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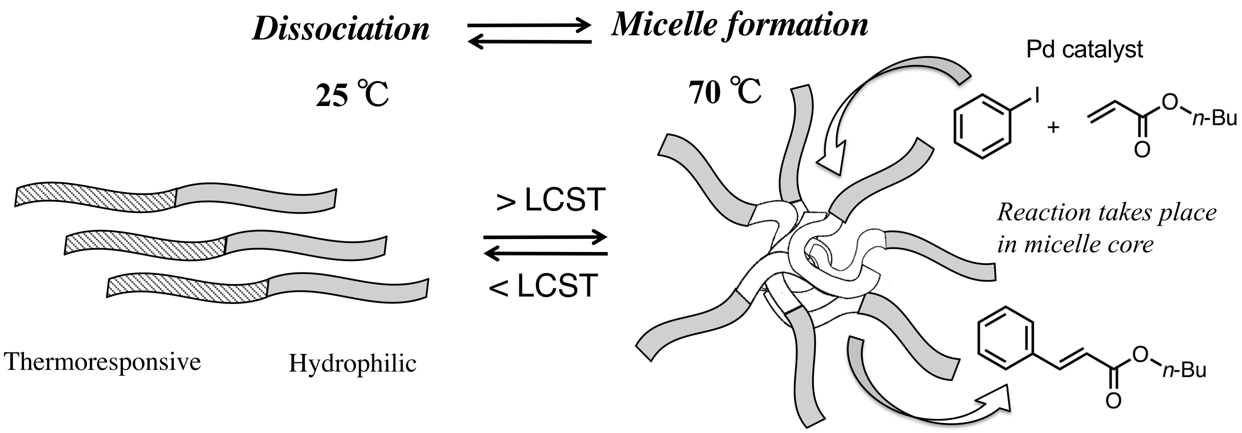

Dissociation
Micelle formation
25 ℃
70 ℃
Pd catalyst
I
+
O
n-Bu
O
> LCST
< LCST
Reaction takes place
in micelle core
Thermoresponsive
Hydrophilic
O
n-Bu
O

Palladium-catalyzed Mizoroki-Heck Reactions in Water using Thermoresponsive Polymer Micelles

Noriyuki Suzuki[1,*], Taiga Takabe[1], Yoshiko Yamauchi[1], Shun Koyama[1], Rina Koike[1], Masahiro Rikukawa[1], Wei-Ting Liao[1,2,†], Wen-Sheng Peng[1,2,‡], Fu-Yu Tsai[2,*]

1) Department of Materials and Life Science, Faculty of Science and Technology, Sophia University, 7-1 Kioi-cho, Chiyoda-ku, Tokyo 102-8554, Japan
2) Institute of Organic and Polymeric Materials, National Taipei University of Technology, 1, Sec. 3, Chung-Hsiao E. Rd., Taipei 10608, Taiwan

Abstract:

Palladium-catalyzed Mizoroki-Heck reactions were carried out in water using thermoresponsive polymer micelles. The micelles were generated from thermoresponsive block copolymers consisting of a poly(*N*-isopropylacrylamide) (PNIPAAm) segment and a hydrophilic segment such as nonionic poly(ethylene glycol) (PEG) (**2**) and anionic poly(sodium *p*-styrenesulfonate) (PSSNa) (**9**). These copolymers exhibited lower critical solution temperature (LCST) behavior at ca. 40–50 °C and showed thermal stimuli-induced formation and dissociation of micelles. The copolymers formed micelles in aqueous solution at higher temperature, where catalytic reactions proceeded. At lower temperature, the micelles dissociated to form a clear solution, enabling efficient extraction of the products from aqueous reaction mixture. In the presence of these copolymers, palladium complexes catalyzed the coupling reactions between aryl iodides and alkene compounds inside the hydrophobic micelle cores in water under relatively milder conditions. Extraction of the products from the aqueous solution of **2** or **9** was found to be efficient enough in comparison with conventional surfactants.

Keywords: thermoresponsive polymer, polymer micelle, palladium, Mizoroki-Heck reaction, *N*-isopropylacrylamide

†) Visiting Researcher at Sophia University (March–April 2017).
‡) Visiting Researcher at Sophia University (May–June 2018).

* Corresponding author. e-mail: norisuzuki@sophia.ac.jp, fuyutsai@ntut.edu.tw

1. Introduction

Applying water as a solvent for organic processes attracts chemists since reducing organic waste is an urgent subject from the point of view of global environment. Palladium-catalyzed reactions are also studied in water; and conducting such catalytic reactions in water in the presence of surfactants would provide promising methodology.[1-5] Reactions inside the micelle core bring about not only reduce organic solvents but also possess benefits such as acceleration of reactions due to concentrated substrates by hydrophobic effects.[3,4,6,7] Nevertheless, the organic products generated in an aqueous reaction mixture must be separated by an extraction process that requires organic solvents. Thus, efficient extraction system must be developed to realize more practical aqueous reactions. We envisioned that stimuli-induced turning on/off the formation of micelles in the aqueous reaction mixture would be able to achieve more efficient extraction. For instance, a thermoresponsive micelle that dissociates at lower temperature might allow more efficient extraction with less organic solvents. Poly(*N*-isopropylacrylamide) (PNIPAAm) is known as a thermoresponsive polymer owing to its lower critical solution temperature (LCST) of 32 °C in water. Its application for thermoresponsive materials have received much attention. [8-12] Preparation of thermoresponsive micelles by using copolymers of PNIPAAm has also been well studied.[13-16] Their application for organic synthesis seems attractive because of tunable formation and dissociation of micelles in water.

On the basis of this idea, we previously reported amphiphilic block copolymers that form thermoresponsive micelles in water depending upon temperature (Figure 1).[17,18] We utilized block copolymers that consisted of PNIPAAm and poly(ethylene glycol) (PEG) blocks. The PNIPAAm chain included L-proline groups, that serve as organocatalysts, by random copolymerization of NIPAAm and 4-hydroxy-L-proline acrylate. The copolymers were dissolved in water at rt to give a clear solution, whilst these formed micelles at 50 °C (Figure 1). Asymmetric cross-aldol reactions were catalyzed by the polymer in water at 50 °C with excellent yield and enantiomeric excess. The mixture was cooled after the reaction, and the products were taken up by extraction. O'Reilly, Monteiro and coworkers reported L-proline tethered thermoresponsive copolymer that include PNIPAAm and poly(*N*-dimethylacrylamide) based on the same idea.[19]

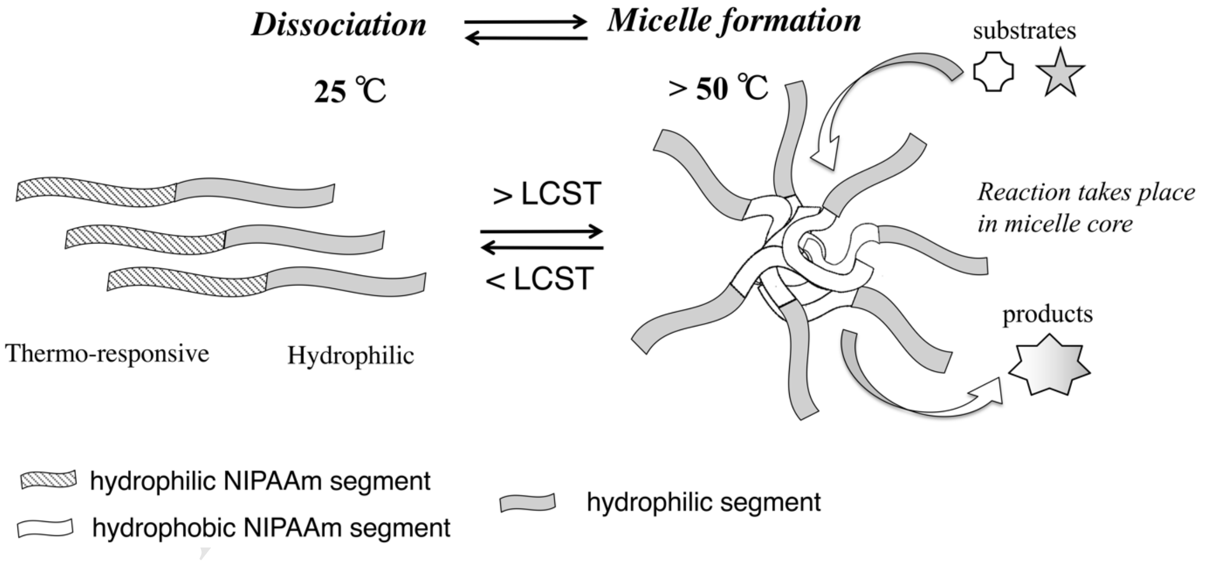
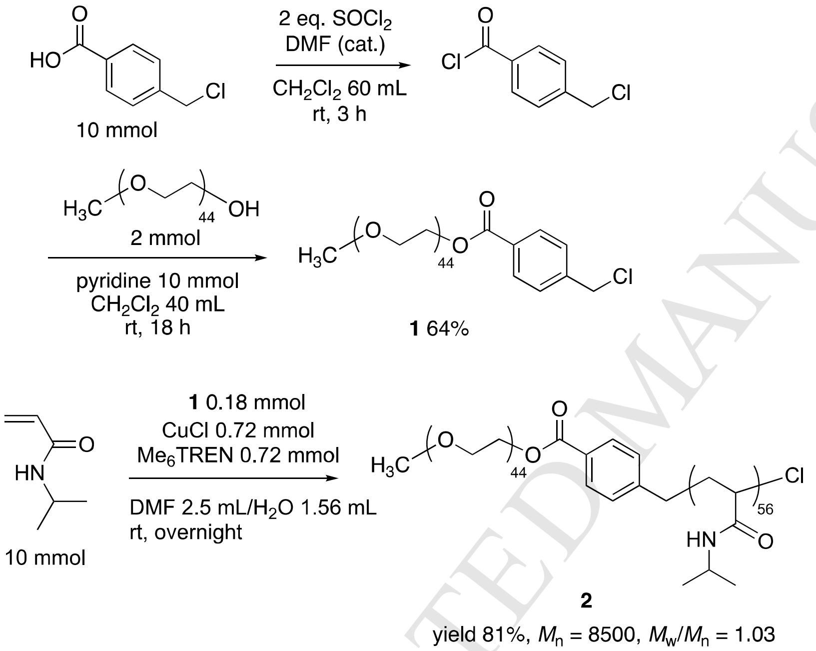


Figure 1. Thermo-responsive micelles switched on/off by temperature.

In order to avoid leaching out of catalyst, immobilizing catalyst molecules onto the polymer chain with a covalent bond is effective for catalytic reactions. However, tethering transition metal catalysts often requires a tedious procedure. Thus, in this study, we investigated a palladium-catalyzed reaction in an emulsified aqueous medium by adding palladium complexes from outside of the micelle. We employed two thermoresponsive amphiphilic block copolymers that have nonionic and anionic segments. The former contains a PEG chain, and the latter a poly(sodium *p*-styrenesulfonate) (PSSNa) segment. Synthesis of both the block copolymers PNIPAAm-*b*-PEG[20-24] and PNIPAAm-*b*-PSSNa[25-31] and their thermoresponsive behavior in aqueous solutions have been reported. To the best of our knowledge, reports on palladium-catalyzed reactions using thermoresponsive micelles are rare.[32,33] It is therefore interesting to investigate palladium-catalyzed reactions in water using thermoresponsive micelles. We also studied the efficiency in extraction of the products from the reaction mixture and compared the copolymers with conventional surfactants.

2. Results and Discussion

2. 1 Thermoresoponsive block copolymer with a nonionic PEG segment



Scheme 1. Preparation of NIPAAm-*b*-PEG **2** with PEGylated ATRP agent.

We first prepared a thermoresponsive amphiphilic block copolymer **2** that has a nonionic PEG chain *via* an atom-transfer radical polymerization (ATRP) technique (Scheme 1). NIPAAm was polymerized using the ATRP initiator tethered on a PEG chain **1** to afford the block copolymer **2**.[21] The molecular weight (M_n) of **2** was typically observed to be 8,500 with narrow distribution ($M_\mathrm{w}/M_\mathrm{n}$ = 1.03). The block copolymer **2** was soluble in water at room temperature, which became opaque when heated. Dynamic light scattering (DLS) analysis showed that the copolymer **2** has LCST at 40–45 °C (Figure 2a). The particle size distribution of **2** in aqueous solution at 25 °C and 60 °C are depicted in Figure 2b. The hydrodynamic diameter found to be larger than 70 nm at 60 °C, while it was 15-20 nm at 25 °C. The DLS results supported the formation of polymer-aggregated micelles at 60 °C. Larger particles (80 nm) were also found in part and these could be caused by the aggregation of polymer-micelles.[26] These results clearly demonstrated that the formation of polymer micelles by **2** was stimuli-induced.

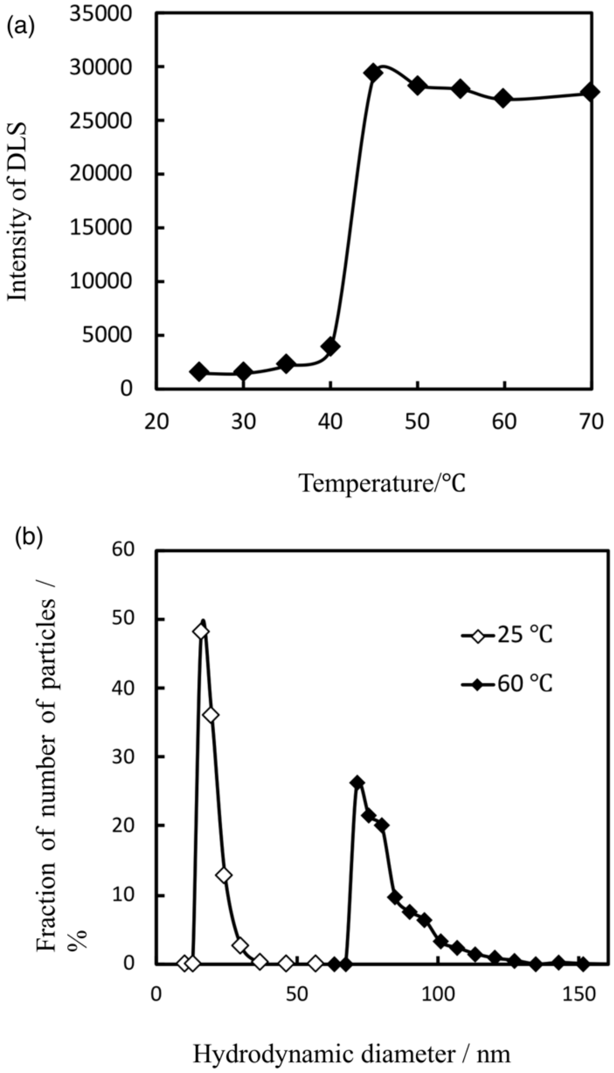


Figure 2. DLS of **2** in aqueous solution; (a) intensity at various temperatures, and (b) particle size distribution.

We then studied palladium-catalyzed Mizoroki-Heck reaction in water in the presence of **2**. Iodobenzene (**3a**) and *n*-butyl acrylate (**4a**) were suspended in 4 mL of water in the presence of 2 mol% of Pd catalyst and 4 wt% of **2**, and the mixture was stirred at 70 °C (Table 1). The product was taken up by repeated extraction with diethyl ether until the product was not observed in the organic layer by thin layer chromatography (TLC). (*E*)-*n*-Butyl cinnamate (**5aa**) was obtained in 96% yield after 48 h (entry 1). No Z-isomer was detected on the basis of ^{1}H NMR spectroscopy. The yield at 24 h was 71% (entry 2), showing that the reaction requires 48 h. Decreasing the amount of **2** (1 wt%) even resulted in good yield of **3** (92%, entry 3), although reaction with 0.5 wt% of **2** yielded **5aa** only in 52% (entry 4). It is noteworthy that the reaction in the absence of **2** afforded **5aa** in 43% (entry 5), showing that 1 wt% of **2** significantly accelerate the reaction. Conducting the reaction at 80 °C resulted in lower yield of **5aa**, although the reason is unclear (entry 6). At 60 °C, the reaction was slow even in the presence of 4 mol% of Pd (entry 7). With 1 mol% of Pd yield was unsatisfactory (entry 8).

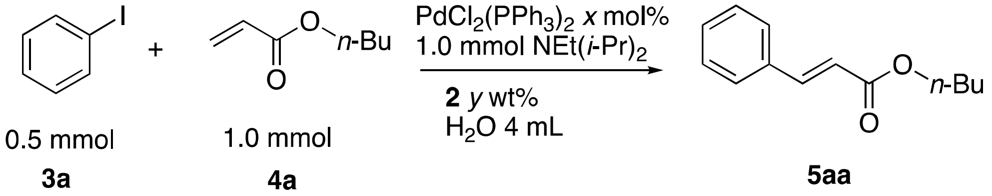
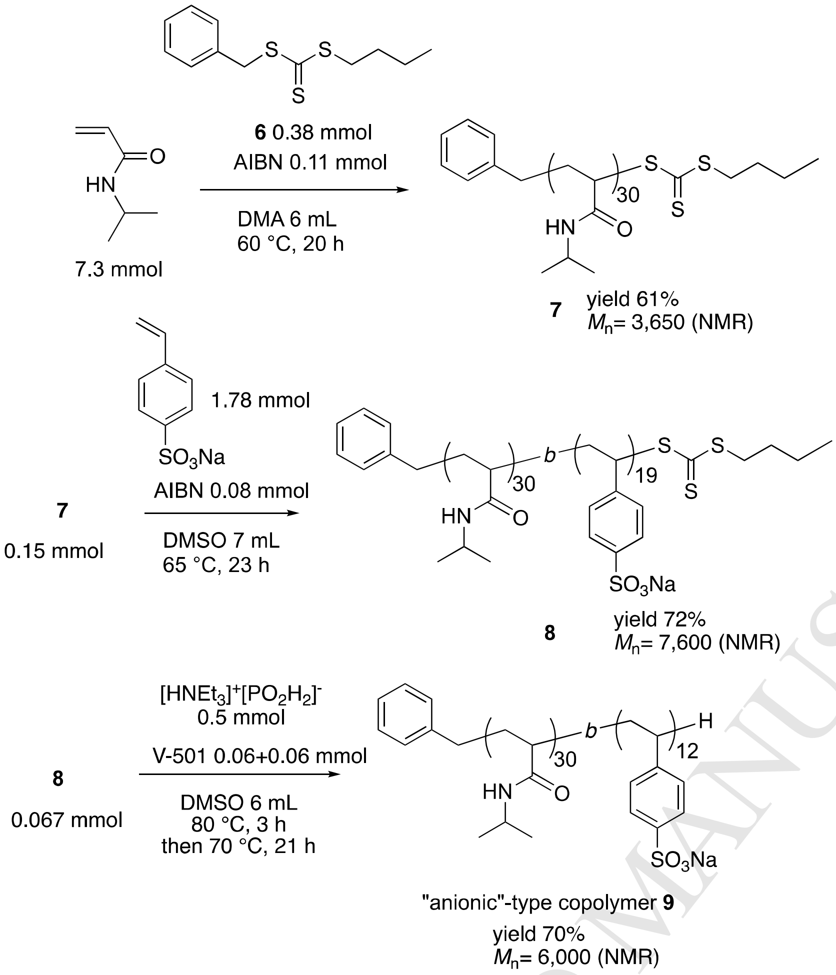


Table 1. Mizoroki-Heck reaction in water in the presence of **2**.

Entry	Pd /*x* mol%	**2** /*y* wt%	Temp/°C	Time/h	Yield
1	2	4	70	48	96
2	2	4	70	24	71
3	2	1	70	48	92
4	2	0.5	70	48	52
5	2	None	70	48	43
6	2	4	80	48	58
7	4	4	60	48	58
8	1	4	70	48	39

2.2 Thermoresponsive block copolymer with an anionic PSSNa segment



Scheme 2. Preparation of PNIPAAm-*b*-PSSNa **9** by RAFT polymerization technique.

Although the copolymer with nonionic segment **2** showed good performance in palladium-catalyzed Mizoroki-Heck reaction, the reaction required 2 mol% of palladium load to achieve good yield. In our previous report on proline-tethered thermoresponsive block copolymer, we found that addition of sodium chloride improved the yield.[17] It is because of salting-out effect that is generally observed in organic reactions in micelles; e.g. more organic solutes move into micelle cores because their solubility in aqueous solution decreases due to the presence of electrolytes in the aqueous phase.[34] Here, we envisioned that salting-out effect owing to the ionic sodium sulfonate groups can be expected if a copolymer with an anionic segment is employed. More concentrated substrates in micelles cores would accelerate the reaction. Thus, we next synthesized a thermoresponsive block copolymer with anionic polymer chain. The block copolymer was prepared by reversible addition-fragmentation chain transfer (RAFT) polymerization (Scheme 2). *N*-Isopropylacrylamide and sodium *p*-styrenesulfonate were polymerized in this order in the presence of the RAFT agent **6**, followed by the removal of trithiocarbonate moiety at the end of the polymer-chain to afford **9**. The polymerization degree of the PSSNa segment in **9** was smaller than that in **8** on the basis of ^{1}H NMR analysis. This might be because of depolymerization of *p*-styrenesulfonate during the radical desulfurization process.

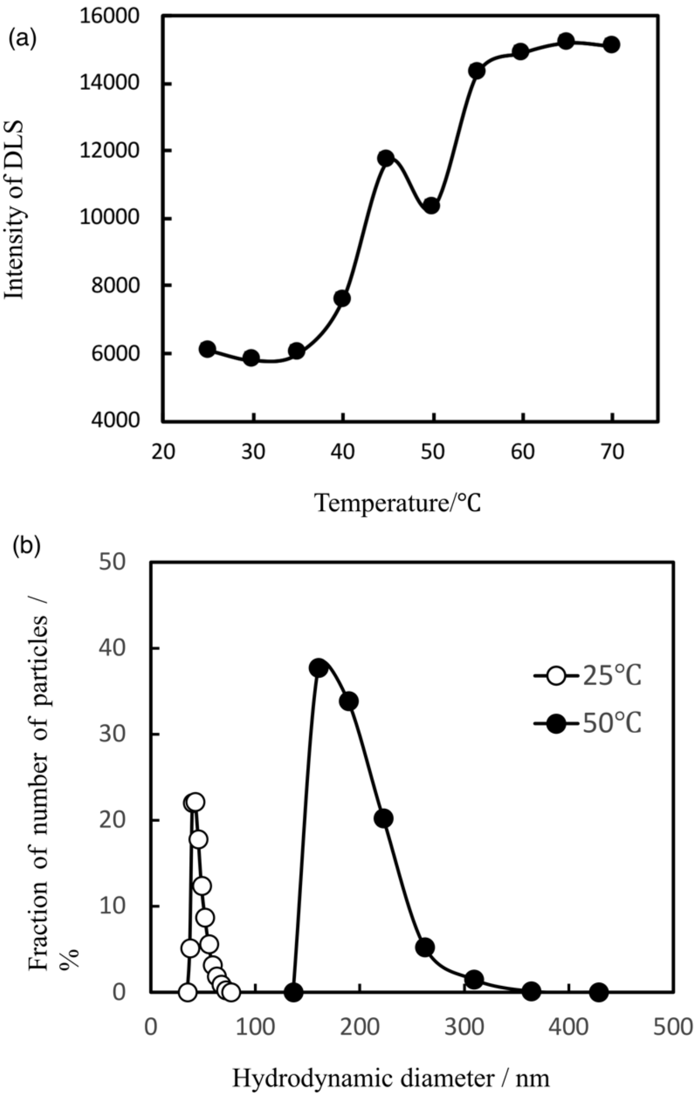
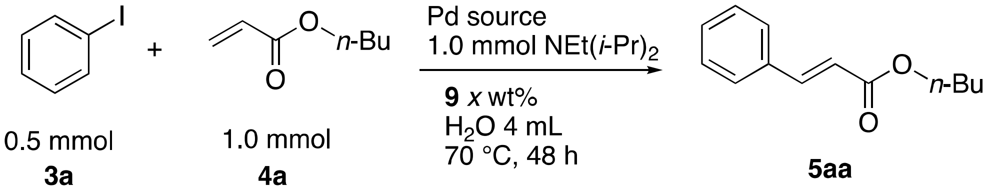


Figure 3. LCST behavior of copolymer with anionic chain **9**.

The DLS analysis of **9** exhibited its LCST behavior at 40–55 °C, although the change was not as steep as that observed in **2** (Figure 3a). The particle size of **9** was 40–60 nm at 25 °C, while 160–220 nm at 50 °C. The larger particle size of **9** compared to **2** is probably due to electrostatic repulsion among the anionic polymer chains. Possibility of the formation of small micelle at 25 °C, however, cannot be ruled out. Palladium-catalyzed Mirozoki-Heck reaction in water in the presence of **9** was studied (Table 2). It should be noted that only 1 wt% of **9** prompted the reaction (entry 1). Moreover, 1 mol% of Pd gave good yield (entry 2). Even 0.5% of Pd resulted in moderate yield (entry 3). We examined various palladium source for the reaction. In order to compare the catalytic activity, we fixed the amount of Pd atom as 0.5 mol% (entry 5-9). The combination of $Pd(OAc)_2$ and 3 equiv PPh_3 gave an optimal yield (entry 7), and that was superior to $PdCl_2(PPh_3)_2$. It is noteworthy that the reaction using conventional anionic surfactant sodium dodecyl sulfate (SDS) gave **5aa** in a siginificantly lower yield compared to entry 1 (entry 10). These results demonstrated that the copolymer with anionic segment **9** was more effective for Mizoroki-Heck reaction in water than **2** that contains nonionic polymer chain.

Table 2. Mizoroki-Heck reaction in water in the presence of **9**.



Entry	**9** /*x* wt%	Pd source	Pd /mol%	yield
1	1	$PdCl_2(PPh_3)_2$	2	99
2	1	$PdCl_2(PPh_3)_2$	1	92
3	1	$PdCl_2(PPh_3)_2$	0.5	58
4	0.5	$PdCl_2(PPh_3)_2$	2	67
5	1	$PdCl_2$+ 2 PPh_3	0.5	40
6	1	$Pd(OAc)_2$+ 2 PPh_3	0.5	19
7	1	$Pd(OAc)_2$+ 3 PPh_3	0.5	71
8	1	$Pd(OAc)_2$+ 5 PPh_3	0.5	42
9	1	$Pd(OAc)_2$+ 3 PCy_3	0.5	18
10[a]	SDS	$PdCl_2(PPh_3)_2$	2	47

a) SDS (1 wt%) was added instead of **9**.

2.3. Mizoroki-Heck reactions in water in the presence of ***2*** *or* ***9*** *with various substrates.*

To study the scope of substrates, we carried out the reactions with various aryl halide and alkenes in water in the presence of **2** or **9** (Table 3). The aqueous reaction mixtures were extracted with diethyl ether or ethyl acetate repeatedly until the products were not observed in the organic layer by TLC. Besides *n*-butyl acrylate (**4a**), a few acrylates **4g-h** and *N*-isopropyl acrylamide (**4b**) gave the corresponding cinnamates **5ag**, **5ah** and cinnamamide **5ab** in good yields (entries 2,12, 13). Styrene (**4c**) and 2-vinylnaphthalene (**4d**) afforded (*E*)-stilbene (**5ac**) and **5ad** in good yields (entries 3,4, 14). 2-Phenylpropene (**4e**), however, resulted in low yield probably because of a steric reason (entries 5, 19). Other substituted styrenes **4i-l** afforded **5ai-5al** in moderate to good yields (entries 15–18).

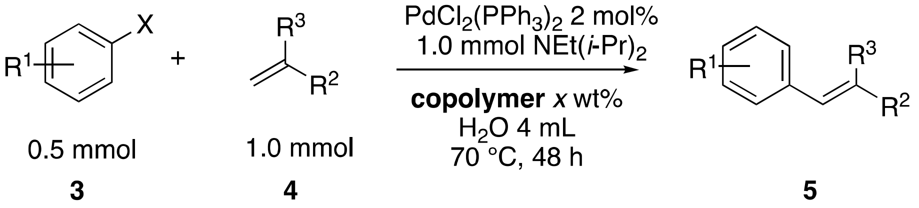
Linear alkene such as 1-hexene (**4f**), however, furnished **5af** in low yields (entries 6, 20).

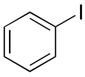
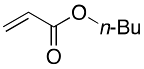
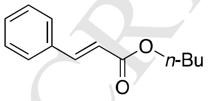
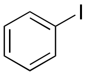
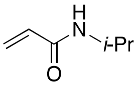
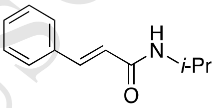
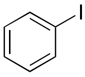
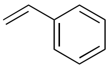
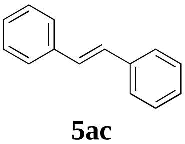
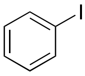
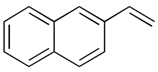
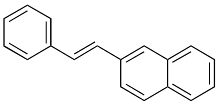
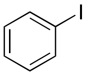
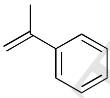
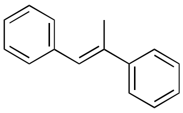
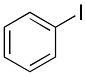
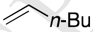
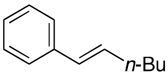
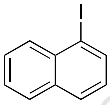
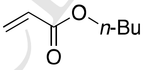
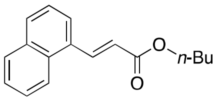
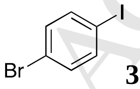
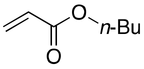
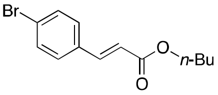
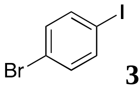
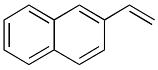
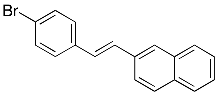
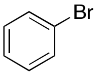
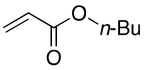
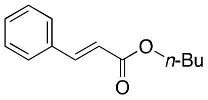
1-Iodonaphthalene (**3b**) and other substituted iodobenzenes (**3c, 3e-g**) also gave the corresponding products (**5ab-ac**, **5ae-eg**) in good yields (entries 7-8, 21-23). When **3c** and **4d**, both are solid at ambient temperature, were employed, **5cd** was given in 14%.

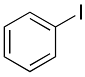
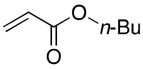
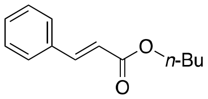
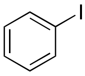
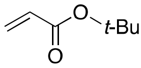
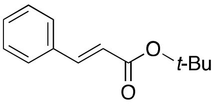
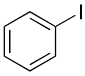
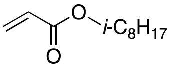
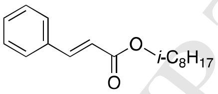
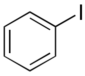
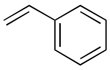
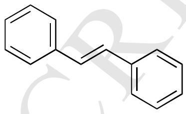
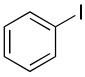
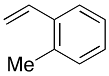
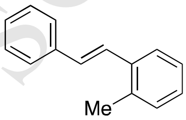
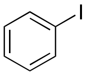
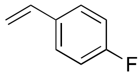
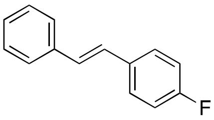
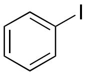
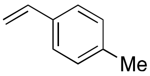
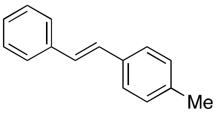
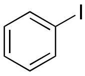
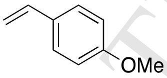
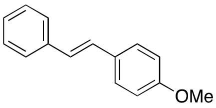
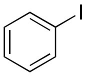
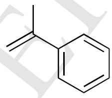
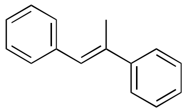
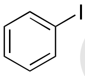
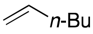
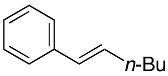
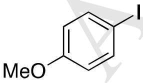
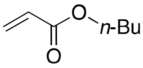
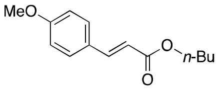
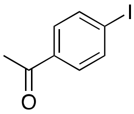
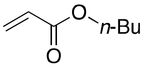
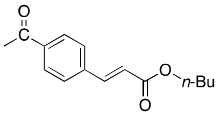
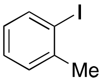
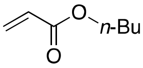
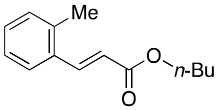
Bromo- and chlorobenzene afforded no desired products under the standard reaction conditions, although bromobenzene (**3d**) gave **5aa** in low yield when $PdCl_2$(dtbpf) [dtbpf =

1,1′-bis(di-*tert*-butylphosphino)ferrocene] was used as a catalyst precursor (entry 10).

Table 3. Mizoroki-Heck reactions with various aryl halides and alkenes in water



Entry	Aryl halide	Alkene	Copolymer	Polymer / *x* wt%	Produnct	Yield [a]
1	 **3a**	 **4a**	**2**	4	 **5aa**	96[b]
2	 **3a**	 **4b**	**2**	1	 **5ab**	82
3	 **3a**	 **4c**	**2**	4	 **5ac**	62
4	 **3a**	 **4d**	**2**	1	 **5ad**	58
5	 **3a**	 **4e**	**2**	4	 **5ae**	12
6	 **3a**	 **4f**	**2**	4	 **5af**	trace
7	 **3b**	 **4a**	**2**	1	 **5ba**	93
8	 **3c**	 **4a**	**2**	1	 **5ca**	73
9	 **3c**	 **4d**	**2**	1	 **5cd**	14
10[c]	 **3d**	 **4a**	**2**	1	 **5aa**	8

11	 **3a**	 **4a**	**7**	1	 **5aa**	99[b]
12	 **3a**	 **4g**	**7**	1	 **5ag**	86
13	 **3a**	 **4h** [d]	**7**	1	 **5ah**	78
14	 **3a**	 **4c**	**7**	1	 **5ac**	98
15	 **3a**	 **4i**	**7**	1	 **5ai**	60
16	 **3a**	 **4j**	**7**	1	 **5aj**	56
17	 **3a**	 **4k**	**7**	1	 **5ak**	69
18	 **3a**	 **4l**	**7**	1	 **5al**	80
19	 **3a**	 **4e**	**7**	1	 **5ae**	12
20	 **3a**	 **4f**	**7**	1	 **5af**	10
21	 **3e**	 **4a**	**7**	1	 **5ea**	73
22	 **3f**	 **4a**	**7**	1	 **5fa**	79
23	 **3g**	 **4a**	**7**	1		77

5ga

a) isolated yield
b) determined by gas chromatography.
c) $PdCl_2$(dtbpf) was used as catalyst
d) 2-ethylhexyl acrylate

2.4 Efficiency of extraction of the product

When reactions are conducted in water, the separation of products from the reaction mixture usually requires an extraction process with organic solvents. Therefore, it is important to reduce the amount of extraction solvents to achieve an environmentally benign system. We examined the extraction efficiency in extracting the Mizoroki-Heck product **5aa** from aqueous model suspension of various surfactants containing the block copolymers **2** or **9**, as well as a few conventional low-molecular surfactants such as SDS and Triton X-100®.

The model mixture was prepared by adding surfactants (1 wt%) and **5aa** to water and stirred at 70 °C. This aqueous mixture was cooled and extracted once with 3 mL of ethyl acetate. The extraction was conducted at 0 °C for 15 min or 30 min with moderate shaking using a shaking apparatus at 120 rpm, and the amounts of extracted **5aa** into the organic layer were determined by gas chromatography. The experiments were repeated to ensure the reproducibility.

The results are summarized in Table 4. The extraction efficiency was estimated on the basis of the amount of the recovered **5aa** within a given period of extraction time. In the absence of any surfactants, 84±6% of **5aa** was recovered within 15 minutes (entry 1). Lower extraction (61±8%) at 30 min in entry 1 is due to a technical problem in pure water suspension, where considerable amounts of dispersed organic particles attached on the wall of the vessel. The extraction efficiency from the suspension of SDS was comparable to that from the water (entry 5), although palladium-catalyzed reaction did not proceed in SDS suspension under the present reaction conditions. Extraction from the solution of the nonionic copolymer **2** was efficient enough that it was slightly lower than the solution of SDS (entry 2). The study on the anionic block copolymer **9**, on the other hand, encountered poor reproducibility. Anyhow the product was obtained in moderate recovery in average (entry 3). Extraction from the actual reaction mixture also gave a similar result (entry 4). Only 6% of **5aa** was extracted in 30 min when Triton X-100 was added (entry 6).

Table 4. Extraction study with ethyl acetate from aqueous solution [a]

Entry	Surfactant	Description	Recovery of **5aa**/%	
			15 min	30 min
1	None	Only water	84(±6)	61(±8)
2	**2**	PNIAAm-*b*-PEG	-	58(±3)
3	**9**	PNIPAAm-*b*-PSSNa	38(±21)[b]	40(±23)[b]
4	**9**[c]	PNIPAAm-*b*-PSSNa	–	45[c]
5	SDS	Anionic surfactant	61(±7)	75(±0)
6	Triton X-100	Nonionic surfactant	-	6(±2)

SDS: sodium dodecyl sulfate, Triton X-100®: octylphenol ethoxylate
a) conditions: **5aa** (0.5 mmol), surfactant 0.042 g, water 4mL, extracted at 0 °C.
b) an average value with sample standard deviation in parenthesis
c) **5aa** was extracted from the reaction mixture with **9**.

Extraction study using diethyl ether as an extrant was also performed (Table 5). In general, the extraction with diethyl ether was less efficient than that with ethyl acetate. A significantly less amount of **5aa** was recovered, in general, compared to the results when ethyl acetate was used. The results showed similar tendency to that observed ethyl acetate. The polymer **9**, however, was more efficient than **2** (entries 2, 3), although the amount of recovered **5aa** was one half to that from pure water (entry 1).

Table 5. Extraction study with diethyl ether from aqueous solution a

Entry	Surfactant	Description	Recovery of **5aa**/%
1	None	Only water	49
2	**2**	PNIAAm-*b*-PEG	17
3	**9**	PNIPAAm-*b*-PSSNa	25
4	SDS	Anionic surfactant	33
5	Triton X-100	Nonionic surfactant	3

a) conditions: **5aa** (0.5 mmol), surfactant 0.042 g, water 4mL, extracted at 0 °C for 30 min.

These results indicate that the thermoresponsive block copolymers PNIPAAm-*b*-PEG **2** and PNIPAAm-*b*-PSSNa **9** were effective not only for palladium-catalyzed Mirozoki-Heck reaction in water but also for efficient extraction from the aqueous reaction mixture.

3. Experimental

3.1. General

The preparation of copolymers was conducted under an argon atmosphere by using either standard Schlenk techniques, unless otherwise mentioned. *N*-Isopropyl acrylamide (NIPAAm) was purchased from Kanto Chemical Co., Inc. and recrystallized from hexane/toluene prior to use. 2,2'-Azobis(isobutyronitrile) (AIBN), copper(I) chloride and dimethylacetamide (DMA) were purchased from Kanto Chemical Co., Inc. and used without further purification. Sodium dodecyl sulfate (SDS) and 4,4'-azobis(4-cyanovaleric acid) (V-501) were purchased from FUJIFILM Wako Pure Chemical Corporation and used as received. Iodobenzene, sodium *p*-styrenesulfonate, *n*-butyl acrylate, tris[2-(dimethylamino)ethyl]amine and α-methylstyrene were purchased from Tokyo Chemical Industry Co., Ltd. and used as received. Styrene and 1-hexene were purchased from Tokyo Chemical Industry Co., Ltd., distilled and kept under argon. Other aryl halides, alkenes and palladium catalysts were purchased and used as received. Triton X-100 was purchased from Sigma-Aldrich Co. LLC. and used without further purification. The PEGylated ATRP agent **1** was synthesized from 4-chloromethylbenzoic acid poly(ethylene glycol) monomethyl ether according to the literature.[35] The RAFT agent **6** was prepared according to the reported method in the literature.[36] Triethylammonium hypophosphite was prepared from triethylamine and hypophosphinic acid in toluene. Dialysis was performed using Spectra/Por® RC tubing (MWCO: 3.5kD). Deionized water was obtained on WE-200 (Yamato Scientific Co., Ltd.). NMR spectra were recorded on JEOL ECX 300, ECA 500 and Bruker Avance III HD400 spectrometers. Gel permeation chromatography (GPC) was measured on HLC-8320 GPC (Tosoh Corporation) equipped with Shodex GPC LF-804 columns (Showa Denko K.K.) using *N*,*N*-dimethylformamide (DMF) (0.1 wt% LiBr) as eluent; the molecular weight of the polymers was determined based on monodispersed poly(ethylene oxide) as standard. Dynamic light scattering (DLS) measurements were made with DLS-8000 (Otsuka Electronics Co., Ltd.).

*3.2. Preparation of the thermoresponsive amphiphilic block copolymer with nonionic PEG segment **2**.*[37]

In a dried 100 mL Schlenk tube, **1** (0.39 g, 0.18 mmol), NIPAAm (1.14 g, 10 mmol), DMF (2.51 mL) and deionized water (1.56 mL) were added. The mixture was degassed in three freeze-pump-thaw cycles, and the flask was filled with argon. Meanwhile, CuCl (1.17 g, 0.72 mmol) and tris[2-(dimethylamino)ethyl]amine (0.166g, 0.72 mmol) were dissolved in degassed water (0.48 mL) to form a blue solution. The Schlenk tube was immersed in a water bath and the blue solution (0.12 mL) was added. The mixture was stirred overnight and tetrahydrofuran (1.2 mL) was added. The mixture was purified with column chromatograph (alumina, methanol/chloroform = 1/1) and the volatiles were removed in vacuo to leave blue oil. The crude product was dissolved in water and purified by dialysis affording **2** as a white solid (1.354 g, 81%). The molecular weight was determined by ^{1}H NMR (M_n = 8,500) and polydispersity was evaluated by GPC (M_w/M_n = 1.03).

^{1}H NMR (D_2O, 500 MHz): δ 1.15 ($CH(CH_3)_2$), 1.4–1.7 (CH_2 in the NIPAAm chain), 2.0–2.1 (C*H* in the NIPAAm chain), 3.38 (s, 3H, OCH_3), 3.67-3.71 (br, OCH_2), 3.81-3.96 (br, $CH(CH_3)_2$), 4.50 (br, $CH_2O(CO)C_6H_4$-), 7.37 (d, *J* = 7.4 Hz, 2H) 7.99 (d, *J* =7.4 Hz, 2H).

*3.3. Preparation of the amphiphilic block copolymer with anionic PSSNa segment **8**.*

A Schlenk tube (25 mL) was thoroughly dried by heating under vacuum and the tube was filled with argon. In this tube, RAFT agent **6** (97 mg, 0.38 mmol), NIPAAm (829 mg, 7.3 mmol), AIBN (18 mg, 0.11 mmol) were dissolved in DMA (6 mL) and degassed in three freeze-pump-thaw cycles. The mixture was stirred at 60 °C for 20 h, and the reaction mixture was poured into hexane/diethyl ether (150/150 mL) to precipitate yellow solid. After the solvent was decanted, the yellow solid was dissolved in chloroform, the solution was collected and dried in vacuo to leave the intermediate **7** as yellow solid (549 mg, 61%). The molecular weight was determined by ^{1}H NMR spectroscopy. DP (degree of polymerization) = 30, M_n = 3,650 by ^{1}H NMR.

The obtained PNIPAAm (**7**) (549 mg, 0.15 mmol) was added to a dried Schlenk tube, and sodium *p*-styrenesulfonate (367 mg, 1.78 mmol) and AIBN (13 mg, 0.08 mmol) werer dissolved in DMSO (7 mL) in the tube. The mixture was degassed in three freeze-pump-thaw cycles. The tube was stirred at 65 °C for 23 h, and the yellow mixture was purified by dialysis for 3 days. The dialyzed yellow solution was dried in vacuo to afford the product polymer **8** as yellow solid (660 mg, 72%). The molecular weight was determined by ^{1}H NMR

spectroscopy. DP of the PSSNa segment was 19, M_n = 7,600 by ^{1}H NMR.
^{1}H NMR (D_2O, 400 MHz): δ: 1.1 (br, CH(C*H*$_3$)$_2$), 1.4–1.7 (br, C*H*$_2$ in the main chain), 2.0–2.2 (C*H* in the main chain), 3.9 (br, C*H*(CH$_3$)$_2$), 4.5 (s, ph-C*H*$_2$-CH$_2$), 6.6–7.7 (br, Ar).

3.4 Removal of the trithiocarbonate terminus in the PNIPAAm-b-PSSNa ***8****: Preparation of* ***9****.*[38]
The PNIAAm-*b*-PSSNa **8** (506 mg, 0.067 mmol), triethylammonium hypophosphite (101 mg, 0.5 mmol) and V-501 (17 mg, 0.06 mmol) were dissolved in DMSO (6 mL) and degassed by the freeze-pump-thaw method. The mixture was stirred at 80 °C for 3 h, and additional V-501 (17 mg, 0.06 mmol) was added to the solution. After the mixture was stirred at 70 °C for 21 h, the yellow solution was dialyzed. The resultant colorless solution with white precipitate was dried in vacuo to obtain the product as white solid (348 mg, 70%). The molecular weight was determined by ^{1}H NMR spectroscopy. DP of the PNIPAAm segment was 30, while PSSNa segment was 12, M_n = 6,000 by ^{1}H NMR.
^{1}H NMR (D_2O, 400 MHz): δ 1.1 (br, CH(C*H*$_3$)$_2$), 1.4–1.7 (br, C*H*$_2$ in the main chain), 2.0–2.2 (C*H* in the main chain), 3.9 (br, C*H*(CH$_3$)$_2$), 4.5 (s, ph-C*H*$_2$-CH$_2$), 6.6–7.7 (br, Ar).

3.5 Mizoroki-Heck reactions in water in the presence of thermoresponsive block copolymer.
Typically, in a test tube with a screw cap **9** (42 mg) was dissolved in water (4 mL) and the mixture was stirred at rt for 0.5 h. To this mixture iodobenzene (**3a**, 102 mg, 0.5 mmol), butyl acrylate (**4a**, 128 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) and diisopropylethylamine (129 mg, 1.0 mmol) were added and stirred at 70 °C for 48 h. The gray mixture was cooled in an ice bath, and diethyl ether (3 mL) was added and stirred for 1 h to extract organic compounds. After stirring the organic layer was collected, and the extraction was repeated. The organic layers were combined and tetradecane (99.2 mg, 0.5 mmol) was added as an internal standard when yield was determined by gas chromatography (99%). Purification by column chromatograph gave *n*-butyl cinnamate (**5aa**).

3.6 Evaluation of extraction efficiencies
Typically, in a test tube with screw cap, the block copolymer **9** (42 mg) was dissolved in deionized water (4 mL) and the solution was stirred for 0.5 h at rt. To this solution, *n*-butyl cinnamate (**5aa,** 102 mg, 0.5 mmol) was added and the mixture was stirred at 70 °C for 1 h. Ethyl acetate was added to this mixture, and this mixture was shaken at 120 rpm in a shaking apparatus at 0 °C for 0.5 h. The mixture was allowed to stand still for 0.5 h at ambient temperature, and then the organic layer was taken up and analyzed by gas chromatograph using tetradecane as an internal standard.

Conclusion

In summary, palladium-catalyzed Mizoroki-Heck reactions were studied in water in the presence of thermoresponsive amphiphilic block copolymers. The reactions were examined using two kinds of copolymers; one consisted of PNIPAAm and a nonionic PEG segment **2** and the other PNIPAAm and an anionic PSSNa segment **9**. The study demonstrated that the copolymer **9** with anionic chain was more effective than **2** for catalytic reactions. Extraction study indicated that extracting *n*-butyl cinnamate form aqueous suspension of **2** or **9** was considerably efficient.

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