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Design and Application of Amphiphilic Polymeric Supports for Micellar Catalysis

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Summary: In this contribution, the synthesis and application of amphiphilic poly(2-oxazoline)s with covalently bound transition metal catalysts for reactions in aqueous media is described. In the first example, bipyridine moieties were introduced via living ring-opening polymerization of functionalized oxazoline monomers and the resulting block copolymers were used as macroligands for ATRP (atom transfer radical polymerization) using Cu(I)Br as active metal species. Furthermore, the fixation of a chiral biphosphane and its use for enantioselective hydrogenation of enamides is presented as well as the fixation of a ruthenium catalyst. The latter one is used for polymerization of diethyl dipropargylmalonate (DEDPM), and represents the first example of an alkyne polymerization using a ruthenium catalyst. In the case of the polymers stable latex particles were obtained

Keywords: ATRP; enantioselective hydrogenation; metathesis; micellar catalysis; poly(acetylene)s

Introduction

After the commercial breakthrough of the Rhone Poulenc process in the mid-eighties, water has become the solvent of choice for transition metal catalyzed reactions due to a variety of economical, ecological, and safety-related reasons.[1] The addition of low weight surfactants like SDS (sodium dodecylsulfates) makes it now possible to convert even highly hydrophobic substrates efficiently in aqueous medium.[2] However, a major disadvantage of micellar catalysis in this simple form, is the often difficult catalyst/product separation. A relatively new approach to this problem, which is inherent to homogenous catalysis, is the immobilization of metal

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complexes on soluble, amphiphilic block copolymers which gives easy access to virtually metal free products, while maintaining high activity and selectivity.

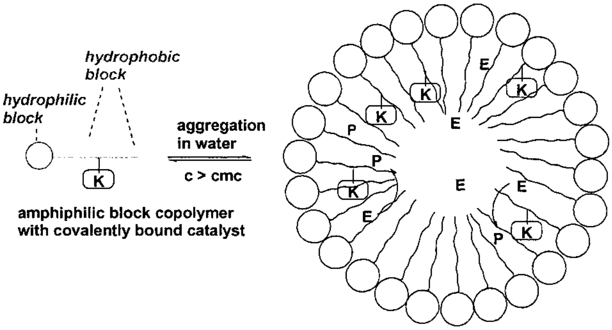


Figure 1. Basic principle of micellar catalysis using amphiphilic block copolymers (E = educt, P = product, K = catalyst).

In this presentation we report on the synthesis of highly defined and versatile amphiphilic polymer supports based on poly(2-oxazoline)s and their successful application in atom transfer radical polymerization (ATRP), enantioselective hydrogenation and metathesis reactions in water.

Choice of polymeric support

Whereas Brij and PEO-PPO based amphiphilic blockcopolymers are commercially available with a wide range of different molecular weights, the amphiphilic poly(2-oxazoline)s used by our group have to be prepared by living cationic polymerisation of 2-oxazoline monomers.[3]

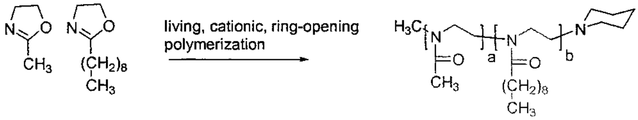


Figure 2. Synthesis of amphiphilic poly(2-oxazolin)e via living cationic polymerization (typical example).

The additional synthetic demand, however, is justified by a unique combination of properties of this monomer/polymer system:

- Highly defined polymer architectures are accessible in a straightforward way
- Exact characterization by means of solution spectroscopy (especially NMR) is possible
- High degree of synthetic flexibility via choice of oxazoline side-chain and sequential polymerization of different monomers
- Number, character and distribution of active groups (e.g. hydroxyl groups, acid groups or ligand functions) along the polymer chain can be easily adjusted to each specific application (whereas commercially available PEG based supports are only end-functionalized)
- In contrast to PEG based systems, amphiphilic poly(2-oxazoline)s remain quantitatively in the aqueous phase under two phase conditions or after extraction (as demonstrated by trace analysis for metal complex-functionalized polymers) allowing for easy catalyst/product separation without the need for expensive ultrafiltation membranes!

Two principal strategies were used by us to introduce ligands, respectively metal complexes into the polymers:

a) Copolymerization of specific monomers with pendant ligands or metal complexes.
b) Polymer analogous coupling reactions, by which the ligand is introduced after the polymerization.

In order to obtain suitable polymeric supports for method b) nucleophilic groups (e.g.-COOH or -OH) have to be protected during the cationic polymerization. Recently we could show that ester groups do not disturb the living character of the polymerization, allowing the simple two step procedure depicted in Figure 3 consisting of the 2-oxazoline polymerization followed by a hydrolysis which gives access to hydroxyl- and carboxylic acid functionalized supports.[4]

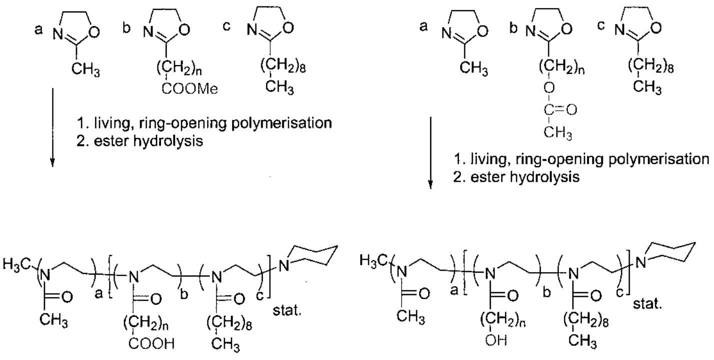


Figure 3. Simple access to versatile supports for polymer-analogous coupling reactions.

Direct and reverse ATRP[5]

Atom transfer radical polymerization (ATRP) has attracted considerable attention in the recent years as one of the most promising methods in the field of controlled radical polymerization as it can be applied to a variety of monomers yielding well-defined polymers.[6] However, one major drawback of this method is the metal catalyst remaining inside the polymer leading to coloured products. For this reason we investigated the application of micellar catalysis for copper catalyzed ATRP. The principal reaction equilibrium of ATRP is shown in Figure 4. In direct ATRP the polymerization is started with RX and the Cu(I) complex, while in reverse ATRP the equilibrium is approached from the right side by using a Cu(II) complex and creating the necessary radicals via conventional radical initiators.

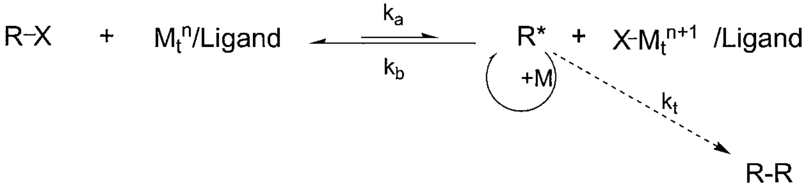


Figure 4. General reaction equilibrium of ATRP.

The equilibrium shown above leads to a very low concentration of free radicals which causes the polymerization (first-order kinetics) being favoured over termination (second-order kinetics). This provides the possibility to synthesize polymers with low polydispersities and to obtain blockcopolymers via a radical pathway and is the main motivation for many research activities. However, low concentration of radicals means that the polymerization rate is slow compared to common free radical polymerization. In addition to a possible catalyst separation it was the driving force of our work to avoid this drawback and achieve higher polymerization rates by separation of the reaction mixture into micelles as nanoreactors. The polymeric catalyst was synthesized via block copolymerization of 2-methyl-2-oxazoline and a 2-oxazoline bearing pendant bipyridine moieties.

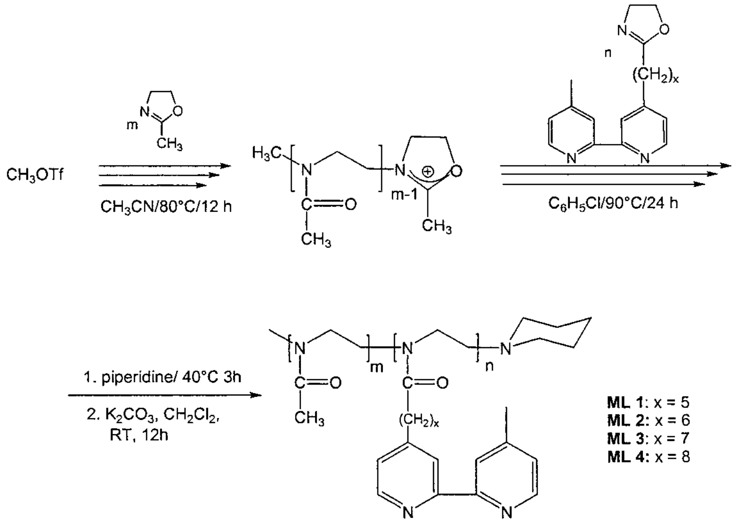


Figure 5. Macroligand synthesis by living cationic polymerization of 2-oxazolines.

These amphiphiles of type ML1 to ML4 were then applied to the ATRP in aqueous micellar system with methyl methacrylate (MMA) as monomer. It could be shown that the polymerization of MMA initiated with ethyl bromoisobutyrate (EBiB) and the polymeric copper complex $(Cu^{I}L_2)^{+}X^{-}$ is very efficient - almost quantitative conversion was observed at 60°C within 3 h.

These are quite mild reaction conditions compared to ATRP in homogeneous solution where temperatures around 90°C are typical for the polymerization of MMA. However, the system still needs further optimization since molar masses of the resulting polymers are higher than calculated but polydispersity indexes (PDI) around 1.7 are lower than in free radical polymerization. Furthermore, the usage of poly(2-oxazoline)s ML3 in reverse ATRP was investigated with water-soluble azo-compounds as radical initiator. Here, initiation occurs like in conventional emulsion polymerization by formation of radicals in the aqueous phase, which after addition of some monomers enter the hydrophobic core of the micelles and start the chain growth. In this case high polymerization rates and PDIs around 1.4. For a better understanding of the reaction mechanism the resulting polymer latexes of direct and reverse ATRP were investigated by transmission electron microscopy (TEM).

In the case of direct ATRP particle sizes of 400 nm to about 1 μm were observed. Therefore, one can assume that suspension and emulsion polymerisation are in competition and take place simultaneously. For reverse ATRP particle sizes of about 200 nm to 400 nm were found, showing that exclusively an emulsion type mechanism takes place. This is in good agreement with the expected behaviour since here the primary radicals are formed in the water phase and then enter the micelles rather than the monomer droplets. Emulsion respectively suspension polymerization in water as reaction medium yield polymer particles which can be cleaved from the copper complex simply by washing with a suitable solvent (e.g. methanol) that dissolves the amphiphilic metal-loaded polymer but not the synthesized PMMA. For this reason white polymers with residual copper contents of 0.06 wt.-% could be obtained. In conclusion, the use of bipyridine-functionalized amphiphilic poly(2-oxazoline)s for ATRP is a promising strategy for a fast and controlled radical polymerization, although molar masses of PMMA are higher than the theoretical values.

Enantioselective Hydrogenation [7]

Using dicyclohexylcarbodiimide (DCC) as activating reagent the chiral diphosphane (2S,4S)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine (PPM) was coupled quantitatively and under mild conditions to carboxylic acid functionalized polymer supports. By reaction with $[Rh(COD)_2]BF_4$ polymer bound rhodium complexes suitable for enantioselective hydrogenation of enamides could be obtained directly in water.

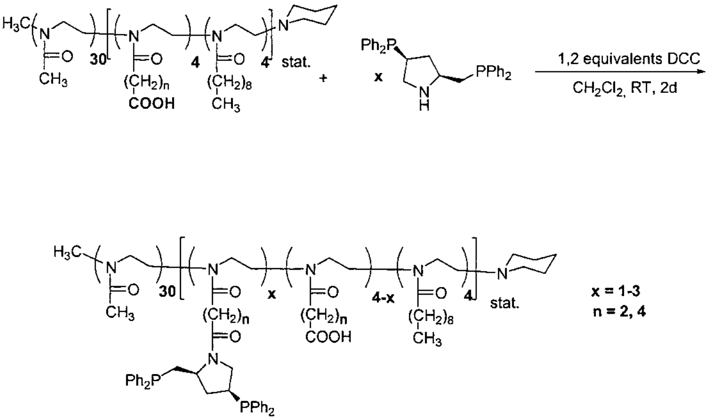


Figure 6. Synthesis of macroligands for the enantioselective hydrogenation of enamides by polymer-analagous coupling reaction.

Using this catalyst system we observed a TOF (turn-over frequency) of 120-140 h^1 and an enantiomeric excess (ee) of 85-86 % for the hydrogenation of the amino acid precursor (Z)-methyl α-acetamidocinnamate.

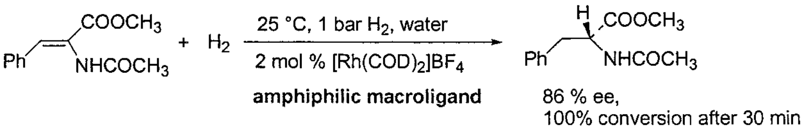
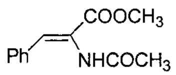


Figure 7. Reaction conditions for the enantioselective hydrogenation of (Z)-methyl a-acetamidocinnamate with macroligands.

After extraction of the products with ethyl acetate, the aqueous catalyst phase could be reused in further cycles. A comparison with data (see Table 1) given by *Anderson* and *Mamström* for the same ligand immobilized on polyacrylic acid (PAA) [8], impressively demonstrates the advantages of an amphiphilic versus a purely hydrophilic polymeric support for the conversion of hydrophobic substrates in water giving access to high reactivity and selectivity in the micellar nanoreactors.

Table 1. Comparison of PAA and amphiphilic poly(2-oxazoline)s as catalyst supports in the enantioselective hydrogenation of (Z)-methyl α-acetamidocinnamate.

Substrate	PAA-PPM	Poly(2-oxazolin)-PPM
 reaction conditions: 1 bar, 25 °C	• Biphasic EtOAc/H_2O • TOF = 2.7 h^{-1} • 100% conversion after 18 h; 66 % ee	• Aqueous-micellar medium • TOF = 140 h^{-1} • 90% conversion after 20 min; 86% ee

Cyclopolymerization of 1,6-heptadiynes

Olefin metathesis has become a powerful method in the formation of carbon-carbon double bonds.[9] Due to their remarkable stability towards moisture and oxygen, ruthenium alkylidene catalysts became of great interest. Nonetheless, despite their activity in metathesis reactions, none of the existing systems were capable of polymerizing alkynes or cyclopolymerizing 1,6-heptadiynes so far. A relatively new approach is the replacement of the chloride ligands in Hoveyda-Grubbs based ruthenium catalysts with electron-withdrawing carboxylic groups, not only to improve their catalytic activity but to give access to a simple way of immobilization.[10] Recently prepared catalysts **K1** and **K2** allow the first alkyne polymerization using ruthenium initiators.

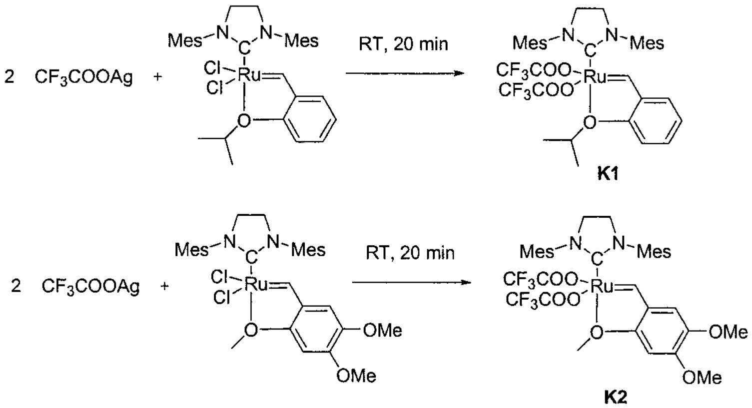


Figure 8. Preparation of catalyst **K1** and **K2**.[11]

Catalysts **K1** and **K2** where obtained via addition of 2 equivalents of CF_3COOAg to the Grubbs-Hoveyda based catalyst precursor. Whereas **K1** is not able to polymerize diethyl dipropargylmalonate (DEDPM) in a controlled/living manner, **K2** gives a linear plot of M_n versus N (monomer equivalents) with PDIs between 1.1 and 1.6. The value for k_p/k_i (ratio of polymerization over insertion) was 3, indicating a well-behaved system. The polymerization of chiral 4-(ethoxycarbonyl)-4-(1*S*,2*R*,5*S*)-(+)-menthoxycarbonyl-1,6-heptadiyne (ECMCH) by these catalysts proceeded in a stereo- and regioselective way, resulting in tactic poly(*trans*-1,3-(cyclopent-1-enylene)vinylene) with >95% stereoregularity as was shown by ^{13}C-NMR spectroscopy. One of the many advantages of ruthenium based catalysis is their tolerance to polar functional groups and water as a reaction medium. Poly(ene)s directly synthesised in form of stable aqueous dispersions are particularly attractive for many industrial applications, since they can be directly deposited on suitable supports such as clays. We therefore tried to establish a system capable of polymerizing DEDPM under aqueous conditions, providing stable latices in one single step. The use of **K1** in combination with micelle forming compounds such as SDS or poly(2-oxazoline)-derived *block* copolymer $Me_{30}Non_6(PenOH)_2Pip$ resulted only in the formation of oligomeric precipitates. We therefore aimed on the fixation of the catalyst on these micelle-forming, amphiphilic *block* copolymers. The synthetic route necessary for the realization of a polymer-bound catalyst had to fulfil two requirements. On the one hand, a perfect mimic of **K1** had to be generated in order to maintain their reactivity and stereoselectivity. On the other hand and in contrast to any suspension/emulsion polymerization, the catalyst had to be *permanently* linked to the block copolymer amphiphile. Preparation of the functionalized block copolymers was accomplished by reacting first $Me_{30}Non_6(PenOH)_2Pip$, bearing two randomly distributed hydroxyl groups in the side chain of the hydrophobic block with hexafluoroglutaric anhydride followed by deprotonation with aqueous NaOH and reaction with $Ag(NO_3)$ to yield a polymer-bound silver carboxylate. The last steps entailed its reaction with the catalyst precursors $RuCl_2(=CH\text{-}2\text{-}(2\text{-}PrO)\text{-}C_6H_4(1,3\text{-bis}(2,4,6\text{-trimethylphenyl})4,5\text{-dihydroimidazolin-2-ylidene})$, followed by reaction with silver trifluoroacetate to endcap the second, unreacted chloro group of the catalyst. It is worth mentioning that all steps are provided quantitatively.

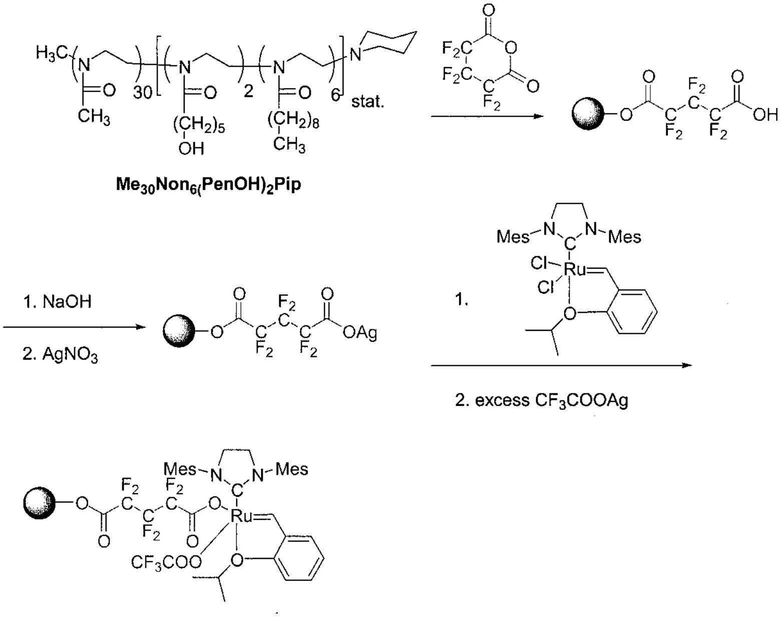


Figure 9. Synthesis of polymer bound metathesis catalyst **K3.**

In course of this two-step chlorine exchange, the corresponding ruthenium compounds were fixed to the support to yield the poly(2-oxazoline)-immobilized catalyst

$Me_{30}Non_6((PenOCO(CF_2)_3COO)(CF_3COO)Ru(=CH$-*o*-O-*i*-Pr-$C_6H_4)(SIMes)))_{0.8}(PenOCO(CF_2)_3COOAg)_{1.2}Pip$ **K3**. Catalyst immobilization was followed by ^1H-NMR, which provided an exact measure for the quality and selectivity of this reaction. The alkylidene proton of the polymer bound catalyst **K3** gave a single signal at $\delta=17.51$ ppm, which is in excellent agreement with the single signal at $\delta=17.58$ ppm in the proton NMR spectrum of the free catalyst. The similarity of these two chemical shifts not only indicative for a selective immobilization, where neither any free catalyst nor any other catalytic species was observed. But furthermore, it underlines the degree of similarity between **K1** and its supported analogue **K3**. Interestingly, gave the use of $Me_{30}Non_4(PenOH)_4Pip$ as possible support for higher catalyst loadings only water-insoluble, ill-defined catalyst-loaded species, whereas $Me_{30}Non_6(PenOH)_2Pip$ could be successfully used for these purposes. Quantification of ruthenium in **K3** by means of ICP-OES measurements indicated that 40 % of the polymeric silver salt had reacted with the catalyst precursor **K1**, leading to ruthenium loadings of the block copolymer of 0.16 mmol/g in **K3**. Poly(DEDPM) prepared with **K3** in water was characterized by lower polydispersity indices (PDIs) < 1.40 compared to poly(DEDPM) prepared by **K1** and due to the increased concentration of DEDPM within the micelles, reaction times required to reach complete conversion *was reduced to 30 minutes* using **K3** compared to 2 hours with **K1** illustrating the catalytic effect of the micellar nanoreactors formed in aqueous medium. Nevertheless, the polymerization itself can not be regarded living. TEM analysis of the resulting polymer latices revealed particle sizes between 100 and 200 nm, which is typical for an emulsion based process and underlines the hydrophobic center of **K3** as the reaction place instead of the monomer drops of DEDPM for a suspension polymerisation.[12]

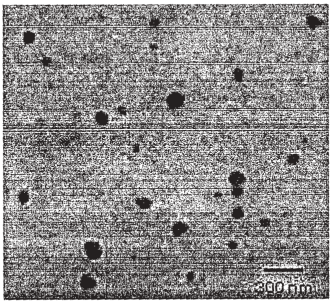


Figure 10. TEM picture of Poly(DEDPM) latex.

Stabilised by the amphiphilic structure of the *block*-copolymer they could be stored over two weeks without any change in terms of latex particle size, molecular weight and UV-Vis absorption maximum. Complementary, the catalyst immobilisation technique allowed also for catalyst/product separation to obtain virtually Ru-free poly(acetylene)s with a Ru-content ≤0.35 ppm. Relevant for technical use, poly(DEDPM) prepared by any of the methods reported here was stable in the solid state under ambient conditions including air and moisture.

Conclusions

We have demonstrated the wide applicability of amphiphilic polymer supports based on amphiphilic poly(2-oxazoline)s as support materials in organic chemistry and polymer chemistry as well. The examples that were studied herein, such as alkyne polymerization, ATRP and enantioselective hydrogenation gave impressive results as examples for poly(2-oxazoline) mediated micellar catalysis in pure water. Not only the controlled living cationic ring-opening polymerization of 2-oxazolines, but also the careful and variable monomer design and block copolymer synthesis is of major importance. Furthermore, catalysis can be conducted under mild conditions, e.g. 60 °C (water) instead of 90 °C (toluene) for ATRP or reduced reaction time for polymerization of DEDPM in water (½ h instead of 2 h in methylene chloride). In all cases virtually metal free products were obtained, due to the fact that the catalyst is *permanently linked* to the support and remains in any case *in the aqueous phase.*

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