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Soluble Polymer-Supported Catalysts Containing Azo Dyes

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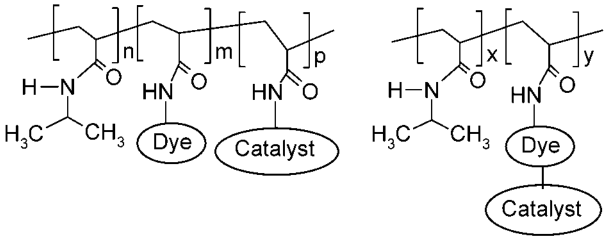
ABSTRACT



Azo benzene derivatives were incorporated into soluble polymer-bound catalysts by two different approaches. The first was to attach the dye to the polymer-bound catalysts, using the dye as an innocent spectator to study the phase preference, concentration, and recoverability of a catalyst. The second approach used an azo dye as a ligand to form an effective soluble polymer-bound Pd(II) catalyst for Heck reactions.

The separation step in organic synthesis and catalysis is of increasing importance in both academic and industrial chemistry. This is because using a "phase tag" for a substrate, reagent, or catalyst simplifies reaction workup, product isolation, and catalyst recovery. Such chemistry is important both in high throughput chemistry and in green chemistry.[1,2] Fluorous biphasic systems and supports,[3,4] aqueous biphasic systems,[5] soluble polymer supports,[6,7] and dendrimers[8] have all been used in this context. Small molecules such as "precipitons" or metal complexing groups can serve a similar purpose.[9,10] Here we describe the use of dye-labeled soluble polyacrylamide co- and terpolymers that provide a simple way to monitor separability, concentration, and recovery for both nonmetallic and metallic soluble polymer-bound catalysts.

Our group has used poly(*N*-isopropyl-acrylamide) (PNIPAM) as a soluble polymer support in synthesis and catalysis.[6,11,12] We have also prepared dye-labeled versions of polymers to monitor separation efficiency of polymers in biphasic or monophasic/biphasic/monophasic reaction schemes.[4,13] However, assays of catalyst recovery typically require additional work. For example, ICP analysis for residual metal from metallic catalysts is a sensitive and

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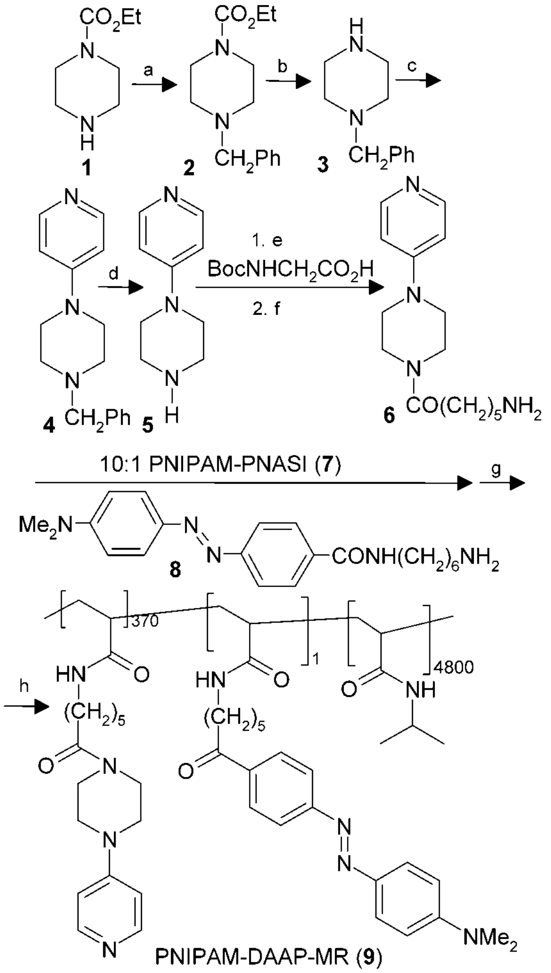
quantitative assay but it requires additional steps. Assays for nonmetallic catalysts and assays that monitor the catalyst stability independent of catalyst activity are more difficult, especially when catalysts are present at a few mol % or less. We show here that dye-labeled co- or terpolymers containing catalysts address these issues. A similar approach using colored dendrimers as supports in synthesis also recently appeared.[14]

To test our ideas, we chose to prepare a soluble polymer-bound version of 4-(dimethylamino)pyridine (DMAP), a commonly used organic base that has been previously attached to many soluble and insoluble polymer supports.[15,16] Using the method shown in Scheme 1, we prepared an analogue of DMAP and attached it to PNIPAM. The loading of the 4-dialkylaminopyridine catalyst on this polymer was ca. 8 mol %. The synthetic scheme was also designed to introduce ca. 0.02 mol % loading of an azo dye that serves as a colorimetric tag for the soluble terpolymer catalyst **9**.

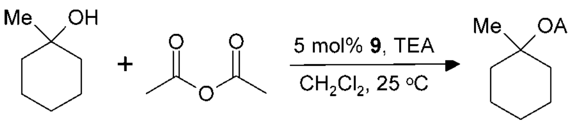
Scheme 1. Synthesis of PNIPAM-DAAP-MR[a]



[a] (a) $NaHCO_3$, $PhCH_2Cl$, 95% EtOH, reflux, 18 h, 99%; (b) KOH, MeOH, reflux, 69%; (c) 4-chloropyridine, xylene, reflux, 15 h, 93%; (d) 2 N HCl, H_2, Pd/C, MeOH, 35 psi, 99%; (e) DCC, CH_2Cl_2, 84%; (f) TFA, CH_2Cl_2, 68%; (g) CH_2Cl_2; (h) *i*-$PrNH_2$.

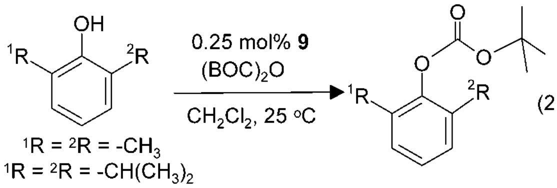
The catalyst loading in the PNIPAM-bound 4-dialkylaminopyridine-methyl red terpolymer **9** (PNIPAM-DAAP-MR) was determined by ^1H NMR spectroscopy. The dye loading was determined by UV analysis ($\lambda_{max} = 430$ nm) assuming the polymer-bound methyl red dye has the same extinction coefficient as **8**. The polymeric catalyst **9** is also designed so that it is predominately PNIPAM. Thus, its solubility mirrors that of the homopolymer PNIPAM. It is soluble in cold water and in many polar organic solvents but insoluble in hot water or in very nonpolar organic solvents (e.g., heptane). The polymer had a M_v of 6.3×10^5 (and an M_w of 1.2×10^6) and thus had a degree of polymerization like similar polymers studied earlier.[11]

The activity of **9** was quantitatively assayed using acylation chemistry typical for DMAP.[15] 1-Methylcyclohexanol reacts readily with acetic anhydride in the presence of 5 mol % **9** using triethylamine as the penultimate base in CH_2Cl_2, (eq 1). The initial rates for acylation of this tertiary alcohol using **9** were measured and compared to DMAP. Catalyst **9** is slightly less reactive than DMAP with rates that are about 60% as large as those for DMAP under the same conditions.



(1)

Catalyst **9** was also effective at relatively low catalyst loadings in acylation of hindered phenols. Kinetic studies of these reactions too showed similar activity relative to DMAP. For example, formation of the hindered 2,6-dialkylphenyl carbonates (eq 2) was examined, and **9** was about 54% as active as DMAP in this chemistry. Other phenols too were readily converted into carbonates with the exception of 2,6-di-*tert*-butylphenol, which was not reactive with **9** as a catalyst. 3,5-Di-*tert*-butylphenol was, however, readily acylated using **9** as a catalyst.



(2)

While the polymeric catalyst **9** was not as active as DMAP, it was fully recyclable. Recovery of polymers such as **9** can be effected in several ways. For example, when the 1-methylcyclohexanol reaction mixture was poured into hexanes, the polyacrylamide catalyst **9** precipitates. This precipitation is quantitative; UV analysis shows <0.1% of **9** remains in solution on the basis of the absence of a detectable absorptionfor the azo dye constituent in **9**. After

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filtration and isolation of the polymer, **9** could be redissolved in CH_2Cl_2 and used again. It was used through four cycles in eq 1 with no loss in activity. Complete retention of activity of the catalysts in these subsequent cycles was determined by comparison of the initial rates of each reaction with one another. An advantage of the catalyst **9** in these comparisons was that the small physical losses expected for filtration and handling of these catalysts (ca. 2% per cycle) do not obfuscate the analysis of catalyst recyclability since the amount of catalyst in each cycle can be easily and accurately quantified by UV spectroscopy.

Recycling of catalyst **9** in carbonate formation using dialkylphenols as substrates was also successful. Using solvent precipitation, catalyst **9** was recycled three times in eq 2 providing a 90% yield of both 2,6-dimethyl- and 2,6-diisopropylphenyl carbonate in each cycle (R = Me, 95%, 91%, 94%; R = ^{i}Pr, 91%, 93%, 89%). We have also been able to use alternative separation schemes (Figure 1) to recover these acylation catalysts.[13,17]

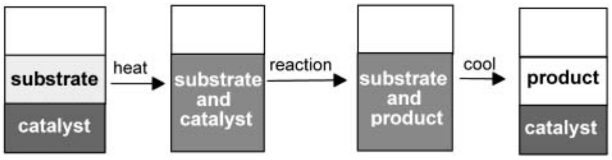


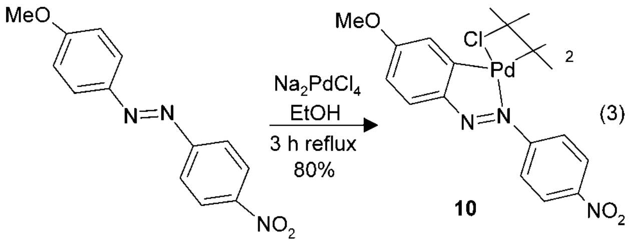
Figure 1. Thermomorphic catalysis using heptane insoluble **9.** The polymeric catalyst is separated as a *N*,*N*-dimethylformamide-rich phase. The heptane phase contains the acylation product.

Specifically, when we dissolved the catalyst **9** (5 mol %) in a liquid/liquid biphasic mixture of *N*,*N*-dimethylformamide (DMF) and heptane (C7) at 25 °C, we found that this polar poly(*N*-isopropylacrylamide)-bound catalyst dissolved selectively in the polar DMF-rich phase. However, **9** was also soluble in the homogeneous solvent mixture that resulted on heating this solvent mixture to 70 °C. On cooling of this thermomorphic mixture back to 25 °C, this catalyst stayed in the DMF-rich phase. The polymer was present in a resting biphasic mixture of heptane (C7) and dimethylacetamide (DMF) exclusively (>99.5%) in the DMF-rich phase as measured by UV analysis of the DMF- and C7-rich phases. This makes it possible to use **9** in a homogeneous reaction and to separate it with a liquid/liquid separation after the reaction. For example, when a substrate phenol and $({}^{t}Boc)_2O$ reagent were added to the DMF−C7 mixture containing **9** and the biphasic mixture was heated, a monophasic solution formed and **9** catalyzed the acylation of 2,6-dialkylphenols by $(Boc)_2O$. After 1 h, the mixture was cooled. The phases separated and the C7-rich phase (the nonpolar phase) containing the relatively nonpolar ^{t}Boc-derivative of 2,6-diisopropyl-phenol was separated from the catalyst-containing DMF-rich phase. Addition of fresh heptane and substrates with a second heating and cooling cycle allowed us to repeat the process. This process was successfully used five times using 2,6-diisopropylphenol in a DMF−heptane thermomorphic system. Similar chemistry using a 90% ethanol−water/heptane thermomorphic system produced >90% yields of phenyl carbonate in the fifth cycle using $(Boc)_2O$ with both phenol and 2,6-dimethylphenol. Our recent report shows that a similar scheme using *N*-octadecylacrylamide polymers allows us to recycle catalysts in a nonpolar phase; so extension of this chemistry should provide a way to recycle catalysts that form polar or nonpolar products.[13]

Titration of the 4-dialkylaminopyridine groups of **9** shows that the basic groups in this polymer have a pK_a of 9.7. This pK_a was estimated using the software program BEST[18] because polymer **9** is insoluble in water at pH values above 10. The same software and titrimetric analysis yielded a pK_a of 9.9 for DMAP, providing further evidence of the similarity of the DAAP groups in **9** to their low molecular weigh analogue DMAP. This experiment also shows that protonation/deprotonation and dissolution/precipitation is another way to recover this soluble polymeric catalyst.

Besides incorporating a dye into a polymer as an innocent bystander to facilitate studies of catalyst isolation/separation/reuse, we also used dyes as both labels and ligands. In this case, we took advantage of the fact that an azo arene dye can be designed to serve as a precursor of a Pd(II) catalyst ligand. Nitrogen-ligated palladacycles have been used previously in reactions such as aromatic C−H activation, aromatic hydroxylation and in carbon−carbon coupling reactions.[19] As shown below, a similar azo dye bound Pd(II) species is useful in Heck chemistry. In this case, the dye serves three roles. It serves as a ligand, as a reporter for catalyst/polymer recovery, and as a probe of catalyst stability.

O-Methyl 4-(4-nitrophenylazo)phenol, an azo dye with a strong electron-donating group on one aromatic ring and an strong electron-withdrawing group on the other, was chosen as a substrate for C−Pd palladation to avoid non-ring specific aromatic palladation. First, a low molecular weight catalyst, **10**, was prepared using the chemistry in eq 3. Then a similar azo dye ligand was prepared and coupled to either a poly(*N*-isopropylacrylamide) or a poly(*N*-octadecylacrylamide) polymer as shown in Scheme 2.



(3)

Catalyst **10** was shown to be active at 0.1 mol % in Heck chemistry using acrylate Heck acceptors and iodoarenes and

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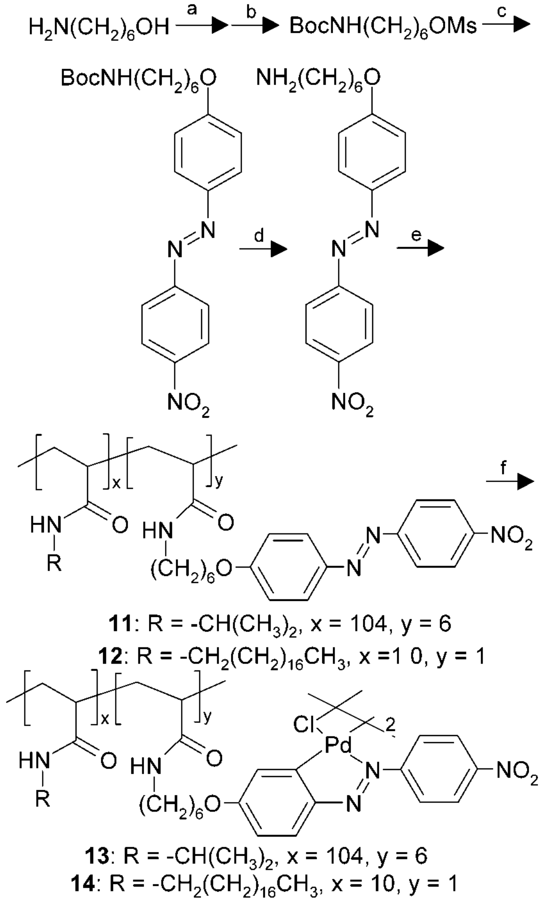
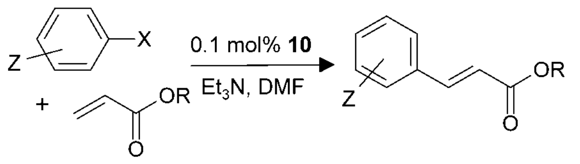
Scheme 2. Synthesis and Palladation of a PNIPAM-Bound Azo-Arene Dye[a]



[a] (a) $(Boc)_2O$, CH_2Cl_2, 12 h, 89%; (b) MsCl, CH_2Cl_2, TEA, 0 → 25 °C, 8 h, 89%; (c) $HOC_6H_4N{=}NC_6H_4NO_2$, K_2CO_3, acetone, reflux, 18 h, 72%; (d) TFA, 6 h, 83%; (e) for **10**: (i) TEA, PNIPAM-NASI, THF, 15 h, (ii) *i*-$PrNH_2$, 4 h, (iii) Amberlyst 15, THF, 6 h; for **11**: (i) PNODAM-NASI, TEA, THF, 15 h, (ii) 4 h, $C_{18}H_{37}NH_2$, (iii) Amberlyst 15, THF, 6 h; (f) for **12**: Na_2PdCl_4, EtOH, 3 h reflux, 98%; for **13**: Na_2PdCl_4, THF, reflux, 20 h, 99%.

activated bromoarenes as Heck donors and served as a model for polymeric catalysts (eq 4, Table 1). Polymer-bound



(4)

versions of **10**−**13** and **14** were also active Heck catalysts.

Table 1. Catalytic Activity of **10** in Heck Chemistry (eq 4)

X	Z	R	temp (°C)	time (h)	yield (%)
I	H	^{t}Bu	110	1	>99
I	H	^{t}Bu	60	14	99[a,b]
Br	Ac	Me	120	30	93
Br	CHO	Me	120	30	87
Br	H	Me	120	72	29[a]

[a] Conversion determined by GC using diglyme as an internal standard. [b] K_3PO_4 was used as the base.

As was true for **9**, recovery of these catalysts in one liquid phase of a thermomorphic solvent mixture could be easily assayed by UV spectroscopy. However, while polymer recovery was very high (>99.9%), we did observe a small amount of catalyst decomposition with **10**, **13**, or **14**. This makes these palladacycles less suitable than other recyclable Heck catalysts we have described.[13,20]

The polymeric azo dye ligands also proved useful in establishing the instability of these polymeric palladacycle Heck catalysts derived from azo dyes through repetitive cycles of Heck chemistry. Heating an azo dye-ligated palladacycle such as **10** for 24 h at 120 °C in DMF containing triethylamine led to significant decomposition (based on the observation of Pd(0) formation) and disappearance of the catalyst absorption peak at 498 nm. Thus, in this case, the polymeric azo dye not only ligates the catalyst and reports on the phase location of the polymer, it serves as a reporter for catalysts' instability.

In summary, by attaching UV-active compounds onto polymer-bound catalysts we have been able to obtain "visible catalysts". Such catalysts simplify development of new isolation and recovery procedures for catalysts and provide a simple probe to assay the extent of catalyst phase preference and recoverability.

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Supporting Information Available: Experimental details of the synthesis and use of the polyacrylamide catalysts and their use in acylation and Heck catalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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