A Synthesis of PEG- and Phosphorylcholine-Substituted Pyridines To Afford Water-Soluble Ruthenium Benzylidene Metathesis Catalysts

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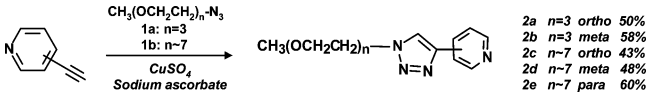
Several years ago we reported a synthesis of pyridine-terminated poly(ethylene glycol) (PEG) ligands, first for the preparation of water-soluble CdSe quantum dots[1] and later to afford water-soluble ruthenium benzylidene metathesis catalysts.[2] The latter topic is particularly important as aspects of preparative organic and polymer chemistry that utilize catalysis move to a lesser dependence on organic solvents. The PEGylated pyridines were prepared by Mitsunobu coupling[3] of 4-hydroxypyridine with PEG-diol or PEG-monomethyl ether. As the separation of the PEGylated ROMP catalysts from excess PEG ligand proved nontrivial,[2] we have been exploring alternative methods for PEGylation of pyridine to increase the applicability of these potentially valuable compounds, both for catalysis and in general. Here we report the synthesis of PEGylated pyridines by the copper-catalyzed azide−alkyne cycloaddition ("click") reaction,[4−8] and the use of these compounds to prepare catalysts suitable for aqueous ring-opening metathesis polymerization (ROMP), an area in which PEGylated catalysts have garnered considerable interest of late.[2,9−11]

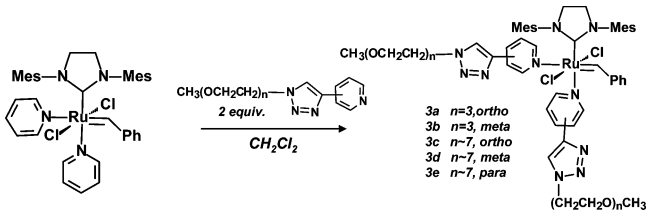
Synthesis of PEGylated Pyridines. The series of alkyne-substituted pyridines (purchased from Aldrich) shown in Scheme 1 was converted to PEGylated versions **2a**−**e** by click cycloaddition with azide-terminated PEG, using $CuSO_4$ and sodium ascorbate in 1:1 ethanol:water. The click reactions were followed by thin layer chromatography as well as infrared spectroscopy by monitoring the azide signal at 2100 cm^{-1} and the alkyne signal at 3200 cm^{-1}. PEGylated products **2a**−**e** were purified by column chromatography on silica gel. In the ^1H NMR spectra of $CDCl_3$ solutions of **2a**−**e**, the triazole proton is seen at ∼8.1 ppm and a triplet for the methylene group attached to the triazole at ∼4.6 ppm. Triazole signals in the ^{13}C NMR spectra appear at ∼144 and 123 ppm. Of the compounds represented in Scheme 1, **2c**−**e** containing n ∼7 are soluble in water.

Catalyst Synthesis and Characterization. As shown in Scheme 2, PEGylated pyridines of type **2** were used to functionalize the Grubbs-type ruthenium benzylidene catalyst. To a dichloromethane solution of the pyridine-functionalized ruthenium catalyst (prepared from the tricyclohexylphosphine-functionalized version purchased from Aldrich) was added the PEG-pyridine ligand (2 equiv of PEG-pyridine per ruthenium), and the desired conversion to **3** was achieved by repeated dissolution and application of vacuum to remove pyridine. The PEGylated ruthenium benzylidene products of type **3** were purified by flash chromatography over silica gel, eluting first with dichloromethane and then dichloromethane−methanol mixtures. The *meta*- and *para*-substituted versions proved more straightforward to isolate and characterize than the *ortho*-substituted **3a**. Compounds of type **3** are green waxy solids,

Scheme 1



Scheme 2



with good solubility in dichloromethane. Compounds **3d** and **3e**, containing PEG chains of average molecular weight 350 g/mol, are also soluble in water (>50 mg/mL) due to the significant PEG character provided by the ligands. In the example of *para*-substituted **3e** (Scheme 2) used in this work, the ^1H NMR spectrum recorded in $CDCl_3$ shows the benzylidene proton resonance at 19.2 ppm, while the ^{13}C NMR spectrum, also in $CDCl_3$, shows the carbene carbon at 317 ppm. Electrospray ionization (ESI) mass spectral analysis of **3e** (Supporting Information) supports a structure containing two PEG-pyridine ligands associated with the catalyst, with the expected breadth of signals (centered at ∼1513 g/mol) characteristic of the ligand. A weaker set of signals centered at ∼1045 g/mol represents the catalyst with one PEG-pyridine ligand, which could be a minor product of the ligand exchange procedure, or the result of ligand dissociation during the ESI measurement. Integration of the ^1H NMR spectrum of **3e** gave a 1:58 ratio of benzylidene-to-PEG methylene protons, further supporting the depicted structure. Unfortunately, the PEGylated catalysts could not be crystallized for structural analysis by X-ray diffraction.

Metathesis Chemistry with PEGylated Ruthenium Benzylidene Catalysts. The amphiphilic nature of PEG allows catalysts with n ∼7 to be used in both organic solvents and water. Using *para*-substituted **3e**, ROMP of oxanorbornene dimethyl ester **4** in dichloromethane proved very effective, giving fast initiation and, within minutes, polymer products of type **5**, in the ∼10−60 kDa range, with exceptionally low polydispersity indices (PDI, or M_w/M_n, of 1.1 or less) characteristic of Grubbs' generation III type (i.e., 3-bromopyridine substituted) ROMP catalysts.[12] The gel permeation chromatography traces of three such polymers run in THF and calibrated against polystyrene standards (and thus providing only estimates of polymer molecular weight) are shown in Figure 1.

PEGylated catalyst **3e** was evaluated for its ability to perform ROMP in aqueous solution with the PEGylated oxanorbornene monomer **6** under a variety of conditions (Figure 2 and Table 1). At room temperature and pH ∼1.5, complete conversion of **6** was achieved in less than 2 h, as judged by ^1H NMR spectroscopy recorded on aliquots removed from the reaction mixture. The PEGylated polyolefins shown as **7** were obtained with considerable molecular weight (>40 000 g/mol, as estimated by GPC in DMF using poly(methyl methacrylate) standards) and polydipsersity indices (PDIs) under 2. Attempted ROMP of **6** at pH 4 and 7 led to significantly lower conversion

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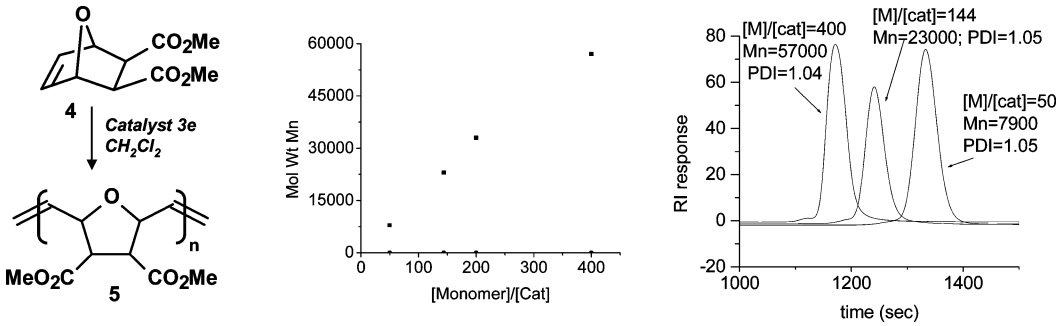


Figure 1. GPC-estimated number-average molecular weights (M_n) of polymer **5** as a function of monomer-to-catalyst ratio and GPC traces (in THF) of polymer **5** recorded on samples prepared using monomer-to-catalyst ratios of 50, 144, and 400.

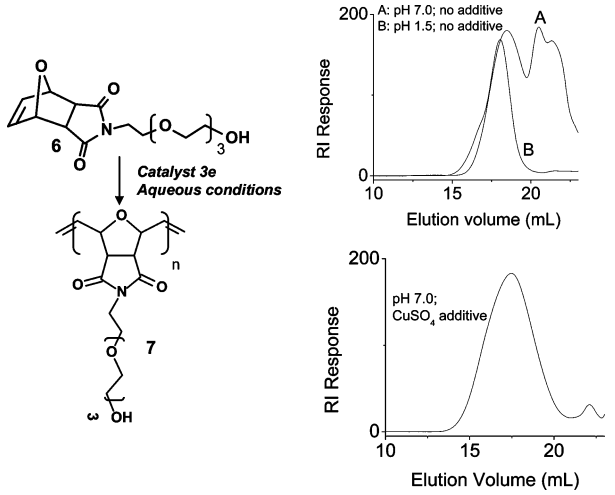


Figure 2. Comparative GPC chromatograms of polymer **7** obtained by ROMP of **6** at pH 7 and 1.5 (top) and with added copper (bottom).

(∼20−40%) and molecular weights and multimodal GPC traces. We rationalize this pH-dependent behavior as possibly stemming from dissociation of equilibrium-protonated pyridine from the metal center, which facilitates productive metathesis. Thus, ROMP in acidic aqueous solution proceeds more effectively than under neutral conditions. That the catalysts reported here lead to any metathesis at pH 7 is distinct from our prior study[2] on ether-linked PEG-pyridine functionalized ROMP catalysts. In that work, no monomer conversion at neutral pH was seen, presumably due in part to the higher basicity of the 4-ethereal pyridines relative to pyridine itself, precluding the ligand dissociation needed to initiate ROMP. In catalysts of type **3**, no substantial electronic substituent effect is imparted on the pyridine. Nonetheless, our observations that ROMP with catalysts of type **3** proceed most effectively in the presence of Bronstead acid will impede its use in conjunction with acid-sensitive monomers. Thus, we explored the addition of copper salts to the ROMP polymerization mixtures, under the presumption that competitive coordination of the pyridine ligands to copper would promote productive metathesis. When $CuSO_4$ or $CuBr_2$ was added to aqueous solutions of **6** with catalyst **3e** at pH 7, nearly 70% monomer conversion (as judged by ^{1}H NMR spectroscopy) was achieved, and PEGylated poly(oxanorbornene) **7** was produced with average GPC-estimated molecular weights over 50 000 g/mol and PDI values in the 1.3−1.5 range. Figure 2 compares GPC traces of polymer **7**, prepared under conditions that demonstrate the beneficial presence of H^+ and copper salts in the reaction mixture. The ability to perform aqueous ROMP at neutral pH, combined with the very simple synthesis of the water-solubilizing PEGylated ligands, is seen as advantageous for future work in aqueous ROMP as well as potentially other metathesis chemistries for the synthesis of small molecules (i.e., ring-closing metathesis and cross-metathesis).

Finally, while PEGylated ROMP catalysts are proving effective in aqueous environments, connecting different hydrophilic substituents to the pyridine ring was also considered. Here we use phosphorylcholine (PC) groups for the preparation of PC-azide **8**. In synthetic polymer chemistry, PC pendent groups have been exploited effectively in methacrylic polymers to provide water solubility and biocompatibility.[13] As shown in Scheme 3, reaction of 6-azidohexanol[14] with 2-chloro-1,3,2-dioxaphospholane 2-oxide (COP) is followed by ring-opening with trimethylamine to give **8**. Click cycloaddition of **8** with 4-alkynylpyridine gives PC-pyridine **9**, which is then used for functionalization of the ruthenium benzylidene catalyst in similar fashion to the PEG case described previously. PC-pyridine catalyst **10** was obtained in good yield as a green, hygroscopic powder that dissolves readily in water, dichloromethane, chloroform, and methanol. Characterization of **10** by electrospray ionization (ESI) mass spectroscopy revealed a peak corresponding to 1414.4 g/mol, in accord with the catalyst

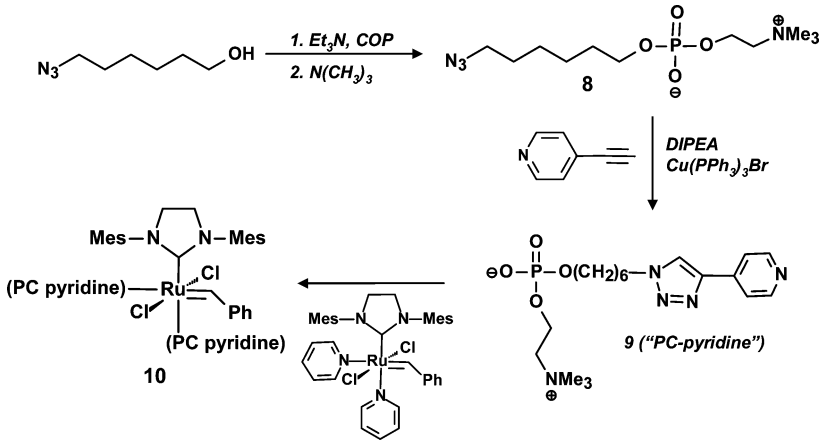
Table 1. ROMP of 6 Using Catalyst 3e

entry	pH	additive	monomer:catalyst ratio	monomer conversion	mol wt (g/mol) by GPC in DMF
1	1.5	none	10	quantitative	M_n 31 500; M_w 41 000; PDI 1.3
2	1.5	none	17	quantitative	M_n 63 800; M_w 120 000 PDI 1.9
3	1.5	none	34	quantitative	M_n 94 000; M_w 141 000; PDI 1.5
4	4	none	20	40%	M_n 2400; M_w 3700; PDI 1.5
5	7	none	20	23%	M_n 12 000; M_w 21 800; PDI 1.8
6	7	$CuSO_4$	20	70%	M_n 54 000; M_w 82 000; PDI 1.5
7	7	$CuBr_2$	20	70%	M_n 54 000; M_w 75 000; PDI 1.4

Table 2. ROMP of 6 Using Catalyst 10

entry	pH	additive	monomer:catalyst ratio	monomer conversion	mol wt (g/mol) by GPC in DMF
1	7.0	none	50:1	quantitative	M_n 9800; M_w 16 000; PDI 1.7
2	1.5	none	50:1	quantitative	M_n 11 100; M_w 18 700 PDI 1.7
3	7.0	$CuSO_4$	50:1	quantitative	M_n 17 800; M_w 28 200; PDI 1.6
4	7.0	none	20:1	quantitative	M_n 8400; M_w 13 800; PDI 1.6

Scheme 3



functionalized with 2 equiv of PC-pyridine ligand **9**; the benzylidene proton in the ^{1}H NMR spectrum of $CDCl_3$ solutions of **9** was seen at 19.2 ppm.

ROMP with PC-pyridine catalyst **10** in aqueous media was carried out in similar fashion as for PEG-pyridine catalyst **3e** by addition of catalyst to an aqueous solution of PEGylated oxanorbornene **6**. The polymerizations were run for 1−2 h, and the increase in molecular weight was monitored by aqueous GPC. The results of these experiments are summarized in Table 2. With monomer **6**, PC catalyst **10** gives quantitative monomer conversion in experiments performed at 20:1 and 50:1 monomer-to-catalyst ratios. Interestingly, this high conversion is observed in both neutral and acidic (pH 1.5) media, giving molecular weights comparable to those targeted and PDI values of 2 or less. While these preliminary experiments indicate that PC catalyst **10** may carry advantages over the PEGylated version **3e**, further experiments are needed to explore the scope and limitations of these hydrophilic ruthenium benzylidene compounds.

In summary, we report the preparation of ruthenium benzylidene catalysts made hydrophilic by PEG and PC substitution of the pyridine ligands that coordinate to the ruthenium metal. This approach is a convenient synthetic alternative to the procedure that integrates PEG into the N-heterocyclic carbene component of the catalyst structure.[9,11] Among the catalysts reported here, the *para*-substituted versions **3e** and **10** proved most convenient to prepare and effective for enabling ROMP of norbornene derivatives. Future studies will evaluate the scope and limitations of these catalysts with various hydrophilic cyclic olefins as well as ring-closing and cross-metathesis chemistry.

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Supporting Information Available: Experimental procedures and characterization. This information is available free of charge via the Internet at http://pubs.acs.org.

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