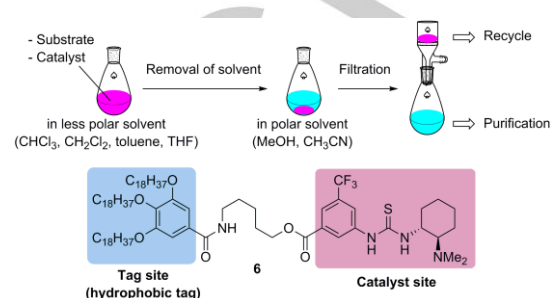


A recyclable hydrophobic anchor-tagged asymmetric amino thiourea catalyst

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Ken-ichi Yamada and Akira Otaka^{*[a]}

A novel recyclable thiourea-based, asymmetric organocatalyst containing a hydrophobic anchor has been developed. The chemical nature of the hydrophobic anchor contributes to the desirable characteristics of the recyclable catalyst. The hydrophobic anchor-tagged thiourea catalyst is highly soluble in less polar solvents compatible to the amino thiourea catalyst-mediated asymmetric reactions, but sparingly soluble in polar solvents used for recycle process. This asymmetric catalyst delivers a catalytic performance comparable to that of a parent catalyst and can be readily recycled from reactions.



Scheme 1. Concept of recycling of the hydrophobic anchor-tagged catalyst.

Access to a wide variety of chiral compounds requires that asymmetric catalysts perform well in the construction of chiral centers. Amongst known efficient asymmetric catalysts, organocatalysts have attracted attention increasingly because they are cost-effective, less toxic, and operationally simple compared with conventional metal catalysts.¹ Amino thiourea catalysts are dual-activating organocatalysts which simultaneously activate both an electrophile and a nucleophile in a highly enantioselective reaction, affording a chiral product.² For example, Takemoto's thiourea catalyst **1** has been applied to a variety of asymmetric reactions (Figure. 1).^{2c}

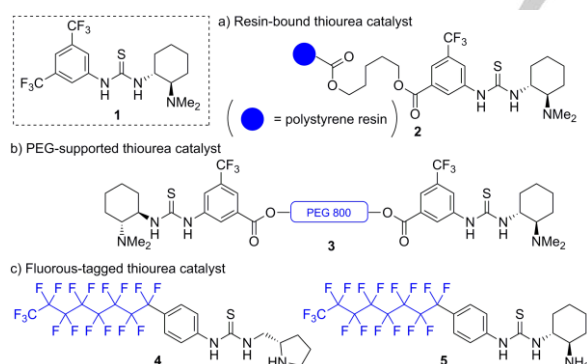


Figure 1. Recyclable thiourea catalysts.

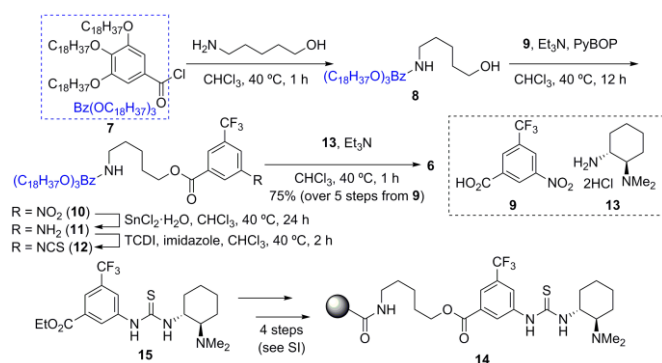
In comparison with the asymmetric metal catalysts, a weak point of organocatalysts is that relatively large amounts of the catalyst load must be used. Because of this, recyclable organocatalysts have been designed to extend the synthetic utility of organocatalysts.³ Recyclable thiourea catalysts that have been developed to date have an insoluble resin support,^{4a,b} a polyethyleneglycol (PEG) moiety,^{4a} or a fluorocarbon carrier^{4c,d} as shown in Figure 1. A poly styrene-type insoluble resin support in a catalyst **2** allows for easy recovery of the catalyst from a reaction, typically by filtration, but the two-phase reaction using a resin-supported catalyst generally results in reduced catalytic activity. PEG as a carrier can be used in solution and leads to a more favourable reaction outcome. A drawback of PEG catalysts such as **3** is that difficulties in the control of the solubility can lead to low efficiency in the recovery. Recently, catalysts **4** and **5** with a perfluoroalkyl chain were independently developed by Cai^{4c} and Miura.^{4d} Such fluorine-containing catalysts have a high affinity for fluorine-containing solvents or silica gel. These features allow the fluoroalkyl catalyst to be separated by extractive or chromatographic work-up using fluorine-containing solvent. Such solvents may however be expensive.

In this context, we envisioned that the use of a hydrophobic anchor tag consisting of an extended alkyl chain as a carrier could be used in the development of a novel recyclable catalyst which can overcome the drawbacks mentioned above. Hydrophobic anchors have been independently developed by Tamiaki and Chiba and Takahashi for use in peptide synthesis.⁵ Generally, such anchors enhance the solubility of the tagged molecules in less polar solvents such as CH₂Cl₂, CHCl₃, toluene, and THF but lead to the precipitation of the tagged molecules in polar solvents, including MeOH and MeCN. The less polar solvents are suitable for reactions catalysed by thiourea and precipitation-inducing polar solvents can solubilize a wide variety of organic molecules involved in the reaction. We speculated that a hydrophobic anchor-tagged thiourea catalyst could function as an ideal recyclable asymmetric catalyst. Reaction protocols that could be envisioned are shown in Scheme 1.

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Scheme 2. Synthesis of recyclable hydrophobic anchor-tagged catalyst **6** and resin-bound catalyst **14**.

A hydrophobic anchor-tagged thiourea catalyst should provide a homogeneous reaction mixture in less polar solvents and thus participate in an asymmetric reaction with efficiency comparable to that of a conventional thiourea catalyst. Replacement of the reaction solvent by polar solvents dissolves the reactants and causes precipitation of the recyclable catalyst. After removal of the catalyst by filtration, the filtrate is subjected to the appropriate purification steps.

Initially, an amino thiourea catalyst **6** possessing an *O*-alkylated gallic acid unit as a hydrophobic anchor was designed (Scheme 2). Using the known benzoyl chloride **7**,⁶ commercially available 5-amino-1-pentanol was reacted in CHCl_3 to afford the hydroxyalkyl benzamide **8**. Esterification of this benzamide **8** with a benzoic acid derivative **9** was achieved by the action of (benzotriazol-1-yloxy) tripyrrolidino-phosphonium hexafluorophosphate (PyBOP) in CHCl_3 to give the ester **10**, whose nitro group was then reduced to an amino group with $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ in CHCl_3 . The resulting aniline derivative **11** was converted to the corresponding isothiocyanate **12** by reaction with 1,1'-thiocarbonyldiimidazole (TCDI) in CHCl_3 . The synthesis was completed by coupling of **12** with the chiral diamine **13** in CHCl_3 to yield the desired hydrophobic anchor-tagged amino thiourea catalyst **6**. In all these reactions, CHCl_3 was used as the solvent because the newly introduced hydrophobic anchor unit facilitated solubilisation of the organic materials. Furthermore, precipitation of the tagged molecules including the final product **6** by the addition of the polar solvents enabled the easy, one-step separation of excess reagents. Catalyst **6** was obtained in 75% isolated yield over five steps from **7**. To compare the efficacy of **6** with a polystyrene-linked counterpart, a recyclable catalyst **14** was prepared through amide-linking of the known thiourea **15**^{4a} to polystyrene resin.⁷

Having obtained the hydrophobic anchor-tagged catalyst **6**, we determined its solubility in various solvents to assess its utility as a recyclable catalyst. Solubility was calculated on the basis of the UV absorbance of **6** (Table 1). The tagged catalyst **6** was readily soluble in CHCl_3 at temperatures from 4 °C to 30 °C (entry 1, Figure 2-a). The solubility of **6** in CHCl_3 , toluene, or THF was affected by changes in temperature and facilitated its practical use as an asymmetric organocatalyst at 30 °C (entries 2–4). The catalyst **6** on the other hand, is practically insoluble in the polar solvents (entries 5–6, Figure 2-b). These data clearly

indicated that the synthesized tagged catalyst **6** satisfies the first criteria for use as a recyclable catalyst.

Table 1. Solubility of catalyst **6** in various solvents.

entry	solvent	solubility (mM) ^[a]		
		4 °C	20 °C	30 °C
1	CHCl_3	141	156	177
2	CH_2Cl_2	6.39	7.53	30.9
3	toluene	1.46	1.71	39.5
4	THF	4.48	4.70	32.4
5	MeOH	N.D.	N.D.	0.10
6	MeCN	N.D.	N.D.	0.06

[a] Determined from UV absorbance in solution.

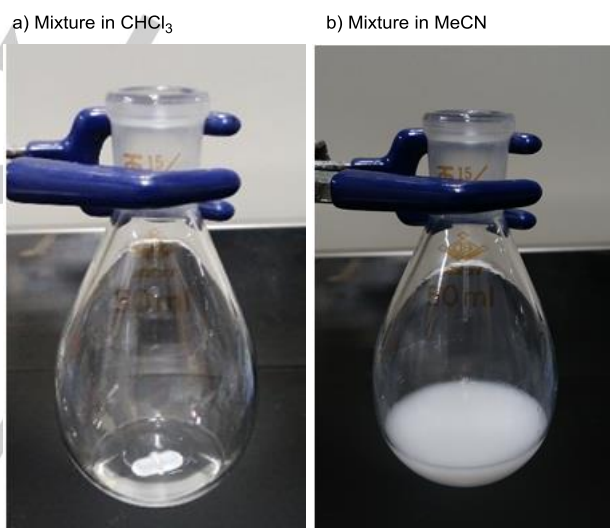


Figure 2. Catalyst **6** is soluble in CHCl_3 , but recovered from MeCN.

In comparison with the parent catalyst **1** and the resin-bound recyclable catalyst **14**, the performance of the hydrophobic anchor-tagged catalyst **6** was evaluated by its application to the aza-Henry reaction (Table 2).⁸ Attempted aza-Henry reaction of 0.1 mmol of an *N*-Boc imine (**16**) with 10 equivalents of nitromethane **17** in CH_2Cl_2 at 30 °C in the presence of 10 mol% of catalyst **6** or **1** proceeded efficiently, yielding the desired product **18** (entries 1 and 2). Additionally, the use of MeCN as a recycling solvent allowed for efficient recovery of the used catalyst. Removal of CH_2Cl_2 followed by addition of MeCN led to the precipitation of the catalyst **6**. Removal by filtration of the insoluble catalyst led to recovery of **6** in 99% yield. On the other hand, the conventional resin-supported catalyst **14** under the same reaction conditions totally

failed to afford **18** (entry 3). Generation of **18** using **14** as catalyst required increases in both catalysis load (30 mol%) and reaction time (6 days) but the chemical yield (15%) remained low (entry 4). Screening the other less polar solvents (CHCl_3 , toluene, and THF) revealed that CH_2Cl_2 was the best solvent for the examined aza-Henry reaction (entries 5–7). The use of CHCl_3 or toluene resulted in reduced chemical yields although optical yields were comparable to that of using CH_2Cl_2 . The one-gram (4.9 mmol) scale reaction also proceeded smoothly to result in reaction outcomes comparable to those of 0.1 mol scale reaction (entry 8).

Table 1. Asymmetric aza-Henry reaction. ^[a]					
entry	catalyst	solvent	catalyst recovery (%) ^[b]	yield (%) ^[c]	ee (%) ^[d]
1	6	CH_2Cl_2	99	77	91
2	1	CH_2Cl_2	---	76	90
3	14	CH_2Cl_2	99	N.R.	---
4 ^[e]	14	CH_2Cl_2	99	15	89
5	6	CHCl_3	95	69	90
6	6	toluene	99	30	91
7	6	THF	99	N.R.	---
8 ^[f]	6	CH_2Cl_2	99	81	91

[a] Unless otherwise noted, reactions were carried out using **16** (0.1 mmol), **17** (1.0 mmol) and solvent (1.0 mL). [b] Recovered by using MeCN. [c] Isolated yield. [d] Determined by chiral HPLC analysis (chiralpak IC3, flow rate 1.0 ml/min, hexane/2-propanol = 85/15). [e] 30 mol% of **14** was used and the reaction was performed for 6 days. [f] Reaction was carried out using **16** (4.9 mmol), **17** (49 mmol) and CH_2Cl_2 (49 mL).

We next examined recycling of the used catalyst **6** (Figure 3). In the first recycle of **6** in the same aza-Henry reaction of **16** with **17**, the desired product was obtained in 72% chemical and 91% optical yields with 99% recovery of the catalyst. The reaction outcomes observed subsequently were comparable to those of the first run. Two further additional runs of the reaction were carried out with no loss of the catalytic activity. Although further trials have yet to be performed, obtained data for the recycling showed that the catalyst **6** could be a potential recyclable catalyst in terms of both activity and recyclability.

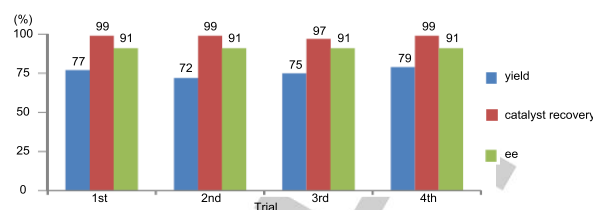
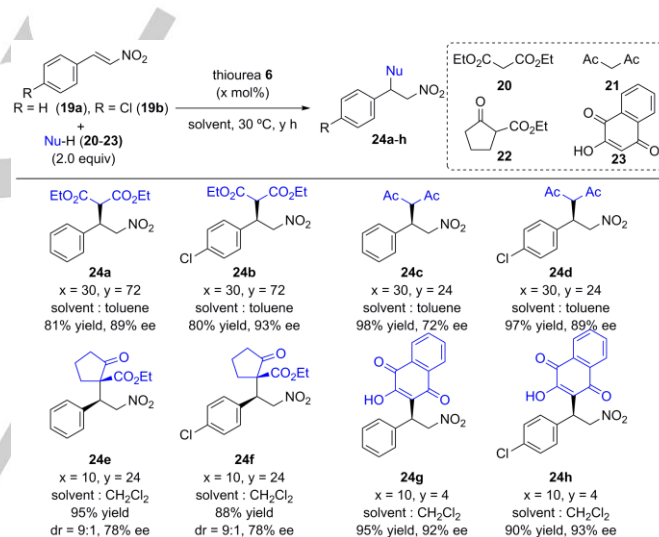


Figure 3. Recycling and reuse of **6** in aza-Henry reaction of **16**.

Application of the recyclable catalyst **6** to an asymmetric Michael reaction was next examined (Scheme 3). The reaction of nitrostyrene **19a** or **19b** with acyclic dicarbonyl compounds such as diethyl malonate **20**⁹ or acetylacetone **21**¹⁰ in the presence of 30 mol% of catalyst **6** in toluene at 30 °C proceeded smoothly to yield desired Michael adducts **24a-d** in high chemical and optical yields. The reaction with cyclic-type nucleophiles **22**¹¹ and **23**¹² in CH_2Cl_2 also proceeded in an enantioselectively, generating desired products **24e-f** and **24g-h** in high chemical yields.



Scheme 3. Asymmetric Michael addition of nitrostyrenes with several nucleophiles catalyzed by **6**.

In summary, development of a hydrophobic anchor-tagged asymmetric recyclable thiourea catalyst has been achieved. Chemical features of the hydrophobic anchor allowed for both the facile recycling and efficient preparation of the tagged catalyst. Use of a less polar homogeneous reaction solution of recyclable catalyst contributes to the high performance of the tagged thiourea catalyst. The recyclable catalyst exhibits catalytic activity comparable to that of the conventional soluble thiourea catalysts. The application of the hydrophobic anchor has to date been limited to amino thiourea catalysts, but other types of recyclable organocatalysts containing a hydrophobic anchor unit are under investigation.

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Keywords: organocatalyst • amino thiourea • asymmetric catalyst • hydrophobic anchor • recyclable catalyst

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Layout 2:

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Catalyst comes back: A novel recyclable thiourea-based, asymmetric organocatalyst containing a hydrophobic anchor has been developed. The hydrophobic anchor-tagged thiourea catalyst is highly soluble in less polar solvents compatible to the amino thiourea catalyst-mediated asymmetric reactions, but insoluble in polar solvents so that the catalyst can be readily recycled only by simple filtration.