* **2004**, *126*, 424.

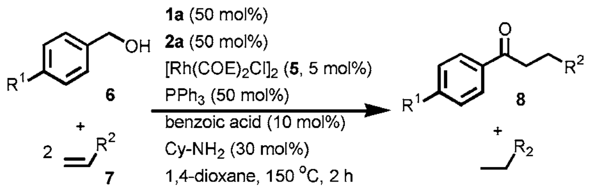
(11) Yoon, J.-H.; Park, Y.-J.; Lee, J.-H.; Yoo, J.-H.; Jun, C.-H. *Org. Lett.* **2005**, *7*, 2889.

(12) Lehn, J. M.; Mascal, M.; DeCian, A.; Fischer, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 461.

ylphosphine oxide, followed by deoxygenation of phosphine oxide, and a subsequent barbiturate formation with urea.

Using a self-assembly system of the barbiturate **1a** and 5-hexyl-2,4,6-triaminopyrimidine (**2a**)[14] in the presence of $[RhCl(COE)_2]_2$ (**5**, 5 mol %), triphenylphosphine (PPh_3, 50 mol %), cyclohexylamine ($Cy\text{-}NH_2$, 30 mol %), and benzoic acid (10 mol %),[15] the hydroacylation of benzyl alcohol (**6a**) with 1-hexene (**7a**) was carried out at 150 °C for 2 h in 1,4-dioxane (Table 1). During the reaction at high temperature the system was homogeneous (because a hydrogen-bonding network might be broken), but it was heterogenized at room temperature to form two phases (liquid/solid) after the reaction (Figure 1). It was found that the barbiturate **1a** stayed in the lower solid phase assembled with **2a**, while the product ketone **8a** stayed in the upper liquid phase. Product **8a** and other catalysts ($[Ph_3P]_xRhCl$, $Cy\text{-}NH_2$, and benzoic acid) were separated from **1a** and **2a** by decanting the upper layer after washing the lower layer with *n*-pentane.

Table 1. Recycling of Organic Catalyst **1a** for Hydroacylation of **6** with **7**



entry	R^1 (**6**)	R^2 (**7**)	ketone (**8**)	isolated yield of product (%)									
				1	2	3	4	5	6	7	8	9	10
1	H(**6a**)	nC_4H_9(**7a**)	**8a**	92	91	88	83	88	91	90	83	87	91
2	CF_3(**6b**)	**7a**	**8b**	50	63	58	50	51	55	66	57	50	69
3	OMe(**6c**)	**7a**	**8c**	78	71	87	80	74	83	87	81	73	45
4	**6a**	$SiMe_3$(**7b**)	**8d**	92	91	88	83	88	91	90	83	87	91

The remaining barbiturate **1a** and pyrimidine **2a** were recycled for the next reaction with an addition of substrates and other catalysts. This process was repeated up to the 10th catalytic reaction, and the product **8a** was obtained in very high yield from each run (Table 1, entry 1). Other alcohols **6** and olefins **7** were applied to this reaction, giving the corresponding ketones in good yields with the repeated use of barbiturate **1a** as a chelation auxiliary (entries 2−4).

To confirm whether ketone **8** was completely separated from the lower solid phase, the reactions were performed using different substrates in every cycle (Table 2), and it was found that any trace amounts of ketone from the previous run were absent in the next run.

The first reaction was carried out using **6a** and **7a** to give **8a** in an 81% isolated yield. The separated barbiturate **1a** and **2a** were reused for the next reaction of **6a** and **7b** to afford **8d** in an 87% isolated yield (100% GC yield) without detecting **8a**. In the third run, using **6b** and **7a**, an 86% isolated yield of **8b** was exclusively obtained, as it was in the second run.

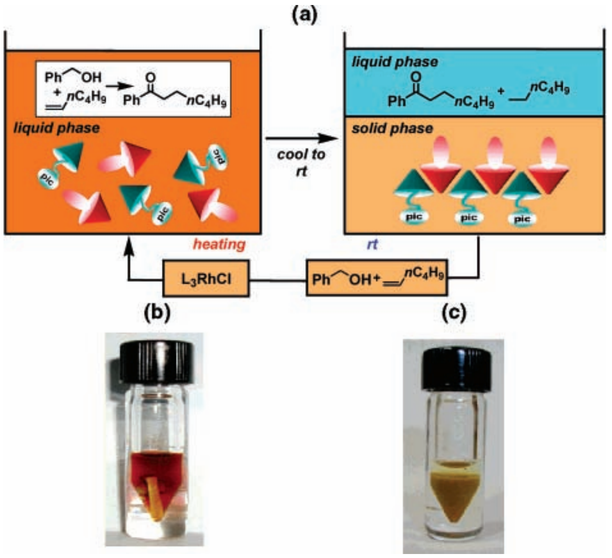
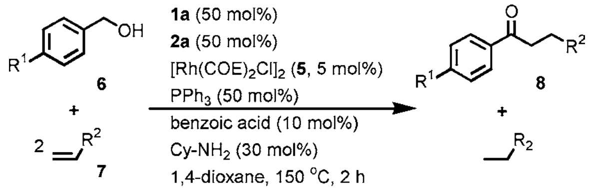


Figure 1. (a) Schematic illustration of the recycling of organic catalyst **1a** assembled with **2a** for hydroacylation. (b) Homogeneous phase consisting of **1a**, **2a**, **6a**, **7a**, **5** with PPh_3, benzoic acid, $Cy\text{-}NH_2$, and 1,4-dioxane after heating (150 °C). (c) Precipitation of hydrogen-bonding supramolecular solid from Figure 1b after cooling to room temperature.

Table 2. Hydroacylation with Different Substrates Showing Complete Separation of the Product in Each Run



run	reactants (**6**, **7**)	isolated yield (%)[a]
1	R^1 = H (**6a**), R^2 = nC_4H_9 (**7a**)	81 (**8a**)
2	R^1 = H (**6a**), R^2 = $SiMe_3$ (**7b**)	87 (**8d**)
3	R^1 = CF_3 (**6b**), R^2 = nC_4H_9 (**7a**)	86 (**8b**)

[a] At each run, 100% GC yield of the corresponding ketone **8** was obtained.

To recycle both organic and transition metal catalysts, PPh_3 in the reaction of Table 1 was replaced by **1b**, triphenylphosphine bearing a barbiturate moiety. The reaction of benzyl alcohol (**6a**) with 1-hexene (**7a**) or vinylsilane (**7b**) was performed at 150 °C for 2 h in 1,4-dioxane/phenol[16] in the presence of **1a** (70 mol %), **1b** (80 mol %), rhodium complex **5** (10 mol %), and 5-hexyl-2,4,6-triaminopyrimidine (**2a**, 150 mol %) with cyclohexylamine (30 mol %) and benzoic acid

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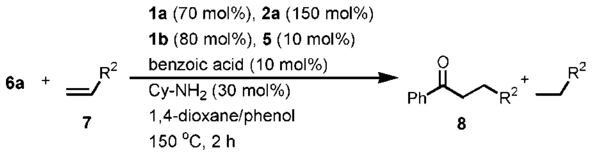
(13) For review: Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

(14) Compound **2a** was prepared by the known method. See ref 11.

(15) $CyNH_2$ and benzoic acid are additives for facile hydroacylation.

(16) Only at the first run, a small amount of dioxane/phenol was added as a solvent. See Supporting Information for details.

Table 3. Recycling of Organic Catalyst **1a** and Organometallic Catalyst **1b** with **2a** for Hydroacylation of **7** with **6a**



			isolated yield of product (%)							
entry	R^2 (**7**)	product (**8**)	1	2	3	4	5	6	7	8[a]
1	**7a**	**8a**	95	88	94	87	82	89	81	91
2	**7b**	**8d**	92	91	77	90	84	93	85	91

[a] At the ninth run, the isolated yield of **8a** and **8d** dropped to 51% and 71%, respectively.

(10 mol %) (Table 3). The ratio of **1** (**1a** and **1b**) and **2** was adjusted to a 1:1 ratio to form a complete supramolecular hydrogen-bonding network. This catalytic system was also homogeneous at high temperature[17] and was heterogenized at room temperature to form two phases (liquid/solid) after the reaction (Figure 2). The ketone **8a** or **8d** was separated from **1a**, **1b**-Rh (with rhodium complex), and **2a** by decanting the upper layer after washing the lower layer with *n*-pentane. The remaining **1a**, **1b**-Rh, and **2a** were recycled for the next reaction, and this process was repeated up to the eighth catalytic reaction. The product **8a** or **8d** was obtained in very high yield for each run (Table 3, entries 1 and 2).

In conclusion, a novel recyclable organic catalyst system for chelation-assisted hydroacylation of olefin with primary alcohol was developed using a self-assembly barbiturate, which possessed a 2-aminopyridin-4-yl group and a phosphinyl group as an organic catalyst and an organometallic catalyst ligand. During the reaction at high temperature, the system is homogeneous and shows an efficient catalytic activity. After the reaction, it is heterogenized at room temperature to form two immiscible liquid/solid phases, allowing an easy recovery of the catalysts. We are currently investigating the application of this recycling catalysis protocol for other catalytic reactions.

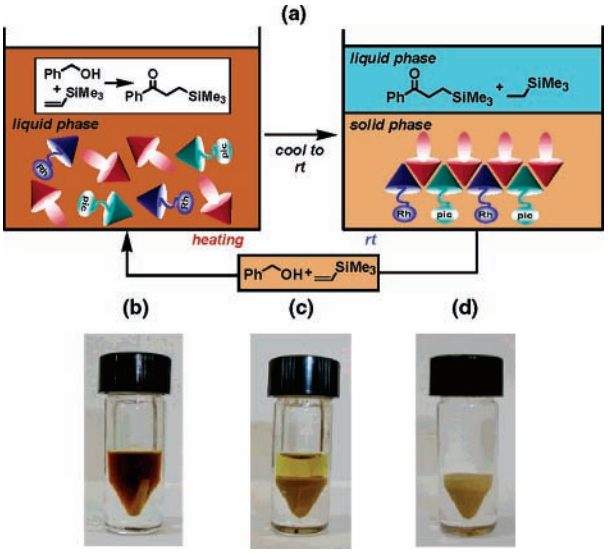


Figure 2. (a) Schematic illustration of the recycling organic and organometallic catalysts, **1a**, and **1b**-Rh with **2a** for hydroacylation. (b) Homogeneous phase consisting of **1a**, **1b**-Rh, **2a**, **6a**, **7b**, benzoic acid, and Cy-NH$_2$ in 1,4-dioxane/phenol after heating (150 °C). (c) Precipitation of the hydrogen-bonding supramolecular solid from Figure 1b after cooling to room temperature (25 °C). (d) Supramolecular solid after addition of *n*-pentane to Figure 2c to enable decanting of the product.

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Supporting Information Available: Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] All solid components turned into a homogeneous solution above 100 °C.