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Articles

Palladium-Catalyzed C−C Coupling under Thermomorphic Conditions

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Abstract: Liquid−liquid biphasic systems that exhibit an increase in phase miscibility at elevated temperature together with soluble polymer-bound catalysts that have a strong phase preference at ambient temperature are described. In such systems, product isolation and catalyst recovery are effected by a liquid/liquid separation. This report describes the use of such thermomorphic catalyst recovery systems for palladium-catalyzed carbon−carbon bond forming reactions. Poly(*N*-isopropylacrylamide) (PNIPAM)-bound phosphine ligands with a Pd(0) catalyst used previously in allylic substitution chemistry are efficient catalysts in Heck, Suzuki, and sp−sp^2 cross-coupling reactions. Air-stable tridentate SCS-Pd(II) catalysts bound to PNIPAM or poly(ethylene glycol) (PEG) are also described. A particular advantage of these SCS catalysts is that no precautions against adventitious catalyst oxidation need be taken with the polymer-bound SCS-PdCl catalysts, thus avoiding time-consuming solvent purification and degassing protocols.

Introduction

The use of polymer supports in catalysis has traditionally relied on a solid−liquid separation to achieve catalyst recovery and product isolation. Such chemistry typically uses cross-linked polymer supports (e.g., a Merrifield or Wang resin) or soluble polymer supports that may be either precipitated from solution[1−3] or isolated via membrane filtration.[4] Catalyst recovery in such systems depends on a filtration process (a solid/liquid separation or permselective membrane). Liquid−liquid separations that are more often used in ordinary organic purification procedures are less often used in polymer-supported chemistry. Nonetheless, liquid/liquid biphasic systems are known to be useful in catalysis. Three examples include phase transfer catalysis,[5] the Shell Higher Olefin Process (SHOP) for the production of α-olefins from ethylene,[6] and the Rhône-Poulenc process for the hydroformylation of propylene.[7] In the first of these examples, the reagent resides in the polar aqueous phase. In the second example, a nonpolar product phase separates from a polar catalyst-containing phase. In the third case, the catalyst resides in the polar aqueous phase. Biphasic catalysis schemes such as these enable catalyst recovery and product isolation through a liquid/liquid separation. Two new strategies for biphasic catalysis—fluorous biphasic chemistry and thermomorphic chemistry—have been highlighted as new options for facile product isolation and catalyst separation and reuse where polymer supports can be useful.[8] These schemes provide many of the same features of aqueous biphasic catalysis but should be more accommodating for typical organic substrates that may not be soluble in water. This report details the use of the latter of these strategies in the development of recoverable catalysts for Pd-catalyzed C−C bond formation.

Fluorous biphasic catalysis was first introduced by Horváth and Rábai[9] and further elaborated by Curran, Gladysz, Leitner, and van Koten among others.[10−14] The success of this chemistry has increased interest in biphasic systems that can combine the activity of homogeneous catalysis with the simplicity of product isolation seen in a biphasic system. Some recent work with fluorinated catalysts has also focused on the use of supercritical CO_2 as a solvent, expanding the library of potential substrates and useful reactions that may be conducted.[15−17]

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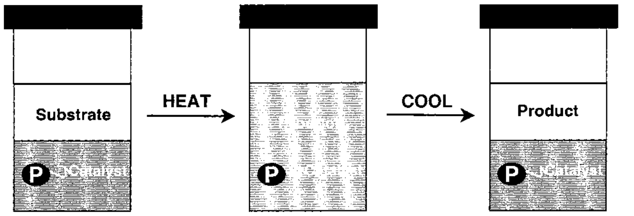


Figure 1. Schematic representation of thermomorphic catalysis. Selective solubility of the polymer support under biphasic conditions ensures quantitative catalyst recovery.

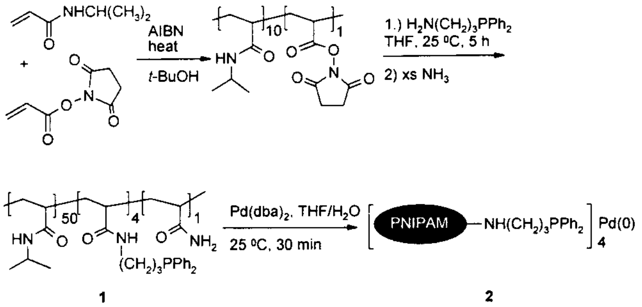


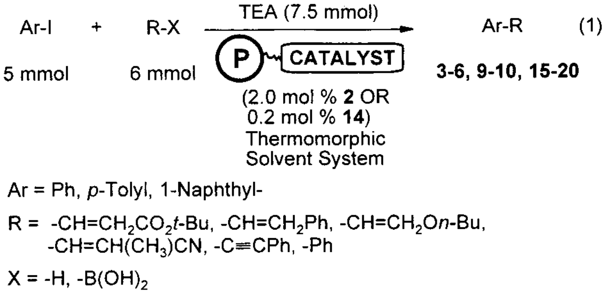
Figure 2. Synthesis of a PNIPAM-bound phosphine and subsequent conversion to (PNIPAM-PPh$_2$)$_4$Pd(0), **2**.

The idea that polymer supports can serve as phase traffic control agents is the essence of the original Merrifield approach for peptide synthesis. This same idea underlies all our work with soluble polymers.[18] We have shown that fluorinated polymers are generic supports for fluorous reagents and catalysts, that amphiphilic polymers serve as water-soluble supports at the right pH, and that polymers with temperature-dependent solubility are useful in both water and aqueous systems.[19,20]

The biphasic catalyst recovery scheme we termed thermomorphic catalysis (Figure 1) can also use a soluble polymer to facilitate catalyst recovery and separation from products.[21] The separation in these systems relies on two ideas. The first is that many binary and ternary solvent systems exhibit a reversible increase in miscibility with increasing temperature. For example, in some systems an originally biphasic mixture becomes miscible and monophasic with mild heating. Such systems have precedence in organometallic chemistry[22] and were also described in the original fluorous paper by Horváth and Rábai.[9] There are also ample precedents for these systems in the literature.[23] The second idea is that a soluble polymer should have a strong phase preference for one phase under biphasic conditions. This leads to a general way to separate a product from a homogeneous catalyst and to recover the catalyst by a simple liquid/liquid-phase separation followed by solvent removal to isolate the product. A preliminary report demonstrated these concepts with Rh(I)-catalyzed hydrogenation and Pd(0)-catalyzed allylic substitution reactions. This paper extends this thermomorphic catalysis to include two important palladium-catalyzed carbon−carbon bond forming reactions, the Heck and Suzuki couplings, other polymers, and other solvent systems. These reactions employ either a poly(*N*-isopropylacrylamide) (PNIPAM)-bound phosphine ligand or a polymer-supported tridentate SCS-Pd catalyst. The use of the latter catalyst represents a significant simplification of reaction protocol. The work described here also shows that complete miscibility of the phases is not required and in some cases may even impede reactions.

Results and Discussion

Pd(0)-Catalyzed Reactions Using PNIPAM-PPh$_2$ under Thermomorphic Conditions. Our initial efforts were focused on the straightforward extension of the Pd(0)-catalyzed reactions previously described[21] to include the carbon−carbon bond-forming processes shown in eq 1. The PNIPAM-bound phosphine **1** (Figure 2) was prepared using reported chemistry[20d] and was then converted to the Pd(0) catalyst **2** via a ligand exchange reaction with a palladium precatalyst, Pd(0)(dba)$_2$.



Using 2 mol % (PNIPAM-PPh$_2$)$_4$Pd(0) and triethylamine (TEA) as the base, iodobenzene was treated with either *tert*-butyl acrylate (Heck reaction), phenylboronic acid (Suzuki reaction), or phenylacetylene. In addition to the Pd(0) catalyst, 5 mol % CuI cocatalyst was used in the cross-coupling reaction. These reactions were conducted in the same heptane/90% aqueous EtOH thermomorphic system used previously. GC analysis showed that these reactions were complete within 48 h at 70 °C. After each reaction, the system was allowed to cool to room temperature, inducing phase separation. Removal of the heptane phase and solvent evaporation furnished the ^{1}H NMR pure products **3**−**5**. Catalyst recycling was achieved for **3** and **4** by adding a fresh heptane solution of the reactants and reheating the system to 70 °C for an additional 48 h. The isolated yields increased each cycle, becoming virtually quantitative in the third cycle. Table 1 summarizes these results.

In the course of studying these reactions, it was found that styrene reacted with iodobenzene only slowly in the heptane−aqueous ethanol mixture. Careful repetition of this experiment indicated that adventitious catalyst oxidation was not the problem in this case. The problem instead is that the monophasic

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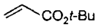
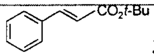
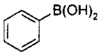
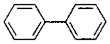
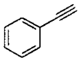
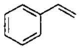
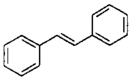
Table 1. Thermomorphic C−C Coupling Reactions Catalyzed by $(\text{PNIPAM-PPh}_2)_4\text{Pd}(0)$ (**2**)[a]

Acceptor	Product	1st Cycle	2nd Cycle	3rd Cycle
	 **3**	71%	89%	>99%
	 **4**	89%	95%	98%
	 **5**	87%[b]	-	-
	 **6**[c]	99%[d]	99%[d]	98%[d]

[a] All reactions were run in 1:1 (v/v) 90% EtOH/C7 with PhI at 75 °C using 2 mol % catalyst and TEA as the base and all yields are for product isolated from the heptane phase unless otherwise noted. [b] 5 mol % CuI was added and recycling experiments were not run for this reaction. [c] This reaction was run in 1:1 (v/v) DMA/C7 at 90 °C. [d] GC yields.

solvent mixture is a poor solvent. Using 2 mol % $(\text{PPh}_3)_4\text{Pd}(0)$ with TEA as the base at 75 °C, it was found that the reaction is approximately four times faster in a polar aprotic solvent such as *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA) than in solvents such as aqueous ethanol or aqueous ethanol/heptane mixtures at 90 °C. This finding was consistent with previous work on solvent effects in the Heck and related reactions[24] and suggested that better rates would be obtained using **2** in a thermomorphic system with DMF or DMA as one of the solvent components.

DMA and heptane are immiscible at room temperature and are miscible in all proportions above 65 °C.[23] To study the potential utility of a DMA/heptane system for thermomorphic catalysis, we first synthesized a PNIPAM-bound methyl red dye **7** (Figure 3). Using this polymer-bound dye, we observed that the polymer was evenly distributed throughout the system under monophasic conditions and resided only in the DMA phase at room temperature. A 1:1 (v/v) mixture of these solvents is therefore exactly analogous to the 90% EtOH/C7 thermomorphic system. We then used 2 mol % of **2** to catalyze the reaction between iodobenzene and styrene in DMA/heptane. Under these conditions, we observed complete conversion to **6** after 48 h at 90 °C. Recycling of this reaction was also successful; each of 3 cycles achieved complete conversion as shown in Table 1.

Pd(II)-Catalyzed Reactions Using PNIPAM-SCS-PdCl under Thermomorphic Conditions. Although the recycling experiments described above using **2** were successful, this phosphine-ligated Pd(0) catalyst is air-sensitive. Care must be taken to avoid a steady deactivation of the catalyst via adventitious oxidation during recycling.[20e] This is a practical limitation for catalyst recycling that could be avoided by the use of a more stable tridentate sulfur−carbon−sulfur (SCS) Pd(II) catalyst.[25] Such palladacycles are thermally and oxidatively robust. At 120 °C in DMF solution, they catalyze the Heck reaction between a number of aryl iodides and acceptor alkenes in air; these catalysts can also readily be bound to poly(ethylene glycol) (PEG). Such PEG-bound SCS catalysts could be recovered by solvent precipitation.

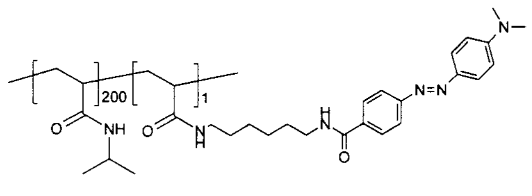


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Figure 3. The PNIPAM-bound Methyl Red dye used in preliminary thermomorphic distribution experiments. The synthesis of PNIPAM-MR has been previously reported.[20a]

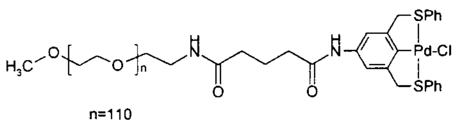

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Figure 4. The poly(ethylene glycol)-supported SCS-PdCl catalyst used in initial thermomorphic C−C coupling reactions. The synthesis of **8** has been previously reported.[25]

The use of an air-stable SCS-Pd(II) catalyst instead of **2** would simplify the reaction protocol involved in thermomorphic catalysis. Thermomorphic catalyst recovery and recycling of these SCS-Pd(II) catalysts would also avoid the need for large amounts of a poor solvent to precipitate the polymer-bound catalyst after each cycle. To study the feasibility of PEG-bound catalyst recovery under thermomorphic conditions, we modified commercially available monomethoxy PEG so that it contained a terminally bound methyl red dye (PEG-MR). This derivative of commercially available PEG contained a significant low molecular weight, heptane-soluble fraction based on the coloration of the upper heptane phase that was seen after several heating−cooling cycles. However, this heptane-soluble fraction of commercially available PEG could be removed simply via continuous liquid−liquid extraction of a 50:50 $\text{EtOH}/\text{H}_2\text{O}$ solution of this polymer with heptane. Repeating the synthesis of PEG-MR with the extracted PEG and subjecting it to the same dye distribution experiment furnished qualitative evidence for its recovery under thermomorphic conditions; no color was observed in the upper phase of a 90% EtOH/C7 system even after several heating−cooling cycles.

The synthesis of PEG-bound SCS-Pd catalyst **8** (Figure 4) has been previously reported[25] and was repeated using an extracted PEG substrate to furnish a catalyst that we could quantitatively recover under thermomorphic conditions. However, solvent effects similar to those observed with **2** precluded the use of **8** for Heck catalysis in 90% EtOH/C7. Moreover, when **8** was dissolved in pure DMA, addition of heptane resulted in a system that was monophasic at room temperature. Poly(ethylene glycol) evidently lowers the critical solution temperature (CST) of this system from 65 to ≤25 °C. However, addition of 10% H_2O (v/v) to the DMA phase (i.e., using 90% aqueous DMA) does produce a biphasic system at 25 °C. While this 90% aqueous DMA/C7 system did not completely miscibilize at any temperature below 100 °C, a significant change in relative phase volume was observed for a 1:2 (v/v) 90% DMA/C7 mixture at 95 °C.

Thus, 0.2 mol % of **8** readily catalyzed the Heck coupling of various aryl iodides and acceptor alkenes in 1:2 (v/v) 90% DMA/C7 at 95 °C with TEA as the base. Reactions with *tert*-butyl acrylate were complete within 10 h; those with styrene were complete within 20 h. All of the reactions with **8** were run in an air atmosphere without any precautions against catalyst oxidation. No catalyst degradation or decrease in rate was

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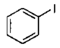
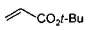
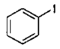
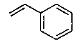
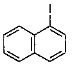
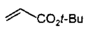
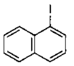
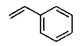
(25) (a) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531. (b) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287. (c) Dupont, J.; Beydon, N.; Pfeffer, M. *J. Chem. Soc., Dalton Trans.* **1989**, 1715. (d) Spencer, J.; Pfeffer, M.; Kyritsakas, N.; Fischer, J. *Organometallics* **1995**, *14*, 2214. (e) Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881.

Table 2. Thermomorphic Heck Coupling Reactions Catalyzed by PEG-SCS-PdCl (**8**)[a]

Aryl Iodide	Acceptor	Product	1st Cycle	2nd Cycle	3rd Cycle
		3	53%	80%	>99%
		6	50%	75%	97%
		9	80%	>99%	>99%
		10	36%	80%	>99%

[a] All reactions were run in 1:2 (v/v) 90% aqueous DMA/C7 at 95 °C using 0.2 mol % **8** and TEA as the base in an air atmosphere. Reactions with *tert*-butyl acrylate were complete within 10 h; those with styrene were complete within 20 h. All yields are for product isolated from the heptane phase.

observed over the three cycles for each reaction. Simply removing the upper heptane phase after reaction and evaporating the solvent achieved product isolation. Adding a fresh heptane solution of the reactants and reheating the system for the required time effected catalyst recycling. After drying under vacuum, all the isolated products were pure single isomers by ^{1}H NMR and ^{13}C NMR spectroscopy. As noted for previous reactions, isolated yields improved with each cycle, generally becoming quantitative by the third cycle. Table 2 summarizes these results. An advantage of this air-stable catalyst is the simplicity of the reaction setup. Since all manipulations could be performed in an air atmosphere, the setup time for each reaction was just a few minutes. Conversely, reactions with the air-sensitive catalyst **2** generally required significant time for setup using standard Schlenk techniques.

The results using **8** show that the polymer support can affect thermomorphic behavior. As described above, **8** induced room temperature miscibility of a DMA/C7 system; addition of water as a cosolvent was used to induce formation of a biphase. While catalyst recycling with **8** was successful in the resulting ternary solvent mixture, other polymer supports whose structure would be more tunable and that could be used in nonaqueous thermomorphic systems were of interest to us. Our success in using the PNIPAM-supported catalyst **2** in the nonaqueous DMA/C7 system prompted us to investigate the use of PNIPAM as a support for SCS-Pd catalysts as well.

The synthesis of a PNIPAM-SCS-PdCl catalyst is depicted in Figure 5. Synthesis of 3,5-bis(phenylthiomethyl)aniline has been previously described.[25] Coupling of this material to *N*-Boc-6-aminocaproic acid was accomplished using 1,1′-carbonyldiimidazole (CDI) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as acylation catalysts. Subsequent deprotection of **11** yielded the amine-terminated SCS ligand **12**. Immobilization of this ligand was then achieved by allowing a 10:1 copolymer of *N*-isopropylacrylamide (NIPAM) and *N*-acryloxysuccinimide (NASI) to react with 0.8 equiv of **12**. The remaining active ester groups were then quenched with NH_3 in MeOH to yield a terpolymer having a 50:1:4 ratio of *N*-isopropylacrylamide, acrylamide, and tethered SCS ligand groups (**13**). Our prior work has shown that substituting another amine for the NH_3 (or by changing the isopropyl group of the NIPAM) allows us to tune polymer solubility. The ^{1}H NMR and ^{13}C NMR of this material were completely analogous to those for the low molecular weight ligand **12**. Palladation of **13** was then achieved using $Pd(PhCN)_2Cl_2$ in refluxing CH_3CN to yield the PNIPAM-bound SCS-Pd(II) catalyst **14**. While the ^{1}H NMR spectrum of **14** was indeed analogous to that for the low molecular weight counterpart, its ^{13}C NMR spectrum was more informative; it clearly showed a peak at δ 149.73 representing the C−Pd bond of the SCS catalyst moiety. Figure 6 shows a selected region of the ^{13}C NMR spectra for **13** and **14**.

While methyl red analogues of **14** were soluble in DMA/C7, the Pd(II)-SCS-catalyst **14** precipitated from a 1:1 DMA/C7 system on heating. The precipitated polymeric catalyst **14** was not active. The polymeric catalyst **14** redissolved in the DMA phase on cooling and we concluded that the problem was due to the insolubility of the catalyst-containing polymer and not catalyst degradation. Evidently the SCS-PdCl catalyst moiety significantly alters the solubility of the PNIPAM polymer support in the heated homogeneous mixture of pure DMA and heptane even though the catalyst loading is only 7%. Fortunately,

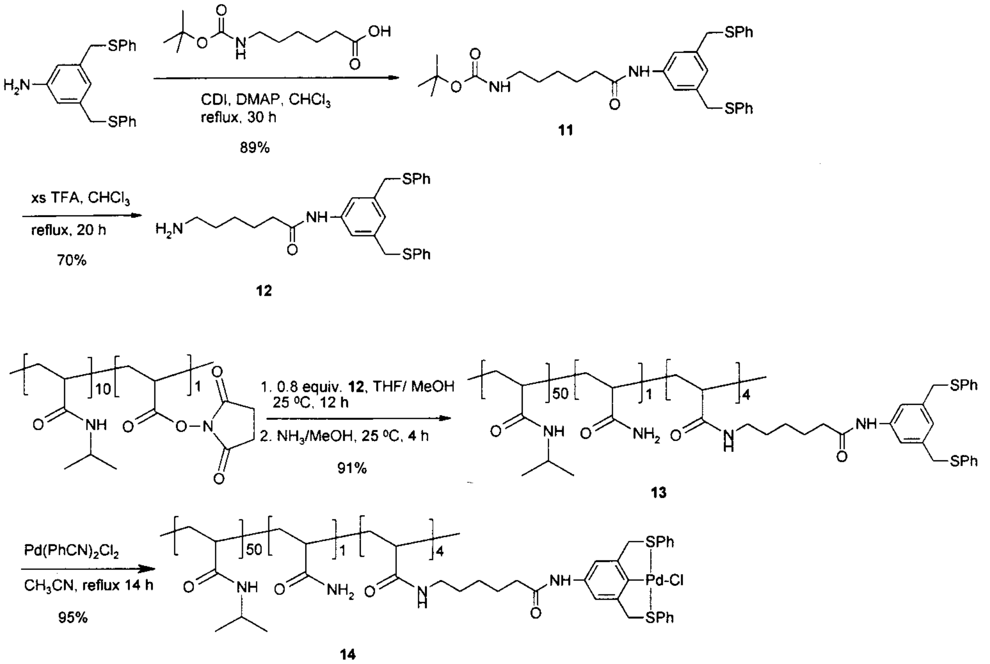


Figure 5. Synthesis of the air-stable PNIPAM-bound SCS-Pd(II) catalyst, **14**.

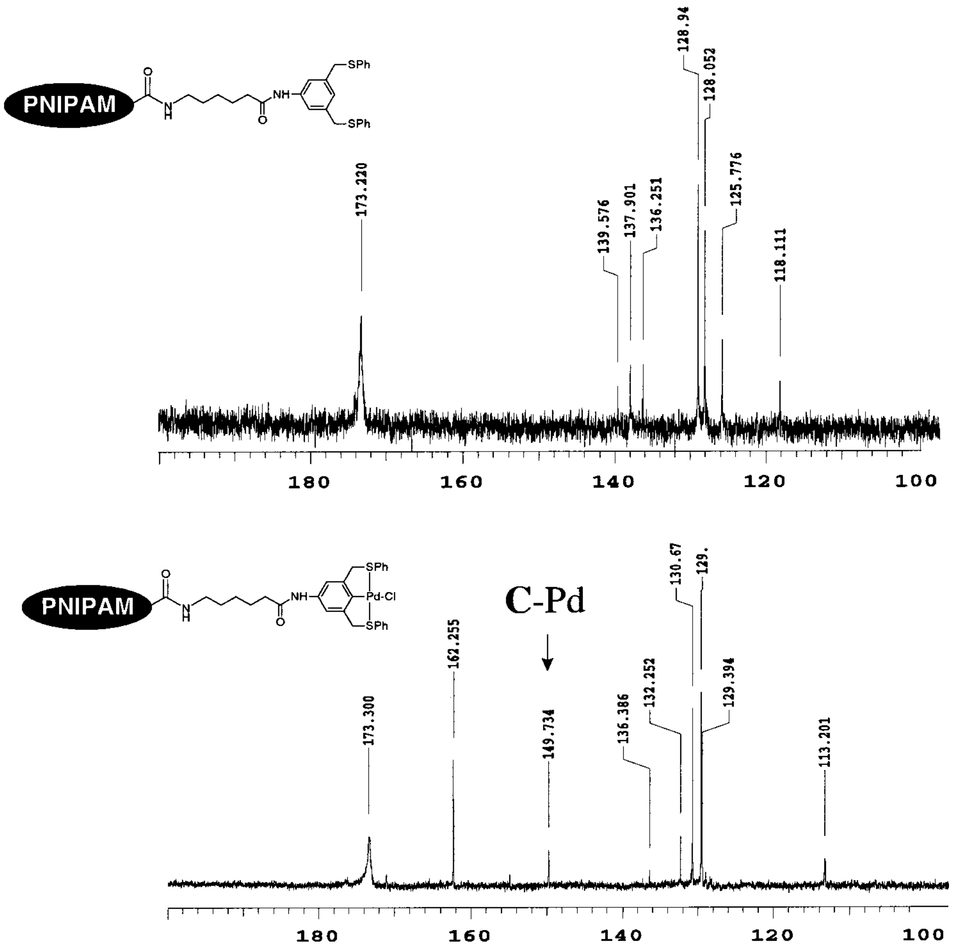


Figure 6. Selected region of the ^{13}C NMRs of PNIPAM-SCS, **13**, and PNIPAM-SCS−PdCl, **14**. Both of these spectra are analogous to those for low molecular weight analogues.[25]

the use of DMA containing 10% water (v/v) in place of pure DMA (i.e., using 90% aq. DMA) prevented this polymer precipitation. Subsequent catalytic reactions with **14** were therefore conducted in solvent mixtures composed of 90% aqueous DMA and heptane.

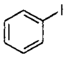
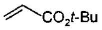
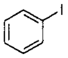
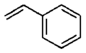
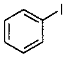
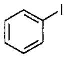
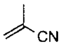
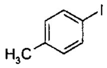
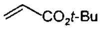
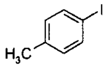
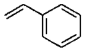
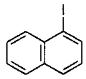
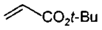
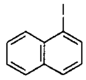
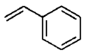
Catalytic experiments using 0.2 mol % of **14** for the Heck coupling of various aryl iodides and acceptor alkenes in 1:2 (v/v) 90% aqueous DMA/C7 at 95 °C using TEA as the base were carried out at reaction times that were comparable to those used with **8** (10−20 h). Thermomorphic reactions with **14** displayed no sensitivity to oxygen; no catalyst degradation was observed, even after five cycles (Table 3, first entry). Product isolation and catalyst recycling were as efficient as with **8**. All the isolated products were pure single isomers by ^{1}H NMR and ^{13}C NMR spectroscopy, except for **15** and **16**, which were mixtures of isomers. Table 3 summarizes these results.

The PNIPAM-supported SCS-Pd complex **14** also catalyzed Suzuki coupling reactions. For example, reaction of various aryl iodides with phenylboronic acid under identical conditions (0.2 mol % of **14**, TEA, 95 °C) yielded biphenyls **4**, **19**, and **20**. All of these reactions achieved complete conversion within 20 h. A significant feature of the results illustrated in Table 4 is that the isolated yields of the biphenyl products in this DMA/C7 system were lower in the first few cycles because of dissolution of the product in the polar DMA phase. High isolated yields were, however, reached within four or five cycles.

Conclusions

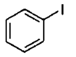
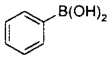
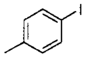
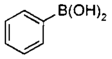
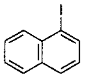
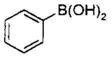
In summary, palladium-catalyzed carbon−carbon bond-forming reactions were successful under thermomorphic conditions. The use of a thermomorphic solvent system in conjunction with a selectively soluble polymer support like PEG or PNIPAM allowed for facile product isolation and catalyst recycling. While effective catalyst recycling was achieved with the phosphine-ligated Pd(0) catalyst **2**, use of an air-stable tridentate SCS-Pd(II) catalyst greatly simplified reaction protocol. Initial work with the PEG-supported catalyst **8** was frustrated by the presence of a significant heptane-soluble fraction in the commercially available polymer and the induced miscibilization of DMA and heptane in the presence of PEG. Successful thermomorphic catalysis was, however, achieved by extractive purification of the PEG support and through the use of water as a cosolvent for the reactions. In fact, the use of a 90% DMA/C7 system demonstrated that complete miscibility of the two phases is not a requirement for acceptable reaction rates. Changing to a PNIPAM-supported catalyst resulted in a different solubility problem; **14** precipitated from DMA/C7 under monophasic conditions, effectively halting reaction. However, this was also overcome by employing a 90% DMA/C7 thermomorphic system and subsequent Heck and Suzuki reactions proceeded with quantitative catalyst recycling. These results serve not only to expand the repertoire of useful reactions that may be conducted under thermomorphic conditions but also begin to demonstrate the flexibility of this catalyst recovery technique. Further refinement of these systems via alternative polymer supports and solvent systems should lead to a nonaqueous thermomorphic catalyst system as well as access to a wider variety of substrates and increased early cycle yields and we are currently working toward these goals.

Table 3. Thermomorphic Heck Coupling Reactions Catalyzed by PNIPAM-SCS-PdCl (**14**)[a]

Aryl Iodide	Alkene	Product	1st Cycle	2nd Cycle	3rd Cycle	4th Cycle
		**3**	80%	98%	>99%	>99%[b]
		**6**	52%	>99%	>99%	-
		**15**	43%	91%	95%	99%
		**16**	10%	43%	68%	85%
		**17**	82%	90%	>99%	-
		**18**	79%	87%	96%	-
		**9**	64%	99%	>99%	-
		**10**	50%	65%	85%	-

[a] All reactions were run in 1:2 (v/v) 90% aqueous DMA/C7 at 95 °C using 0.2 mol % **14** and TEA as the base in an air atmosphere. All reactions were complete in under 10 h, except those involving styrene; these required up to 20 h for completion. All yields are for product isolated from the heptane phase. All products were the trans isomer, except **15** (a 3:1:1 mixture of *Z*, *E*, and internal isomers by ^{1}H NMR) and **16** (a 2:1 mixture of *Z* and *E* isomers by ^{1}H NMR). [b] Five cycles were run for this reaction; the 5*th* cycle isolated yield was also quantitative.

Table 4. Thermomorphic Suzuki Coupling Reactions Catalyzed by PNIPAM-SCS-PdCl (**14**)[a]

Aryl Iodide	Acceptor	Product	1st Cycle	2nd Cycle	3rd Cycle	4th Cycle	5th Cycle
		**4**	32%	55%	70%	77%	92%
		**19**	43%	60%	72%	90%	-
		**20**	56%	70%	>99%	>99%	-

[a] All reactions were run in 1:2 (v/v) 90% aqueous DMA/C7 at 95 °C using 0.2 mol % **14** and TEA as the base in an air atmosphere. All reactions were complete within 20 h. All yields are for product isolated from the heptane phase.

Experimental Section

General. All reagents and solvents were obtained from commercial sources and were generally used without further purification. However, the commercially available monomethoxy PEG (M_n = 5000) contained a significant low molecular weight, heptane-soluble fraction, which was removed before use by continuous liquid−liquid extraction of a 50% aqueous ethanol solution of the polymer with heptane. 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 ID). ^{1}H NMR spectra were recorded on Varian VXR-300 or Unity p300 spectrometers at 300 MHz. Chemical shifts are reported in ppm with either tetramethylsilane (TMS, 0.0 ppm) or hexamethyldisiloxane (HMDS, 0.055 ppm) as internal standards. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ or DMSO-d_6 as the internal reference. The syntheses of **2**,[21] **8**,[25] and 3,5-bis(phenylthiomethyl)aniline[25] have been reported previously.

Synthesis of *N*-3,5-Bis(phenylthiomethyl)phenyl-(*N*′-boc-6-amino)caproamide (11). To a solution of 3,5-bis(phenylthiomethyl)-aniline (0.501 g, 1.43 mmol) and *N*-Boc-6-aminocaproic acid (0.529 g, 2.29 mmol) in 30 mL of $CHCl_3$ was added 1,1′-carbonyldiimidazole (0.373 g, 2.30 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.176 g, 1.44 mmol). The resulting homogeneous solution was refluxed for 30 h. After reaction, the $CHCl_3$ solution was washed with 10 M NaOH (2 × 15 mL), 5% HOAc (2 × 15 mL), and brine (1 × 20 mL). The organic phase was then dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was then purified by column chromatography (silica gel, 1:1 hexane/EtOAc) to yield 0.717 g (89%) of **11** as a white solid material after drying under vacuum: ^{1}H NMR ($CDCl_3$) δ 1.34 (m, 2 H), 1.41 (s, 9 H), 1.60−1.71 (m, 4 H), 2.27 (t, 2 H), 3.07 (br q, 2 H), 4.00 (s, 4 H), 4.63 (br s, 1 H), 6.93 (s, 1 H), 7.10−7.23 (m, 10 H), 7.41 (s, 2 H), 7.73 (s, 1 H).

Synthesis of *N*-3,5-Bis(phenylthiomethyl)phenyl-6-aminocaproamide (12). To a solution of **11** (0.940 g, 1.67 mmol) in 20 mL of $CHCl_3$ was added trifluoroacetic acid (0.32 mL, 4.18 mmol). The resulting homogeneous solution was heated to reflux for 20 h. After this time, TLC (silica gel, 1:1 hexane/EtOAc) showed complete deprotection of **11**. Amberlyst-15 (8.0 g), cleaned according to a reported procedure,[26] was added to the reaction solution and the resultant mixture shaken at ambient temperature for 16 h. The mixture was then filtered and the Amberlyst-15 washed with 35 mL each of hexane, THF, and MeOH. The resin was then added to a 4.0 M solution of NH_3 in MeOH. This heterogeneous mixture was then shaken at room temper-

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(26) Liu, Y.-S.; Zhao, C. X.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471.

ature for 6 h. After this time the mixture was then filtered and the solvent removed from the filtrate under reduced pressure. The resulting residue was dried under vacuum to yield 0.61 g (80%) of pure **12** as a pale yellow oil: ^{1}H NMR (CDCl$_3$) δ 1.30−1.51 (m, 4 H), 1.67 (m, 2 H), 2.30 (m, 4 H), 2.69 (m, 2 H), 4.01 (s, 4 H), 6.95 (s, 1 H), 7.10−7.31 (m, 10 H), 7.41 (s, 2 H), 7.69 (s, 1 H).

Synthesis of 50:1:4 P(NIPAM-AM-SCS) (13). To a solution of 10:1 P(NIPAM-NASI) (351 mg, 0.270 mmol; prepared according to a published procedure)[20a] in 20 mL of 9:1 THF/MeOH was added **12** (100 mg, 0.216 mmol) and triethylamine (0.102 mL, 0.732 mmol). The resulting solution was stirred at ambient temperature for 12 h. Then, 10 mL of 4 M NH$_3$ in MeOH was added and the solution stirred for an additional 4 h at ambient temperature. The solvent was then removed from the reaction solution under reduced pressure. The residue was redissolved in 10 mL of THF and poured into 100 mL of hexanes, precipitating **13** as a white powder. This material was filtered, washed with further portions of hexanes, and dried under vacuum to yield 320 mg (91%) of **13**: ^{1}H NMR (DMSO-d_6) δ 0.95−1.20 (br, 60 H), 1.21−1.40 (br, 20 H), 1.80−2.10 (br, 10 H), 3.82 (br s, 10 H), 4.13 (br s, 3.2 H), 7.12 (br s, 0.8 H), 7.17−7.22 (br m, 8 H), 7.51 (br s, 1.6 H); ^{13}C NMR (DMSO-d_6) δ 22.29 (br), 25.13, 27.89, 29.01, 30.03, 36.70 (br), 50.09, 60.18 (br), 118.11, 125.78, 128.05, 128.94, 136.25, 137.90, 139.58, 173.22 (br).

Palladation of 50:1:4 P(NIPAM-AM-SCS) (14). A solution of **13** (1.06 g, 0.548 mmol SCS ligand) in 8 mL of DMF was prepared in a three-necked flask fitted with a condenser. The system was sealed and the air removed with a vacuum pump and then replaced with dry N$_2$. The flask was purged with N$_2$ for 30 min and then Pd(PhCN)$_2$Cl$_2$ (209.34 mg, 0.548 mmol) was added rapidly and the system resealed. The resulting dark red homogeneous solution was stirred at room temperature for 1 h and then refluxed for 14 h. After the reaction, the solution was filtered while hot to remove any insoluble material. The filtrate was then poured into 35 mL of diethyl ether, precipitating a yellow solid material. This solid was isolated by filtration and redissolved in 10 mL of THF. This THF solution was then poured into 50 mL of hexanes, again yielding a yellow precipitate. This precipitate was filtered again, washed with further portions of hexanes, and dried under vacuum to yield 1.01 g (95%) of the catalyst **14**: ^{1}H NMR (DMSO-d_6) δ 0.96−1.12 (br s, 60 H), 1.16−1.38 (br m, 20 H), 1.80−2.10 (br, 10 H), 3.80 (br s, 10 H), 4.71 (br s, 3.2 H), 7.41 (br s, 1.7 H), 7.39 (br m, 4.8 H), 7.78 (br m, 3.2 H); ^{13}C NMR (DMSO-d_6) δ 22.23 (br), 24.89, 26.03, 28.51, 36.29, 38.19 (br), 41.63 (br), 49.99, 66.92, 113.20, 129.39, 129.50, 130.67, 132.25, 149.73 (C−Pd), 162.25, 173.30 (br).

General Procedure for Thermomorphic Catalysis with 2. A solution of the aryl iodide (5 mmol), alkene (6 mmol), and triethylamine (7.5 mmol) in 20 mL of heptane was prepared and the flask sealed. The air in the flask was removed by vacuum pump and replaced with dry N$_2$. The solution was allowed to purge with N$_2$ for 15 min. Three pump−purge cycles were performed. This solution was then added via forced siphon through a cannula to a previously prepared, N$_2$ flushed (three pump−purge cycles) solution of **2** (0.1 mmol Pd; 0.25 mmol CuI was also added for the cross-coupling) in 20 mL of either 90% EtOH or *N*,*N*-dimethylacetamide. The resulting biphasic system was heated to either 75 or 90 °C, with stirring, to induce miscibilization. The reactions were monitored by gas chromatography and were generally complete within 48 h. After the system was cooled to ambient temperature to induce phase separation, the upper heptane phase was removed by forced siphon through a cannula into a N$_2$-flushed receiving flask. Removal of the solvent followed by drying of the residue under vacuum furnished the pure coupling products **3**−**5**. Catalyst recycling was effected by adding a fresh heptane solution of the reactants and reheating the system. Three cycles were run for each reaction except the cross-coupling. Occasionally, after the three cycles some accumulation of a black precipitate, presumably Pd metal, was observed. The products **3**−**5** are all known compounds.

General Procedure for Thermomorphic Catalysis with 8 and 14. A solution of either **8** or **14** (0.01 mmol of Pd; corresponding to 56 mg of **8** or 21 mg of **14**) in 5 mL of 90% aqueous DMA was prepared in a 30 mL screw-cap vial and a Teflon stirbar was added. Then, a solution of the aryl iodide (5 mmol), acceptor (6 mmol), and triethylamine (7.5 mmol) in 10 mL of heptane was added to the first solution and the tube sealed with the screw cap. For the Suzuki coupling reactions, phenylboronic acid (6 mmol) was first dissolved in the 90% DMA phase due to its low solubility in heptane. The tube was heated to 95 °C in an oil bath and the stirred reaction monitored by TLC (silica gel, heptane). After reaction, the system was cooled to ambient temperature, the upper heptane phase was removed by pipet, and the solvent was removed under reduced pressure. Drying of the remaining residue under vacuum provided the pure coupling products **3**−**4**, **6**, **9**−**10**, and **15**−**20**. Catalyst recycling was effected by adding a fresh heptane solution of the reactants (plus a fresh portion of phenylboronic acid to the DMA phase for the Suzuki reactions), resealing the system, and reheating to 95 °C. At least three cycles were run for all reactions. No catalyst decomposition or rate decrease was observed, even after five cycles. All of the products are known compounds and were isolated as pure single isomers, except **15** and **16**, which were isolated as mixtures of 3:1:1 *Z*/*E*/internal and 2:1 *Z*/*E* isomers (based on ^{1}H NMR spectroscopy), respectively. Selected spectral data are given below:

4-Methyl-*tert*-butyl cinnamate (17): ^{1}H NMR (CDCl$_3$) δ 1.50 (s, 9 H), 2.34 (s, 3 H), 6.29 (d, 1 H), 7.17 (d, 2 H), 7.39 (d, 2 H), 7.55 (d, 1 H); ^{13}C NMR (CDCl$_3$) δ 21.56, 28.35, 80.40, 119.20, 128.08, 129.71, 132.03, 140.43, 143.68, 166.61.

***β*-(*p*-Tolyl)styrene (18):** ^{1}H NMR (CDCl$_3$) δ 2.38 (s, 3 H), 7.05 (s, 2 H), 7.17 (d, 2 H), 7.23 (d, 1 H), 7.37−7.42 (m, 4 H), 7.46 (d, 2 H); ^{13}C NMR (CDCl$_3$) δ 21.44, 113.82, 126.59, 127.58, 127.86, 128.30, 128.47, 128.81, 129.04, 129.58, 134.71, 137.68

***β*-(1-Naphthyl)-*tert*-butyl acrylate (9):** ^{1}H NMR (CDCl$_3$) δ 1.90 (s, 9 H), 6.43 (d, 1 H), 7.42−7.50 (m, 3 H), 7.74 (d, 1 H), 7.84 (d, 2 H), 8.20 (d, 1 H), 8.43 (d, 1 H); ^{13}C NMR (CDCl$_3$) δ 28.51, 80.85, 123.06, 123.68, 125.14, 125.71, 126.41, 127.00, 128.95, 130.48, 131.66, 132.22, 133.91, 140.81, 166.48.

***β*-(1-Naphthyl)styrene (10):** ^{1}H NMR (CDCl$_3$) δ 7.19 (d, 1 H), 7.32 (m, 2 H), 7.42 (t, 2 H), 7.55 (m, 2 H), 7.62 (d, 2 H), 7.80 (q, 2 H), 7.91 (m, 2 H), 8.23 (d, 1 H); ^{13}C NMR (CDCl$_3$) δ 123.93, 124.07, 126.03, 126.17, 126.43, 127.02, 128.03, 128.12, 128.29, 128.37, 128.95, 129.08, 132.05, 134.05, 135.27, 137.89.

Biphenyl (4): ^{1}H NMR (CDCl$_3$) δ 7.36 (t, 1 H), 7.43 (t, 2 H), 7.59 (d, 2 H); ^{13}C NMR (CDCl$_3$) δ 127.35, 127.43, 128.94, 141.40.

4-Phenyltoluene (19): ^{1}H NMR (CDCl$_3$) δ 2.39 (s, 3 H), 7.22 (m, 3 H), 7.40 (d, 2 H), 7.48 (d, 2 H), 7.58 (d, 2 H); ^{13}C NMR (CDCl$_3$) δ 21.27, 126.99, 127.16, 128.90, 129.65, 136.86, 138.50, 141.34.

1-Phenylnaphthalene (20): ^{1}H NMR (CDCl$_3$) δ 7.37 (m, 5 H), 7.42 (m, 4 H), 7.78 (d, 1 H), 7.82 (d, 2 H); ^{13}C NMR (CDCl$_3$) δ 125.73, 126.12, 126.38, 127.29, 127.58, 127.99, 128.62, 128.89, 129.31, 130.43, 132.46, 134.14, 137.76, 140.59.

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