Poly(*N*-isopropylacrylamide) Soluble Polymer Supports in Catalysis and Synthesis

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ABSTRACT: Co- and terpolymers of *N*-isopropylacrylamide exhibit inverse temperature solubility in water with the polymer's lower critical solution temperature (LCST) being dependent on the polymer's microstructure and the concentration of salt in the water solvent. This solubility behavior has been used to prepare "smart" recoverable homogeneous catalysts and substrates. These catalysts' activity reversibly turns first off and then on as the temperature is first raised and then lowered due to changes in the polymer support's solubility. Such catalysts can be recovered by heating the aqueous solution or by adding brine. Catalysts prepared include both phosphine-ligated transition metal catalysts and acid catalysts. The transition metal catalysts are active in alkene hydrogenation, C−C coupling, and allylic substitution reactions. The acid catalysts are active in acetal hydrolysis. Substrates can be attached to these polymers and their activity likewise can be turned off and on by heating or cooling. Substrate activity on such supports can equal that of a low molecular weight analogue. NMR spectroscopic studies show that a vinyl group bound to PNIPAM has peaks whose line widths in ^{1}H NMR spectroscopy are like those of a low molecular weight compound when a nine-carbon tether chain is used to attach the vinyl group to PNIPAM.

Insoluble and soluble polymers are now being widely used in synthesis due to the development of combinatorial chemistry.[1−3] Polymer supports also have significant applications in catalysis chemistry.[4,5] Most of this chemistry relies on cross-linked polystyrene supports—the system originally developed by Merrifield for peptide synthesis in the 1960s. We and others have focused our attention on soluble polymer supports for use in synthesis and catalysis.[6−8] Our early work used terminally functionalized polyethylene oligomers in catalysis and synthesis.[9−11] Much of the other work on soluble polymers has focused on terminally functionalized poly(ethylene oxide) polymers.[7,8] Other soluble polymers have received less attention. Nonetheless, such polymers can be very useful, as seen in Janda's work where a linear polystyrene was used as a support in the synthesis of a prostaglandin.[12] Here we describe the use of another soluble polymer support, poly(*N*-isopropylacrylamide) (PNIPAM). This polymer and its supported substrates or catalysts are soluble in cold water but insoluble in hot water. As a result, PNIPAM-supported species can be separated and recovered from aqueous solutions by simple heating and then reused after adding fresh cold water. This heating-induced insolubility also leads to "smart" thermoresponsive behavior for both catalysts and substrates.

Introduction

Although cross-linked insoluble polymers have found widespread use in synthesis and catalysis, different reactivity of bound species, synthetic problems, and characterization problems have led others to study soluble polymers. Poly(alkene oxide)s are among the most commonly studied soluble polymer supports. Polymers including polyethylene oligomers and polystyrene have also received attention.[6−8,13] Other vinyl additon polymers are also useful as supports for reagents and catalysts. For example, a polyacrylate has been used to support a prolinol-derived chiral auxiliary and to then separate it from low molecular weight reagents and products using a semipermeable membrane in continuous reactors.[14] More recently, dendrimers also have been used as soluble polymer supports in construction of combinatorial libraries.[15] The main role of the polymer in all of this chemistry is to facilitate separation of the polymeric reagent, substrate, or catalyst from the reaction mixture.[16] In all of these cases, this separation is possible because of the size of the polymer. Separation strategies such as solvent precipitation using a "poor" solvent, membrane filtration, and thermal precipitation all rely on effects of polymer size to facilitate separation. This paper describes advantages of an alternative polymer support, poly(*N*-isopropylacrylamide) (PNIPAM), that precipitates on heating above its lower critical solution temperature (LCST).[17−19]

Precipitation of a polymer from solution on heating is a common feature of polymers both in strongly interacting solvents (e.g., water) and in weakly interacting organic solvents. Protein denaturation is a common example of the former process. Phase separation of polymers such as polystyrene from toluene above the boiling point of toluene or of poly(isobutylene) from pentane at 75 °C are examples of the latter process.[20,21] PNIPAM is like a protein in that it precipitates below the boiling point of the solvent. Moreover, copolymerization of NIPAM with other monomers of varying hydrophilicity leads to copolymers that precipitate at varying temperatures. Unlike a protein, PNIPAM redissolves on cooling. Thus, PNIPAM is a support that can be used to design "smart" catalysts, "smart" substrates, and recoverable catalysts and substrates.[18,19]

A second issue in polymer-supported synthesis and catalysis deals with the reactivity and characterizability of polymer-supported species. In the case of soluble polymers such as poly(alkene oxide)s and polyethylene,

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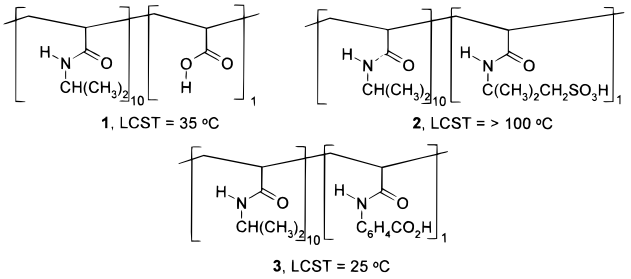
terminal substitution facilitates characterization and makes the substituent's reactivity essentially identical to that of an electronically equivalent low molecular weight analogue. In the case of reagents, substrates, or catalysts present as pendant groups on vinyl polymers, the reactivity and characterizability may not be equivalent to that of a low molecular weight analogue—issues that we have studied below in the case of PNIPAM derivatives.

Poly(*N*-isopropylacrylamide) is readily prepared by radical polymerization.[18] High molecular weight copolymers can be prepared by using mixtures of *N*-isopropylacrylamide and other acrylamide derivatives or acrylic acid derivatives. Both PNIPAM homopolymers and copolymers have been studied previously. PNIPAM and PNIPAM derivatives have received particular attention as materials for use in drug delivery and as coatings due to their thermally sensitive solubility or swellability in water.[17−19]

The feature of PNIPAM that makes it an attractive polymer support for synthesis and catalysis chemistry is its inverse temperature-dependent solubility. This property is often discussed in terms of the temperature at which the polymer phase separates from a solution—the lower critical solution temperature (LCST).[19] In water, PNIPAM has an LCST of 31 °C. This behavior results from the unfavorable entropy changes associated with polymer dissolution and is affected by the presence of a comonomer. For example, the copolymer **1** has an

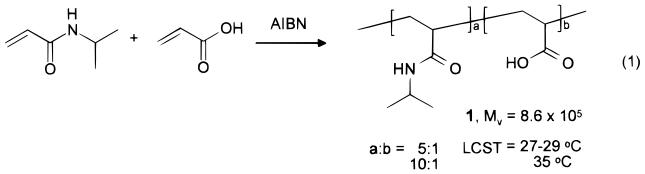


LCST of 35 °C, **2** has an LCST of >100 °C, and **3** has an LCST of 25 °C. Adding a more hydrophobic third comonomer (*tert*-butylacrylamide) or a third more hydrophilic comonomer (acrylamide) lowers or raises the LCSTs of **1**−**3**, affording additional control over the LCST temperature of PNIPAM derivatives.

The LCST of PNIPAM derivatives allows PNIPAM derivatives to be separated and recovered from solutions of other polymers, substrates, or reagents by simple heating. Subsequent centrifugation and trituration allows recovery of the PNIPAM-bound species. PNIPAM's high molecular weight (addition homo- and copolymerizations typically yield polymers whose M_v is $>5 \times 10^5$ Da) makes solvent precipitation and membrane filtration, separation techniques of demonstrated utility with PEO-bound reagents, substrates, and catalysts, useful with PNIPAM polymers. This paper details our initial studies with catalysis and synthesis using PNIPAM derivatives, work that highlights the utility of this soluble polymer support in the design of responsive functional polymers for synthesis.[22,23]

Results and Discussion

We have explored two general approaches to synthesize PNIPAM derivatives for use in synthesis and catalysis. The first is based on copolymerization of an appropriately functionalized acrylamide or acrylate monomer with a 5−20-fold excess of *N*-isopropylacrylamide (NIPAM). For example, copolymerization of acrylic acid with NIPAM or of a mixture of *tert*-butylacrylamide and 2-acrylamido-2-methylpropanesulfonic acid with a 10-fold excess of NIPAM produced carboxylic acid and sulfonic acid-containing PNIPAM co- and terpolymers **1** and **4** (eqs 1 and 2). Further modi-



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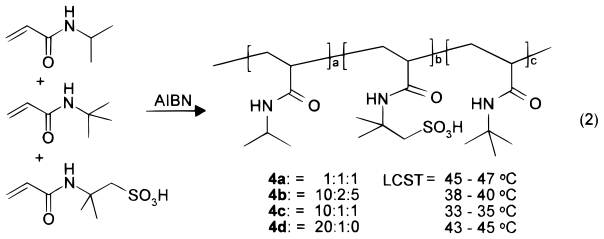

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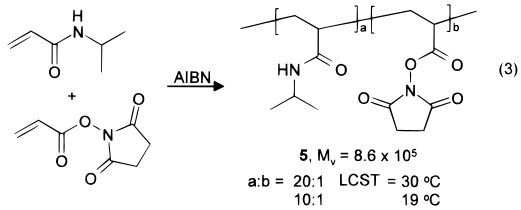
fication of polymers such as **1** via carboxylic acid group activation (CDI or DCC) and attachment of various amines affords functional PNIPAM copolymers.

A second and more generally useful approach to PNIPAM derivatives for use in synthesis and catalysis chemistry involved copolymerization of *N*-isopropylacrylamide with *N*-(acryloyloxy)succinimide (NASI) (eq 3). This procedure has been used previously as a route



(3)

to derivatives of PNIPAM,[24] and the copolymers **5** are used as starting materials in most of the syntheses discussed here.

The presence of more polar monomers increased the LCST of PNIPAM copolymers as noted above. In the case of the sulfonic acid-containing copolymer **2**, the LCST was above 100 °C while **1** had an LCST of 35 °C. These LCSTs can be changed by adding a comonomer. Copolymerizing 10 equiv of NIPAM with 1 equivalent of 2-acrylamido-2-methylpropanesulfonic acid (1 equiv) and 1 equiv of the hydrophobic monomer *tert*-butylacrylamide lowers the LCST from >100 °C to 33−35 °C (**4c**). Lowered LCSTs are also attained by using salt solutions. For example, the LCST of a 10:1 PNIPAM−NASI copolymer was decreased from 19 °C to about 8 °C in the presence of 1×10^{-2} M NaCl.

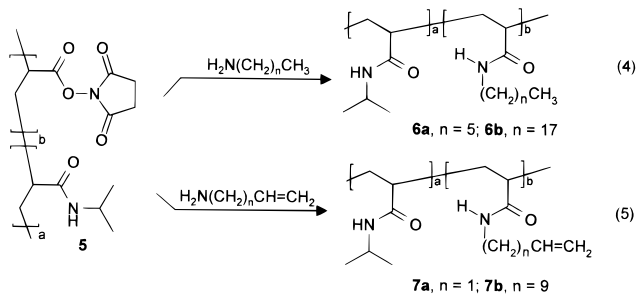
A critical issue associated with all chemistry involving polymer-bound species is the facility with which polymer-bound species are characterized. For organic chemists, this issue often reduces to a question of NMR spectroscopic analysis of the polymer-bound substrate. Insoluble, cross-linked polymers have broad ^{1}H NMR signals, although some information can be gleaned from spectra of swollen gel-type polymers.[25,26] This situation has been addressed using graft spacer groups that facilitate NMR analysis of substrates. However, the

Table 1. ^{1}H NMR Parameters of PNIPAM and PNIPAM-Bound Hexylamine (6a) and Octadecylamine (6b)[a]

molecule	T_1 (s)[b]	peak width (Hz): central peak, $-CH_3$ triplet	peak width (Hz): HMDS, $-CH_3$ singlet
hexylamine	6.8 ± 0.4	0.82	0.43
octadecylamine	4.6 ± 0.7	0.95	0.44
poly(*N*-isopropylacrylamide)	0.4 ± 0.1	28.03	0.85
PNIPAM-NHC$_6$H$_{11}$ (**5**, $n = 5$)	2.7 ± 0.8	4.39	0.53
PNIPAM-NHC$_{18}$H$_{36}$ (**5**, $n = 17$)	4.1 ± 0.7	1.88	0.82

[a] ^{1}H NMR spectra were obtained using 3×10^{-2} M solutions of **6a** or **6b** in $CDCl_3$ at ambient temperature on a 200 MHz NMR spectrometer. [b] T_1 measurements were based on the terminal methyl groups.

large spacers involved necessarily lead to resins whose loading levels are reduced. For example, the popular Tentagel resins have poly(ethylene oxide) grafts with a degree of polymerization of the PEO graft of 70.[27] In contrast, ^{1}H NMR spectroscopy studies show that readily synthesized (eqs 4 and 5) soluble PNIPAM



derivatives such as **6** or **7** require only small spacer groups to significantly change a bound substrate's ^{1}H NMR spectroscopic behavior so that it resembles that of a small molecule.

To study the effectiveness with which spacers affect side chain bound groups in soluble PNIPAM derivatives, we coupled **5** to two simple amines, hexylamine and octadecylamine. The resulting polymers **6a** ($n = 5$) and **6b** ($n = 17$) are insoluble in water but are soluble in organic solvents (THF, CH_2Cl_2, $CHCl_3$). We then measured the T_1 relaxation time of the terminal carbon of the isopropyl group of the NIPAM and of the terminal methyl group of the C_6 and C_{18} side chains as solutions in $CDCl_3$ at ambient temperature. We also measured the line widths of the central peak in the virtually coupled triplet of the terminal $-CH_3$ groups. Comparison of the line widths listed in Table 1 to those for the parent amines and the homopolymer (PNIPAM) show that even small spacers on a soluble polymer are sufficient to afford small molecule-like NMR behavior.

Longitudinal relaxation is more efficient at higher molecular weights where the tumbling rate is slower. Thus, polymers typically have shorter T_1 relaxation times than small molecules. Indeed, the T_1 relaxation times of the methyl groups of the homopolymer PNIPAM are much smaller than those of the hexyl- or octadecylamine small molecules (Table 1). The T_1 relaxation time of the $-CH_3$ group of the polymer-bound hexyl chain is significantly lower than that of the parent amine. However, the T_1 relaxation time values for the $-CH_3$ group of the free and polymer-bound octadecylamine were experimentally indistinguishable.

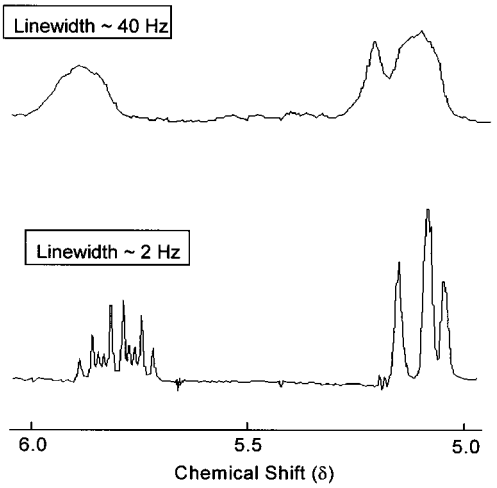


Figure 1. ^{1}H NMR spectrum of PNIPAM-bound allylamine (**7a**) (top) and undecenylamine (**7b**) (bottom) in $CDCl_3$ at ambient temperature, showing solution-like resolution for a vinyl group with a modest-sized spacer.

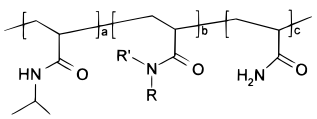
To study the effect of spacer length on ^{1}H NMR spectral resolution, allylamine and 11-undecenamine were bound to PNIPAM-*c*-NASI (**7a** ($n = 1$) and **7b** ($n = 9$), eq 5). The vinyl regions of the ^{1}H NMR spectra of **7a** and **7b** (δ 5−6 ppm) are shown in Figure 1, where it is obvious that extending the side chain by just eight carbon atoms markedly improves the spectral resolution.

Preparation of the PNIPAM-*c*-NASI copolymers and derivatization of these copolymers with amines follows an established procedure. The copolymer products were characterized by IR spectroscopy (imide peaks at 1813 and 1785 cm^{-1}, carbonyl at 1735 cm^{-1}) and ^{1}H NMR spectroscopy (the broad singlet at 2.8 ppm in D_2O confirmed the presence of NASI). The M_v was determined to be 8.7×10^5 Da using values of 9.59×10^{-3} and 0.65 for K and a, respectively, in THF at 30 °C.[24] Modification of this copolymer with an amine was carried out by stirring the copolymer with excess amine in THF for 24 h. Subsequent addition of *i*-PrNH$_2$ or ammonia and further stirring for 4 h ensured that all of the NASI groups were consumed—a supposition that was verified by ^{1}H NMR spectroscopy and by IR spectroscopy.

The reactivity of the active ester groups of PNIPAM-*c*-NASI was studied briefly. These studies examined the stability of PNIPAM-*c*-NASI in aqueous media (D_2O). ^{1}H NMR spectroscopy was used to follow the disappearance of the NASI peak at 2.8 ppm. Hydrolysis of the active ester was confirmed by the appearance of a new singlet at 2.6 ppm due to free *N*-hydroxysuccinimide. The active ester in PNIPAM-*c*-NASI is more stable than an NASI derivative of PEG toward hydrolysis. In the case of PNIPAM-*c*-NASI, only 15% of the NASI of the PNIPAM-*c*-NASI hydrolyzed after 24 h in D_2O at 20 °C at pH 7. In contrast, an NASI-modified PEG derivative ($M_n = 5000$ to 10 000) has a half-life of less than 0.5 h at pH 8.[28] The higher molecular weight of PNIPAM-*c*-NASI might be partially responsible for this slower hydrolysis rate. Another factor could be that the NASI groups in the PNIPAM copolymer are more sterically hindered.

Modification of PNIPAM to include sites for chemical attachment of substrates or catalysts used the same chemistry we used to prepare NMR spectroscopic probes.

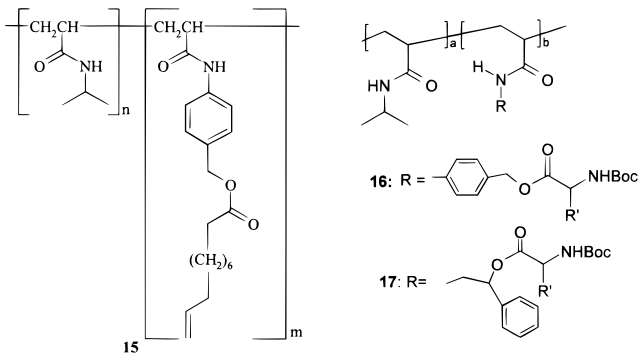
In this way, we have attached phenolic groups (*p*-aminophenol) (**8**), carboxyl groups (*p*-aminobenzoic acid)



8;	R = -C_6H_4OH	R'=H	LCST = 27 °C	a:b:c = 20:1:0
9;	R = -$C_6H_4CO_2H$	R'=H	LCST = 29 °C	a:b:c = 20:1:0
10a;	R = -$C_6H_4CH_2OH$	R'=H	LCST = 38 °C	a:b:c = 29:1:0
10b;	R= -$CH_2CH(OH)C_6H_5$	R'=H	LCST = 5 °C	a:b:c = 10:1:0
11;	R = -$C_6H_4NO_2$	R'=H	LCST = 26 °C	a:b:c = 20:1:0
12;	R = -$CH_2CH_2CH_2P(C_6H_5)_2$	R'=H	LCST = 23-24 °C	a:b:c = 50:2:3
13;	R = -$CH_2CH_2P(C_6H_5)_2$	R'=R	LCST = 18-19 °C	a:b:c = 100:1:9

(**9**), benzyl alcohol groups (*p*-aminobenzyl alcohol **10a** and 2-amino-1-phenylethanol **10b**), nitro groups (*m*-nitroaniline) (**11**), phosphines (**12**, **13**), and tethering groups **7**. In this chemistry, copolymerization was used to prepare **8**, **9**, and **11**. Substitution of an NASI copolymer or substitution of a NIPAM/acrylic acid copolymer (after CDI activation) was used to prepare the other substrates.

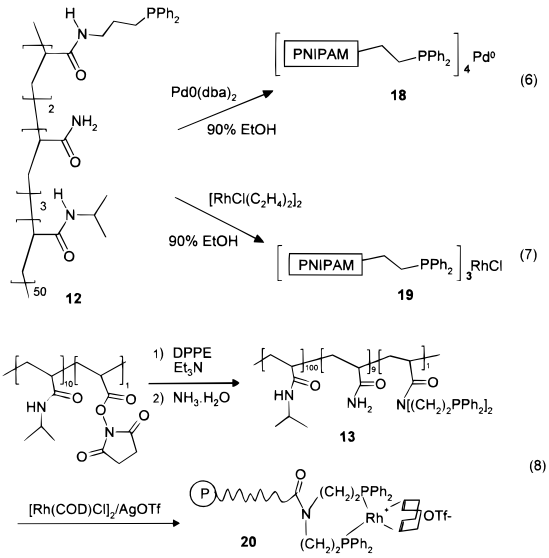
In cases where the resulting PNIPAM had reactive groups (e.g., **9** or **10**), they could be used to bind alcohol substrates such as 10-undecenol or a simple amino acid (e.g., **15**−**17**). The phosphines (**12, 13**) were used to bind Rh(I) and Pd(0) catalysts.



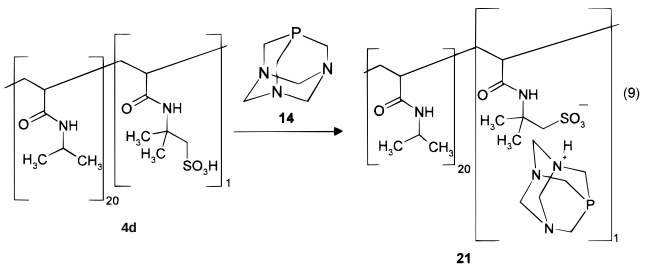
A critical issue in using this PNIPAM-support is the extent to which the support can be recovered at the end of a reaction. We have demonstrated that these polymer supports precipitate completely and are quantitatively removed from solution by using a PNIPAM-bound methyl red (NIPAM:methyl red = 200:1) as a probe.[29] UV−visible spectroscopy studies of this species showed that PNIPAM-bound methyl red had its maximum absorbance at 503 nm at pH = 2; all further UV studies were then done under these conditions. A 0.5% aqueous solution (by weight) of this copolymer had an absorbance of 2.9 at 20 °C (below its LCST of 30 °C). The solution was then heated to 45 °C to precipitate the polymer. The PNIPAM-bound methyl red was then removed, and the supernatant was analyzed by UV−visible spectroscopy. Control experiments with low molecular weight methyl red showed that a 2.5×10^{-11} M solution of methyl red could be detected ($A = 0.001$). The absence of any detectable absorbance in the supernatant from the solution of the polymer-bound dye indicated that >99.96% of the polymer-bound species was recovered from solution.

The synthesis of the PNIPAM-bound phosphine ligand **13** illustrates both a problem and feature of this PNIPAM chemistry. Use of the bis[2-(diphenylphosphino)ethyl]amine (DPPE) alone in reaction with **5** produced a PNIPAM-bound phosphine that was too hydrophobic to dissolve even in cold water. While the resulting phosphine functions well as a ligand in organic solvents or in mixed aqueous/organic solvents (vide infra), further "tuning" of the PNIPAM microstructure was required if a water soluble polymeric ligand were desired. Two approaches can be used to make phosphine-containing PNIPAM copolymers water-soluble. This can be accomplished using a different co- or terpolymer starting material (e.g., a terpolymer of NIPAM, NASI, and $H_2C{=}CHCONHC(CH_3)_2CH_2SO_3H$). However, the simpler expedient of using only 0.1 equiv of the bis[2-(diphenylphosphino)ethyl]amine and then completing the reaction using aqueous ammonia served equally well as a route to a water-soluble polymer. In this latter case, a portion of the NASI groups is transformed into the more hydrophilic acrylamide group with the balance becoming a hydrophobic phosphine ligand, producing a product polymer with an LCST of 18 °C.

Modification of PNIPAM to attach catalysts proceeded by coordination of Rh(I) or Pd(0) to phosphine ligands. In the case of phosphine ligands **12** and **13**, catalyst attachment generally involved coordination to a transition metal using chemistry like that shown in eqs 6−8.



Thus, a ligand exchange reaction between an appropriate precatalyst like Pd(0)(dba)$_2$, [RhCl(C$_2$H$_4$)$_2$]$_2$, or [Rh(COD)Cl]$_2$ and polymeric phosphines **12** and **13** in aqueous ethanol or THF affords PNIPAM-bound catalysts **18**−**20**. Ionic attachment of phosphines followed by coordination of catalysts was also successful, and this route was used to prepare ionically bound phosphine **21** from **4d** and PTA (**14,** 1,3,5-triaza-7-phosphatricyclo-[3,3,1,1^{3,7}]decane) as shown in eq 9.[30] This ligand **21** was also used to make Rh(I) cationic catalyst **22** using a procedure similar to that described in eq 8.

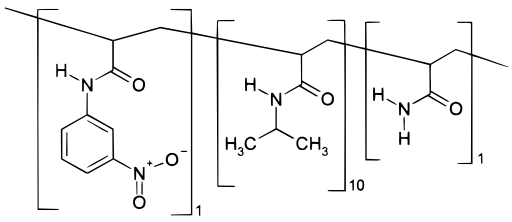


Direct attachment of metals by formation of a metal carboxylate salt from NIPAM derivative **1** was also possible, but this was only briefly explored by our group. In some cases (e.g., in the case of Pd(II) with a cross-linked PNIPAM-*c*-PAA resin), we observed that heating and cooling such PNIPAM−palladium(II) carboxylates (in the presence of $NaBH_4$) led to PNIPAM/Pd(0) dispersions. The "smart" activity of these sorts of catalyst dispersions has recently been reported by Akashi's group.[31]

Reactions of PNIPAM-Bound Substrates. Hydrogenations of substrates such as **11** with Pt/C in solvents below the polymer's LCST or in solvents where LCST behavior was not seen showed that this polymer-bound nitroarene's reactivity was not substantially affected by the polymer. Indeed, comparison of the rate of hydrogenation of this polymer-bound nitro group with the rate of hydrogenation of 3-acetamidonitrobenzene in EtOH at 0 °C (Table 2) shows essentially no effect of the polymer. This was expected on the basis of earlier studies from our group, showing that hydrogenation rates of terminally substituted poly(ethylene oxide)-bound nitroarenes are normal when the polymer has good solubility.[32]

As noted in Table 2, the PNIPAM-bound nitroarene's reactivity is substantially diminished above **11**'s LCST. However, in EtOH, **11** had temperature-dependent reactivity that followed Arrhenius kinetics. It is also noteworthy that these temperature effects on the reactivity of this PNIPAM-bound substrate are completely reversible. Three cycles where **11** was hydrogenated at 0 °C, heated to 45 °C (cessation of reactivity), and finally cooled once more to 0 °C (renewed activity) showed the reversibility of this behavior.

The conclusion of our initial studies of hydrogenation of **11** and of hydrogenations using poly(alkene oxide)-bound catalysts[33] was that LCST behavior of a polymer could usefully affect the reactivity of substrates or catalysts. This conclusion was reinforced by another simple nitroarene hydrogenation study, this time using a terpolymer prepared from NIPAM, *N*-(3-nitrophenyl)-acrylamide, and acrylamide (AAM). When the three monomers (monomer feed ratio of 10:1:1) were copolymerized with AIBN in *tert*-butyl alcohol, a product polymer **23** was prepared that contained these three



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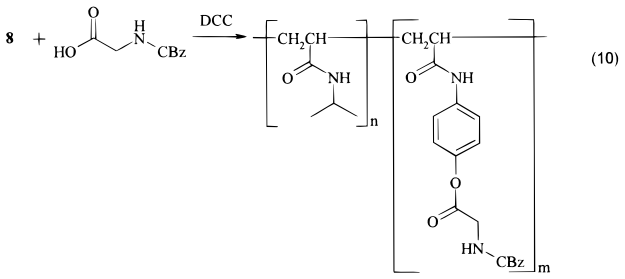
monomers in a ratio that roughly corresponded to the ratio of monomers in the feed based on ^1H NMR spectroscopy. This polymer had a surprisingly low LCST temperature of 18.5 °C. While a higher LCST value for this polymer than that seen for **11** was expected on the basis of the presence of the more hydrophilic acrylamide, the reactivity ratios for these monomers are not known and it may be that the product polymer was more blocky than random. Nonetheless, the nitroarene in **23** still exhibited the same sort of thermoresponsive reactivity seen for **11**. Hydrogenation of **23** with 5% Pt/C in water occurred readily at 0 °C, ceased at 23 °C, and recommenced when the solution was cooled back to 0 °C.

Table 2. Hydrogenation Rates of Polymer-Bound Nitroarenes[a]

substrate	temp (°C)	solvent	rate (mL of H_2/min)
11	0	EtOH	3.7×10^{-2}
3-acetamidonitrobenene	0	EtOH	3.0×10^{-2}
11	0	water	4.9×10^{-2}
11	10	water	7.2×10^{-2}
11	23	water	4.5×10^{-2}
11	33	water	4.4×10^{-2}
11	39	water	$<1 \times 10^{-3}$

[a] Hydrogenations were conducted at the temperature indicated using solutions that were ca. 2×10^{-3} N in nitroarene with 5% Pt/C. Rates were measured with a H_2-filled gas buret, and all refer to reactions carried out under atmospheric pressure.

Preliminary work with other substrates bound to PNIPAM copolymers shows that the temperature-dependent solubility observed for the nitroarenes **11** and **23** has potential utility in synthesis. When a CBz-protected glycine (CBz-Gly) was attached to the phenolic hydroxyl group of a PNIPAM copolymer (**8**) containing *N*-*p*-(hydroxyphenyl)acrylamide, a new copolymer **24** with a 2 °C higher (∼29 °C) LCST was formed. This polymer-bound amino acid was shown to be inert to hydrogenolysis above 38 °C in water but reactive when in solution (7 °C). In the synthesis of **24** the polymer



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also provided a means of separating the product from the reaction mixture and the reagents. After hydrogenolysis, the PNIPAM-bound amino acid was kept in solution by keeping the reaction mixture below the support's LCST. Filtration then separated the polymer from the catalyst. Recovery of the glycine was then effected by cleavage of the glycine from the polymer using aqueous NaOH. In this hydrolysis reaction, the polymer **8** was then recovered by heating the reaction mixture above 30 °C and decanting the solution of glycine from the precipitated polymer.

The above experiments show that PNIPAM effectively controls the reactivity of a bound functional group in reaction with macroscopic heterogeneous catalysts. These experiments also show that isolation and reuse of a PNIPAM-bound substrate in multiple steps is feasible. Other experiments with **15** also show that PNIPAM-based soluble polymeric supports can effectively alter the reactivity of bound groups in reactions with homogeneous reagents. For example, when the PNIPAM-bound alkene **15** was hydrogenated using the water-soluble organometallic catalyst [Rh(PTAH)-$(PTA)_2$Cl]Cl, "smart" hydrogenation activity was seen. At 23 °C the reaction mixture was homogeneous and the polymer-bound substrate was reduced. Heating to 35 °C precipitated **15**, leading to cessation of hydrogenation. Recooling to 24 °C led to renewed hydrogenation

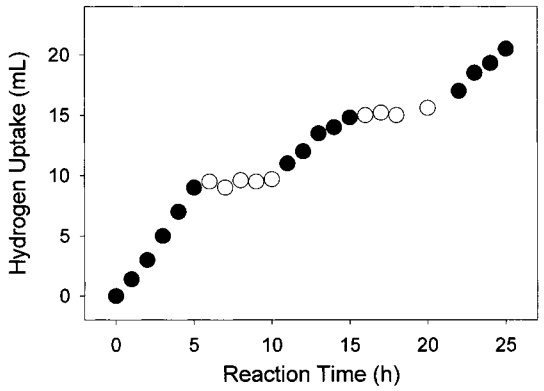


Figure 2. On/off behavior exhibited for the Rh(I) hydrogenation catalyst (**22**) bound ionically to a PNIPAM derivative where that hydrogenation activity is on at 22 °C (●) and off at 55 °C (○). [Rh] = 3×10^{-4} M. [Rh]:[substrate] = 1:2000.

at the original rate. After the reaction, PNIPAM-bound substrate was separated from the catalyst by gentle heating. Decantation followed by successive washings of the polymer with aliquots of warm water completely separated the catalyst from the polymer. In these cases, reactions could also be followed by analysis of the polymer-bound substrate by solution state ^{1}H NMR spectroscopy (cf. Figure 1, vide supra).

Reactions of PNIPAM-Bound Catalysts. Several PNIPAM-bound catalysts have been prepared. These include phosphine-ligated catalysts such as **18, 19, 20, 22 (**neutral Pd(0) catalysts, neutral Rh(I) catalysts, cationic Rh(I) catalysts with chelating ligands, cationic Rh(I) catalysts with **21** as the ligand) and acidic catalysts **1** and **2**. All of the homogeneous transition metal catalysts exhibit "smart" activity with reactions such as hydrogenations turning off and then on as the polymer-bound catalyst dissolves and precipitates. This behavior is illustrated in Figure 2 below for hydrogenation of allyl alcohol by **22**.

While the sort of "smart" catalytic activity noted for the ionic catalyst like **20** and **22** is generally seen for PNIPAM-bound hydrogenation catalysts, catalysts containing cationic Rh(I) catalysts were generally not as active as their low molecular weight analogues, especially when hydrogenations were carried out in water. To understand this lower activity, we separately examined allyl alcohol hydrogenations using a low molecular weight analogue of **20** in aqueous dioxane (water:dioxane = 12:1) in the presence and absence of the PNIPAM homopolymer. *N*,*N*-bis[2-(diphenylphosphino)ethyl]acetamide **25** was used to prepare the cationic Rh(I) catalyst **26**. The results listed in Table 3 show significant deactivation of the cationic Rh(I) catalyst in the presence of PNIPAM. This deactivation was minimized if the PNIPAM was absent or if the reaction was carried out above PNIPAM's LCST. This suggests that the basic amides of the PNIPAM may be coordinating to the cationic Rh(I) center and deactivating it.

PNIPAM does not affect the hydrogenation activity of neutral Rh(I) catalysts. Table 4 compares the activity of a neutral PNIPAM-bound Rh(I) catalyst **19** and a low molecular weight analogue, **27** (*N*,*N*-bis[2-(diphenylphosphino)ethyl]acetamide-modified Wilkinson's catalyst). These catalysts were used to hydrogenate allyl alcohol in ethanol. The neutral Rh(I) catalysts show essentially the same activity regardless of whether PNIPAM was present. The PNIPAM-bound Pd(0) catalyst **18** is soluble in aqueous and mixed aqueous/organic media.

Table 3. Hydrogenation of Allyl Alcohol Using a Rh(phosphine)$_2^+$Tf$^-$ Catalyst in Water in the Presence or Absence of PNIPAM at Various Temperatures[a]

catalyst	solvent	temp (°C)	PNIPAM added	TOF [mol of H_2/(mol of Rh h)]
20	water	0		2.1
20	water	45		0
26	water:dioxane = 12:1	0	no	7.4
26	water:dioxane = 12:1	45	no	17.3
26	water:dioxane = 12:1	0	yes	2.4
26	water:dioxane = 12:1	45	yes	15.2

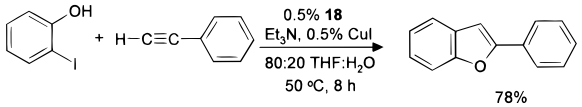
[a] In all reactions, hydrogenations were conducted at the temperature indicated using solutions that have [Rh] = 3×10^{-4} M and [Rh]:[substrate] = 1:2000. Reaction rate (TOF) were estimated by the hydrogen uptake versus the amount of catalyst in certain amount of time and all referred to atmospheric pressure.

Table 4. Hydrogenation of Allyl Alcohol Using Neutral Rh(I) Catalysts in Ethanol in the Presence or Absence of PNIPAM[a]

catalysts	solvent	temp (°C)	PNIPAM added	TOF [mol of H_2/(mol of Rh-h)]
19	ethanol	25		2.2
27	ethanol	25	no	2.7
27	ethanol	25	yes	2.6

[a] In all reactions, hydrogenations were conducted at the temperature indicated using solutions that have [Rh] = 3×10^{-4} M and [Rh]:[substrate] = 1:2000. Reaction rates (TOF) were estimated by the hydrogen uptake versus the amount of catalyst in a certain amount of time and all referred to atmospheric pressure.

It has high activity in nucleophilic allylic substitution reactions and in sp−sp^2 coupling reactions of aryl iodides with terminal alkynes.[34] For example, 2-iodophenol reacted with phenylacetylene in the presence of 0.5% **18** in aqueous THF gave 2-phenylbenzofuran in 78% yield. The PNIPAM-bound Pd(0) catalyst **18** used in this reaction can be readily recovered and reused. The catalyst **18** can be recovered either by heating above the LCST (in water) or by adding a poor solvent—hexane (in aqueous THF). The recovered catalyst can be dissolved in fresh water or aqueous THF, new substrates can be added, and the catalyst activity resumes. We were successful in recycling **18** up to 15 times in either the allylic substitution reaction or C−C coupling reaction with only a very modest loss of the activity. In these reactions, the yield of the furan product in eq 11 changed from 78% to 58% in cycle 5.



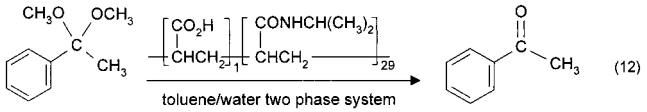
(11)

In cycle 5, we reexamined the catalyst by ^{31}P NMR spectroscopy. These NMR spectroscopy studies showed that some adventitious oxidation of the phosphine ligand had occurred, which we believe accounts for the slight loss of activity.[35]

While analysis of the PNIPAM-bound catalysts by ^{31}P NMR spectroscopy was useful in determining the presence or absence of phosphine oxide, the catalysts on these polymers did not yield the clean spectra expected for simple Rh(I) or Pd(0)−phosphine ligated catalysts. For example, PNIPAM-bound neutral Rh(I) catalyst **19** has a main broad doublet centered at 47.8 ppm (CD_3COCD_3) and PNIPAM−Pd(0) catalyst **18** has a broad singlet at 17.0 ppm (CD_3OD). Separate studies with low molecular weight analogues of the PNIPAM bound Rh-

(I) and Pd(0) catalysts by ^{31}P NMR spectroscopy do not show these broad peaks. The differences between the PNIPAM-bound catalysts and their low molecular weight analogues may be the result of chemical heterogeneity or intramolecular exchange. Chemical heterogeneity is the result of the presence of varying microstructures in the polymer chain. Exchange of metal between phosphines on the same polymer molecule may also contribute to line broadening. The greater line width of the ^{31}P NMR (121 MHz, $CDCl_3$) spectroscopy signal of a PNIPAM-bound phosphine **12** (60 Hz) versus its low molecular weight analogue, [3-(diphenylphosphino)-propyl]butyric amide (0.7 Hz), may arise in part due to this postulated chemical heterogeneity.

Acid catalysis of acetal hydrolysis was studied using acid-containing PNIPAM copolymers **1** and **2**. In these reactions, hydrolyses such as those in eqs 12 and 13



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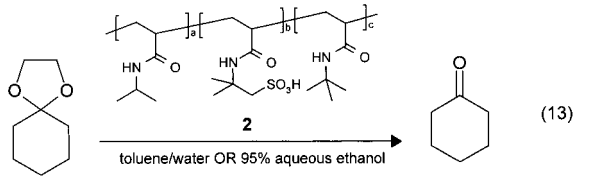

(13)

were studied as a function of temperature.

These studies showed activity that was not strictly "on" and "off" at temperatures below and above the LCST in hydrolysis of the acetal of acetophenone using **1** as a catalyst. Hydrolysis at 24 °C occurred at a rate approximately 4 times that at 1 °C. This was expected since the temperature increased by about 20 °C. Similarly, if the reaction catalyzed by the PNIPAM copolymer had normal temperature dependence, the rate would increase by another factor of ca. 4 when increasing the temperature from 24 to 48 °C. However, **1** has inverse temperature-dependent solubility, and it precipitates at 48 °C. If **1** were to exhibit "smart" behavior like that of the transition metal catalysts, the hydrolysis reaction should have ceased. However, the observed hydrolysis rate was between these two extremes. In this case, we believe that the acetal partitions itself into the precipitated polymer gel phase where hydrolysis can still occur. This result is significant in that it illustrates that precipitation of a catalyst does not necessarily result in zero catalyst activity.

Additional studies of hydrolysis of dioxospirodecane with **2** illustrate a second important consideration in catalysis with PNIPAM-bound catalysts. In this case, **1** was not a strong enough catalyst to hydrolyze this more stable substrate. However, hydrolyses in the presence of **2** were successful at elevated temperature. In this instance, the residual activity of **2** was shown to result from the presence of low molecular weight polymer that remained in solution when high molecular weight **2** precipitated. It is known that high molecular weight polymer exhibits LCST behavior but that low molecular weight polymer does not. To show that low molecular weight polymer was present above **2**'s LCST, the terpolymer **2** was dissolved in water and heated to precipitate **2** and the aqueous phase was decanted. The aqueous phase was shaken with a solution of methyl red dye in toluene. If low molecular weight, acid-containing polymer were present it would protonate the methyl red, making it water soluble and resulting in the colorless aqueous phase turning pink. This indeed occurred. However, after washing the precipitated polymer five times with water, this test showed no acid remained in solution about the LCST. Under these conditions, no hydrolysis occurred at temperatures above **2**'s LCST. This result is significant in that it affirms the necessity of using high molecular weight washed PNIPAM derivatives to effect catalyst/reagent/substrate recovery or reaction regulation. Indeed, since these studies with **2** were carried out early in the project, the PNIPAM-bound phosphines or PNIPAM-bound substrates used above were repeatedly precipitated and washed with warm water before use.

Summary

The studies described here show how co- and terpolymers of *N*-isopropylacrylamide can be used to prepare recoverable "smart" catalysts and substrates. The facility of analysis of species attached to the polymer and some of the limitations of these polymers are discussed and described. Ongoing work in our group aims to further exploit these sorts of soluble polymers in combinatorial synthesis and catalysis chemistry.

Experimental Section

General Methods. All reagents and solvents were obtained from commercial sources and used without further purification unless otherwise stated. THF was distilled from sodium benzophenone ketyl. NIPAM was recrystallized from hexanes/benzene (10% benzene). Melting points were determined with a Thomas-Hoover Unimelt capillary melting point apparatus. Gas chromatographic analyses were performed on a Shimadzu instrument equipped with a 15-m SPB-5 (poly(5%-diphenyl-95%-dimethylsiloxane)) normal phase fused silica capillary column (0.53 i.d.). ^1H and ^{13}C NMR spectra were recorded on a Varian XL200E spectrometer at 200 MHz (50 MHz for ^{13}C) or on a Unity p300 at 300 MHz (75 MHz for ^{13}C). Chemical shifts are reported in ppm using HMDS (0.055 ppm) as an internal reference. ^{31}P NMR spectra were recorded on the Unity p300 at 121 MHz using H_3PO_4 (80%) as an external reference. Infrared spectra were recorded as thin films between sodium chloride plates or as pressed KBr pellets using a Mattson Galaxy 4021 FT-IR spectrometer at room temperature. The transmission spectra are reported in wavenumbers (cm^{-1}) and were recorded with a resolution of 2 cm^{-1}.

General Kinetics Procedure for Hydrogenation Reactions with PNIPAM-Bound Substrates. Hydrogenation reactions were carried out in a 250-mL, three-necked, round-bottomed flask fitted with a stopcock adapter fitted with a rubber septum, a stopcock adapter connected to an aspirator, and an adapter connected to a hydrogen gas buret with a leveling bulb. The gas buret had a three-way stopcock, which connected one arm to the reaction flask and the other to a manifold attached to a hydrogen gas cylinder. The reactions were run at atmospheric pressure and constant temperature in ethanol, water, or ethanol−water mixtures. In a typical reaction, 1 mmol of **11**, 0.1 g of the 5% Pt/C, and 50 mL of solvent and a magnetic stirrer were placed in a reaction flask. The system was closed and evacuated via the aspirator. After 5 min, the stopcock was shut and the system was filled with hydrogen. The system was evacuated and filled with hydrogen three times. After the last hydrogen intake, the system was purged with hydrogen for 15 min and opened to the gas buret. Stirring was started and the rate of the reaction was followed by measuring the uptake of hydrogen by the system. Upon completion of the reaction, the catalyst was recovered by filtering the mixture and washing the catalyst with small portions of the reaction solvent.

Poly(*N*-isopropylacrylamide-*c*-acrylic acid) (1). A three-necked flask equipped with a condenser was evacuated and flushed with N_2 three times. A solution of NIPAM (2.44 g, 22 mmol) in 25 mL of *tert*-butyl alcohol was added via syringe, followed by the addition of 0.14 mL (2 mmol) of freshly distilled acrylic acid via syringe. The solution was placed in an oil bath and heated. A solution of AIBN (30 mg, 0.2 mmol) in 2 mL of *tert*-butyl alcohol was added via syringe once the oil bath temperature reached 78 °C. The reaction was stirred at 78 °C overnight. The solvent was removed under reduced pressure, and the resulting solid was dissolved in THF and precipitated into hexanes to yield 2.5 g of the copolymer.

Preparation of *p*-Acrylamidobenzoic Acid (Comonomer for 3 and 9). *p*-Aminobenzoic acid (10 g, 72 mmol) in cold (0 °C) CH_2Cl_2 (100 mL) and acryloyl chloride (3.26 g, 36 mmol) were allowed to react in a literature procedure[36] to yield 5.5 g (80%) of the product amide as pale yellow crystals (recrystallized from acetone/H_2O); mp 222 °C (lit.[35] mp 218 °C); IR (KBr, cm^{-1}) 3306, 3139, 2677, 1671, 1610, 1409, 1297, 976; ^{1}H NMR (200 MHz, CD_3OD) δ 5.72 (q, 1H), 6.30 (m, 2H), 7.62 (d, 2H), 7.86 (d, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 120.4, 127.1, 128.8, 131.8, 132.1, 144.1, 166.4, 169.6.

Synthesis of *N*-Isopropylacrylamide/*p*-Acrylamidobenzoic Acid Copolymer (3 and 9). *N*-isopropylacrylamide (10.0 g, 88 mmol) and *p*-acrylamidobenzoic acid (0.841 g, 4.4 mmol) in *tert*-butyl alcohol (60 mL) were polymerized using AIBN initiation as described above. The product polymer (9.5 g) was dissolved in THF and was isolated by successive precipitations into hexane: IR (KBr, cm^{-1}) 3307, 3266, 3050, 2973, 2935, 2878, 1656, 1542, 1459, 1385, 1368, 1253, 1173, 1129; ^{1}H NMR (200 MHz, CD_3OD) δ 1.1, 1.6, 2.1, 3.95, 7.65, 7.96, 7.98.

Poly(NIPAM-*c*-NTBAM-*c*-AmMPSA) (4). A mixture of 1.26 g (11.1 mmol) of recrystallized NIPAM, 1.4 g (11 mmol) of NTBAM, and 2.3 g (11.1 mmol) of AmMPSA was copolymerized with AIBN initiation in *tert*-butyl alcohol as described above. The white, crusty solid polymer product isolated after solvent removal was dissolved in methanol and reprecipitated into ether. The dissolution and reprecipitation step was repeated one time. The resulting white powder was dried in vacuo giving 4.00 g (81% yield) of the terpolymer: ^{1}H NMR δ 1.0 (br s, 4 H), 1.2 (br s, 7 H), 1.4 (br s, 8 H), 1.9 (br s, 3 H), 3.2 (br s, 2 H), 3.75 (br s, 1 H). Integration showed that the ratio of NIPAM:NTBAM:AmMPSA in the product polymer was approximately 1.4:1.0:1.3, according to NMR spectroscopic analysis.

Poly(*N*-isopropylacrylamide-*c*-*N*-acryloxysuccinimide) (5). Preparation of the PNIPAM-*c*-NASI copolymers and derivatization of these copolymers with amines follows an established procedure.[24] The commercial NIPAM was recrystallized before use from hexane:benzene (10:1). We have made a series of such copolymers. For the reactions described below, we used a 10:1 (NIPAM:NASI) copolymer. The product copolymer **5** (15 g) was purified by repeatedly dissolving in THF (~250 mL) and precipitating into hexanes (~700 mL). The final product was put on a high vacuum system for 24 h to yield the pure copolymer: IR (KBr, cm^{-1}) 2970 and 2920 (C−H stretch), 1818, 1785 (imide peaks), 1735 (C=O of ester), 1652 (amide I), 1532 (amide II); ^{1}H NMR (300 MHz, D_2O) δ 1.15 (br s, 6H), 1.40−2.09 (m, 3H), 2.93 (br s, 0.4H), 3.96 (br s, 1H). We found that the ratio of the two monomers in the final coopolymer product (^{1}H NMR spectroscopy) is in accord with the ratio of monomers in the feed. The M_v was determined to be 8.7×10^5 Da using values of 9.59×10^{-3} and 0.65 for K and α, respectively, in THF at 30 °C.[24]

Modification of PNIPAM-*c*-NASI. Modification of this copolymer with an amine was carried out by stirring the copolymer with excess amine in THF for 24 h. Subsequent addition of isopropylamine or ammonia and further stirring for 4 h ensured that all of the NASI groups were consumed—a supposition that was verified by ^{1}H NMR spectroscopy and by IR spectroscopy.

Preparation of *p*-Acrylamidophenol (Comonomer for 8). Following a literature procedure,[37] *p*-aminophenol (10 g, 92 mmol) in acetone (150 mL) was allowed to react with acryloyl chloride (4.57 g, 50.5 mmol). The product amide was isolated in 65% yield (5.3 g) as a white powder: mp 187−189 °C (lit.[37] mp 193 °C); IR (KBr, cm^{-1}) 3306, 3161, 1657, 1629, 1598, 1444, 1222; ^{1}H NMR (200 MHz, acetone-d_6) δ 5.65 (q, 1H), 6.37 (m, 2H), 6.79 (d, 2H), 7.55 (d, 2H); ^{13}C NMR (50 MHz, acetone-d_6) δ 115.8, 121.8, 126.1, 132, 132.7, 154.4, 163.5.

Synthesis of *N*-Isopropylacrylamide/*p*-Acrylamidophenol Copolymer (8). *N*-isopropylacrylamide (2.5 g, 22 mmol) and *p*-acrylamidophenol (0.18 g, 1.1 mmol) in *tert*-butyl alcohol were copolymerized with AIBN initiation as described above. The polymer isolated after solvent removal (2.5 g) was purified by successive precipitations from a THF solution into hexane: ^{1}H NMR (300 MHz, CD_3OD) δ 1.15, 1.6, 2.1, 3.95, 6.7, 7.4, 7.6, 7.98. Further purification of this polymer was accomplished by successive precipitations of the product polymer from water at 45 °C (above **8**'s LCST). This process removes low molecular weight polymer that likely results from chain transfer.

Preparation of Benzyl Alcohol-Functionalized Poly(*N*-Isopropylacrylamide) (10a). To a solution of 2 g of PNIPAM-*c*-AA (26:1) in 50 mL of chloroform under nitrogen in a dry flask was added 1,1′-carbonyldiimidazole (0.227 g, 1.4 mmol) and 4-aminobenzyl alcohol (0.172 g, 1.4 mmol). The solution was stirred for 17 h, at which time the solvent was removed under reduced pressure. Warm water (30 mL, ~35 °C) was added to the obtained solid and then gently decanted. This rinsing procedure was repeated four times. The solid was then dried under vacuum for 12 h. The solid was dissolved in THF (40 mL) and precipitated from hexane (200 mL). The polymer was filtered off, washed three times with hexane, twice with benzene, and three times with hexane, and dried under vacuum to give 1.94 g of a white powder: ^{1}H NMR (300 MHz, CD_3OD) δ 1.1, 1.59, 2.1, 3.95, 4.6, 7.1, 7.6, 8.0.

Preparation of Benzyl Alcohol-Functionalized Poly(*N*-Isopropylacrylamide) (10b). Copolymer **10b** was obtained by reaction of PNIPAM-*c*-NASI with excess 2-amino-1-phenylethanol. The copolymer product was dissolved in THF and purified by successive reprecipitations of a THF solution using hexane and diethyl ether: ^{1}H NMR (CD_3COCD_3) δ (1.13, 1.4−2.3, 2.5−2.8, 3.5, 4.0, 7.3.

Synthesis of *N*-Isopropylacrylamide/*N*-*m*-Nitrophenylacrylamide Copolymer (11). *N*-Isopropylacrylamide (5.0 g, 44 mmol) and *N*-(*m*-nitrophenyl)acrylamide (0.421 g, 2.2 mmol) in *tert*-butyl alcohol (30 mL) were copolymerized with AIBN initiation. The residual material isolated after solvent removal was dissolved in THF (15 mL) and precipitated by pouring the solution into hexane (250 mL). The polymer (5.11 g) was purified by successive precipitations from a THF solution by pouring into hexane: IR (KBr, cm^{-1}) 3433, 3307, 3061, 2932, 2874, 1659, 1461, 1385,1367, 1173; ^{1}H NMR (200 MHz, CD_3OD) δ 1.1, 1.6, 2.1, 3.95, 4.6, 7.6, 7.9, 8.7; ^{13}C NMR (50 MHz, CD_3OD) δ 22.8, 36.1, 42.5, 44.5, 116, 119, 126, 141, 150, 176.

Synthesis of PNIPAM-Phosphine (12). PNIPAM-*c*-NASI **5** (5 g) was dissolved in 150 mL of THF and 0.75 g of (3-aminopropyl)diphenylphosphine in 10 mL of THF was added under N_2. The mixture was stirred at room temperature for 5 h, and an excess of NH_3 (saturated aqueous solution) was added to quench any unreacted active succinimide groups. The mixture was again stirred at room temperature for 5 h, and any precipitate was removed by centrifugation. The product polymer was then purified by precipitating the polymer with excess hexane. Two such reprecipitations yielded a polymer that we then used in the chemistry below. IR spectroscopy showed that this phosphine-containing polymer **12** did not have any succinimide groups (no signals at 1810, 1780, and 1735 cm^{-1}). The polymer **12** had a poor quality ^{1}H NMR ($CDCl_3$) spectrum with broad peaks at 1.13, 1.20−2.30, 2.60, 3.70, 4.00, and 7.30−7.41 ppm. However, the ^{31}P NMR spectrum of **12** ($CDCl_3$) cleanly showed a broad singlet at δ −15.5 ppm and a very minor peak (<5%) at δ 34 ppm (which corresponds to the phosphine oxide).

Synthesis of PNIPAM-Phosphine (13). A similar procedure as described above for making **12** was used, except that dioxane was used as the solvent and the reaction was run at 100 °C for 15 h under argon. A ^{31}P NMR spectrum of **13**

($CDCl_3$) had a broad singlet at −19.7 ppm and a very minor peak (less than 5%) at 37.0 ppm (corresponding to the phosphine oxide).

Attachment of 10-Undecylenic Acid to Benzyl Alcohol-Functionalized Poly(*N*-Isopropylacrylamide) (15). In a dry 100-mL round-bottomed flask was placed 1.87 g of **10a**, 10-undecylenic acid (0.368 g, 2.0 mmol), and 50 mL of EtOAc/DMF (8:3). The flask was purged with N_2, and the solution was cooled to 0 °C. DCC (0.413 g, 2.0 mmol) was then added, and the resulting mixture was stirred for 1 h at 0 °C. The solution was allowed to return to room temperature and stirred for 18 h. The solution was filtered, washed with EtOAc/DMF, and then cooled in an ice bath for 20 min. Any additional precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The polymer product residue was dissolved in THF (35 mL) and the polymer precipitated from hexane (220 mL). The solid was filtered off, washed with hexane, and dried under vacuum. Warm water (30 mL, ∼35 °C) was added to the obtained solid and then gently decanted. This rinsing procedure was repeated four times. The solid was then dried under vacuum for 12 h. The solid was dissolved in THF (40 mL) and precipitated from hexane (220 mL). The polymer was then filtered off, washed three times with hexane, twice with benzene, and three times with hexane, and dried under vacuum to give 1.78 g of a white solid (**25**): ^{1}H NMR (300 MHz, D_2O) δ 1.1, 1.59, 2.1, 3.95, 4.3, 4.9, 5.8, 7.1, 7.3, 7.7, 8.0.

Synthesis of (PNIPAM-PPh_2)$_4$Pd(0) (18). A solution of **12** (250 mg) in 20 mL of 90:10 THF:H_2O was prepared under N_2. A solution of Pd(0)$(dba)_2$ (25 mg, 0.044 mmol) in 10 mL of the same solvent was also prepared under N_2. After we ensured that all of the Pd(0) precatalyst had dissolved (ca. 5 min), the precatalyst solution was added to the polymer solution using a double-tipped needle and N_2 pressure. Within ca. 5 min the resulting solution changed from dark purple to golden yellow. The solution was then allowed to stir for an additional 15 min. After this time, ca. 70 mL of petroleum ether was added, under N_2, to the polymer solution, precipitating **12** as a golden yellow solid. The light yellow supernatant was then removed, leaving the polymer catalyst ready for dissolution and use in aqueous solution.

Synthesis of (PNIPAM-PPh_2)$_3$RhCl (19). A solution of **12** (75 mg) in 40 mL of 90% EtOH was prepared under nitrogen. To this was added a solution of $[RhCl(C_2H_4)_2]_2$ (8 mg, 0.0086 mmol) in 1 mL of dioxane. The resulting light yellow solution was used for hydrogenations after stirring under N_2 flow for approximately 15 min.

Synthesis of Ionically Bound PNIPAM-PTA (21). The purified copolymer **4d** (4.5 g) was dissolved in water and 0.288 g of PTA[30] (1,3,5-triaza-7-pyhosphatricyclo[3.3.1.1^{3,7}]decane) was then added to this solution under N_2. The solution was stirred at 25 °C for 20 min, and then the resulting copolymer **21** was collected by raising the temperature to above 50 °C. The ^{31}P NMR spectrum of **21** (D_2O) had a single peak at −91 ppm (PTA itself has a singlet at −98 ppm in D_2O).

General Procedure for the Synthesis of PNIPAM-Bound Cationic Rh(I) Catalysts 20 and 22. A mixture of 8.0 mg (16 μmol) of $[Rh_2Cl_2(COD)_2]$ and 8.0 mg of AgOTf were dissolved in 2 mL dioxane:water (10:1 v:v) under argon. The resulting AgCl precipitate was removed by centrifugation. The yellow solution was transferred by forced siphon into a water solution containing the PNIPAM-bound phosphine ligand (35 μmol of monophosphine or 17.5 μmol of bisphosphine). The mixture was stirred for 15 min, and the yellow solution was used immediately for hydrogenations.

General Procedure for Hydrogenations Using PNIPAM-Bound Cationic Rh(I) Catalysts. A Schlenk reaction flask with an adapter leading to a H_2 gas buret was purged with H_2 for 10 min. Then 35 mmol of allyl alcohol and the cationic Rh(I) catalyst described above were introduced. Water was added to this flask so that a total volume of 50 mL of reaction solution was reached. The temperature of the reaction was controlled through an ice bath or an oil bath. Measurement of the H_2 uptake volume at a constant stirring rate was used to follow the rate of the hydrogenation. The H_2 uptake volume for a given amount of catalyst used in 1 h was used in rate comparisons. To confirm that hydrogenation occurred, an aliquot of the reaction mixture was taken and analyzed by GC.

Carbon−Carbon Coupling Reactions by PNIPAM-Bound Pd(0) Catalyst (18). 2-Iodophenol (2.2 g, 10 mmol), 1.03 g (10 mmol) of phenylacetylene, and 2.6 g of triethylamine were dissolved in 20 mL of THF:water (80:20 by volume) and added to a reaction flask that had 30 mL of a solution of PNIPAM−Pd(0) **18** (0.05 mmol in Pd) in THF:water (80:20 by volume) under argon. The reaction was stirred for 5 min and then 50 μmol of CuI was added to this solution. The reaction temperature was raised to ca. 50 °C, and the reaction was stirred at this temperature for 8 h. After cooling to 25 °C, adding 100 mL of hexane to this solution led to precipitation of PNIPAM−Pd(0) catalyst. The precipitate was collected by filtration and could be reused in a fresh reaction mixture. The solution was collected, washed with brine (3 × 20 mL), and dried over $MgSO_4$. After the solvent was removed, the pure product was obtained by column chromatography (silica gel, hexane:ethyl acetate = 10:1) in 78% yield, mp 117−118 °C (lit.[38] mp 118−119 °C). ^{1}H ($CDCl_3$): δ 7.02 (s, 1H), 7.23−7.60 (m, 7H), 7.84−7.88 (m, 2H). ^{13}C ($CDCl_3$): δ 101.1, 111.3, 120.9, 122.9, 124.3, 124.9, 128.5, 128.8, 129.2, 130.5, 154.8, 155.9.

Synthesis of *N*-Isopropylacrylamide/*p*-Acrylamidophenol Copolymer-Bound CBz-Glycine (24). Into a dry 100-mL round-bottomed flask was placed 2.03 g of **8**, CBz-glycine (0.428 g, 2.04 mmol), and 50 mL of EtOAc/DMF (8:3). The flask was purged with nitrogen, and the solution was cooled to 0 °C. DCC (0.423 g, 2.1 mmol) was then added, and the resulting mixture was stirred for 1 h at 0 °C. The solution was allowed to return to room temperature and stirred for 18 h. The solution was filtered, washed with EtOAc/DMF, and then cooled in an ice bath for 1 h. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (25 mL), and the polymer was precipitated by pouring this solution into hexane (175 mL). The solid was recovered by filtration, washed with hexane, and dried under vacuum. Warm water (30 mL, ∼35 °C) was added to the obtained solid and then gently decanted. This rinsing procedure was repeated four times. The solid was then dried under vacuum for 12 h. The solid was dissolved in THF (40 mL) and precipitated from hexane (200 mL). The polymer was then collected by filtration, and washed three times with hexane, twice with benzene, and three times with hexane, and dried under vacuum to give 1.94 g of a pale yellow powder: ^{1}H NMR (300 MHz, CD_3OD) δ 1.1, 1.59, 2.1, 3.95, 5.1, 6.73, 7.35, 7.62, 8.0.

Synthesis of Copolymers (16) and (17). In a procedure similar to that described above, copolymers **16** and **17** were obtained by the coupling reactions of copolymers **10a** or **10b** with excess BOC-glycine and DCC. ^{1}H NMR (300 MHz, CD_3OD): copolymer **16**, δ 1.13, 1.45, 1.5−2.3, 4.0, 5.2, 7.28, 7.54; copolymer **17**, δ 1.14, 1.46, 1.5−2.4, 3.95, 5.1, 7.43.

Hydrogenolysis of *N*-Isopropylacrylamide/*p*-Acrylamidophenol Copolymer-Bound CBz-Glycine. Hydrogenolysis of an aqueous solution of CBz-glycine bound to copolymer **8** was accomplished using 10% Pd/C at atmospheric pressure. H_2 uptake was observed at 7 °C, indicating that hydrogenolysis occurred. Hydrogenolysis of **24** was confirmed by ^{1}H NMR spectroscopy of the polymer product. The polymer product was recovered by heating the reaction mixture to 40 °C, filtering the precipitate, and washing with warm water (40 °C). The precipitate was then dissolved in MeOH and the catalyst removed by filtration. The solvent was evaporated from the filtrate under reduced pressure to yield a crude product, which was characterized by ^{1}H NMR spectroscopy ((300 MHz, CD_3OD) δ 1.12, 1.6, 2.1, 3.6, 3.95, 6.73, 7.35, 7.62, 8.0). The amino acid was easily cleaved from the polymer support by basic hydrolysis. When a similar reaction was carried out at 42 °C (above the polymer's LCST), no H_2 uptake was seen and no hydrogenolyzed product was seen in ^{1}H NMR spectroscopy of the product polymer.

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