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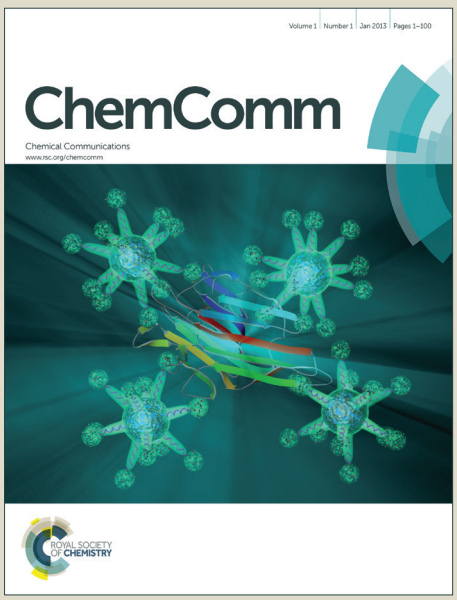

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Aqueous asymmetric cyclopropanation reactions in polymersome membranes

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Copper-bis(oxazoline) complexes have been immobilised in the hydrophobic domain of a polymersome membrane to perform asymmetric cyclopropanation reactions in aqueous media with enhanced conversions and enantioselectivities.

Chiral bis(oxazoline)-metal complexes have been used extensively in the past decades in asymmetric cyclopropanation reactions.[1] This popularity can be attributed to their excellent activities and selectivities for a broad range of substrates.[2] However, application of these catalysts in aqueous systems is rather troublesome.[3] Unstable transition states, undesired side-reactions and low solubilities for both substrates and catalyst make water an unfavourable solvent, despite its many apparent advantages. In the past few years progress has been made in overcoming incompatibility issues between homogeneous transition-metal catalysts and water. Research groups have designed nanoreactors consisting of homogeneous metal catalysts immobilised on polymeric supports that could perform various catalytic reactions in aqueous systems, *i.e.* cross-coupling reactions,[4] hydrolytic kinetic resolutions[5] and asymmetric allylic substitutions.[6] Regardless of the great merit of their work, alternative synthetic pathways in water already exist for most of these reactions. Asymmetric cyclopropanation reactions on the other hand, often require a metal-carbene complex, which poses a great challenge on the design of the catalyst in water. Recently, Carreira and coworkers[7] developed a hydrophobic iron(III)-porphyrin complex capable of performing cyclopropanation reactions between olefins and *in situ* generated diazomethane in 6M KOH. Arnold and coworkers[8] further exploited the catalytic nature of iron porphyrins and engineered a cytochrome P450 enzyme that could catalyse the reaction between styrene and ethyl diazoacetate in water with high enantiomeric selectivity.

Inspired by these results, we developed a strategy for the immobilisation of a copper-bis(oxazoline) catalyst inside a polymersome membrane. Polymersomes, artificial vesicles consisting of amphiphilic block copolymers, have emerged as powerful nanoreactors in the last few years.[9] A recent publication by our group shows the ability of polymersomes to form Pickering emulsions, in which a biphasic biocatalytic reaction could be realised.[10] We also reported a one-pot cascade reaction which was achieved by selective compartmentalization of three different enzymes in a polymeric vesicle.[11] Extension of this methodology to transition-metal catalysts would increase the versatility of these vesicles and pave the way for future metal- and biocatalysed cascade reactions. Furthermore, we reasoned that affixation of the catalyst inside the hydrophobic domain of the bilayer would yield a protective environment in which the catalyst and the substrates are shielded from external influences. Herein we report the synthesis of cross-linked polymeric vesicles functionalised with chiral bis(oxazoline)-copper catalysts. We show that these catalytic polymersomes have a positive effect on the rate and enantioselectivity of asymmetric cyclopropanation reactions in water. Moreover, we prove that the polymeric nanoreactors exhibit substrate selectivity based on the hydrophobicity of the starting alkene.

In order to provide an anchor for chiral bis(oxazoline)-copper catalysts inside the hydrophobic bilayer, we designed a poly(ethylene glycol)-*b*-poly-(styrene-*co*-4-vinylbenzyl azide) (PEG-*b*-P(S-*co*-4-VBA)) polymer. Since azide moieties are not stable at elevated temperatures during polymerization, we started off with the synthesis of a poly(ethylene glycol)-*b*-poly-(styrene-*co*-4-vinylbenzyl chloride) (PEG-*b*-P(S-*co*-4-VBC) polymer. A PEG_{44} chain transfer agent was prepared which was used to polymerise styrene and 4-vinylbenzyl chloride (4-VBC) *via* reversible addition-fragmentation chain-transfer polymerization (RAFT).[12] We chose a 90:10 ratio between styrene and 4-VBC as the initial monomer composition to offer sufficient handles for catalyst loading and at the same time ensure the integrity of the polymeric bilayer. Subsequent post-modification of the polymer with NaN_3 provided (PEG-*b*-P(S-*co*-4-VBA) polymer **P1** with a number-average molecular weight (M_n) of 19.5 kDa and a PDI of 1.31 (determined by Mulitangle Laser Light Scattering (MALLS) and ^{1}H-NMR, see Figures S1 and S4).

Next we investigated the introduction of a Cu(II)-bis(4-phenyl-2-oxazoline) catalyst, which has proven to give high yields and enantioselectivities in asymmetric cyclopropanation reactions. To prepare the catalyst for immobilisation *via* a Copper(I)-catalysed Azide-Alkyne Cycloaddition (CuAAC) reaction,[13] 2,2'-methylenebis[(4*S*)-4-phenyl-2-oxazoline] had to be modified with an alkyne functionality. This was achieved by deprotonation of the

methylene bridge with BuLi, followed by alkylation with propargyl bromide. We envisioned that double alkylation at this position would not only preserve the C_2-symmetry of the catalyst, but would also result in a fully cross-linked system, which would increase the stability of the polymersomes during extraction. After coordination with $Cu(OTf)_2$, catalyst **C1** was obtained in an overall yield of 66%.

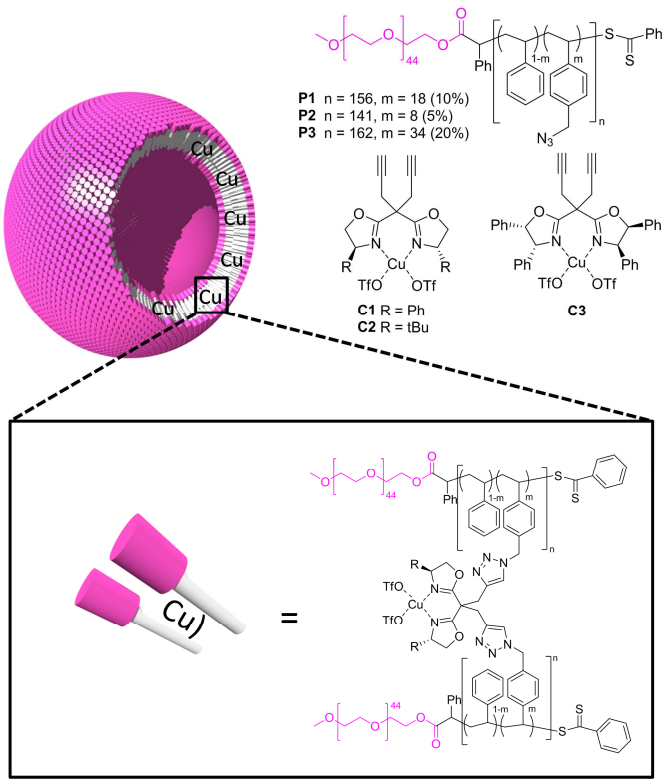


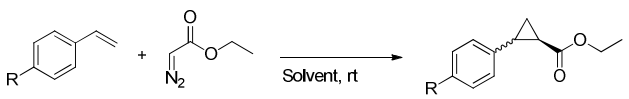
Figure 1. Chemical structures of azide-functionalised block copolymers and modified Cu-bis(oxazoline) catalysts (top) and a schematic representation of a Cu-bis(oxazoline) loaded polymersome (bottom).

The polymeric vesicles were prepared with the cosolvent method.[14] Ultrapure water was slowly added to a solution of block copolymer **P1** in THF until a H_2O:THF ratio of 50% was reached. During the addition the solution changed from colourless to turbid, indicating the presence of polymersomes. Next, a solution of catalyst **C1** in THF was added, together with $CuSO_4 \cdot 5H_2O$, bathophenanthroline sulfonated sodium salt and ascorbic acid. The CuAAC reaction was monitored by Fourier Transform Infrared (FTIR) spectroscopy. After stirring for 3 days at room temperature, the azide peak at 2095 cm^{-1} had completely disappeared (Figure S8). The polymersomes were subsequently transferred to a dialysis membrane and dialysed against ultrapure water for 72 hours to remove THF and the CuAAC catalyst.

To confirm the integrity of the polymersomes after functionalisation they were analysed with Transmission Electron Microscopy (TEM, Figure S10a) and Cryogenic Scanning Electron Microscopy (Cryo-SEM, Figure S10b). Figure S10a shows the spherical morphology of the polymeric vesicles, while the cross section in Figure S10b reveals their empty inner cavity. The thickness of the membrane was estimated to be 25-35 nm. Dynamic Light Scattering (DLS, Figure S9) studies proved that the diameter of the vesicles did not change after functionalisation, having an average diameter of 450-500 nm. The distribution of copper in the polymersomes was characterised with Energy-Dispersive X-ray Spectroscopy (EDX). The overlap between the copper signal in the X-ray map (Figure S10c) and the contours of the vesicles in the Scanning Transmission Electron Microscopy (STEM) image (Figure S10d) demonstrate the highly localised concentration of copper in the polymersome bilayer. The copper loading of the functionalised polymersomes was 93% (determined with Inductively Coupled Plasma Mass Spectrometry (ICP-MS)).

With these functionalised polymersomes in hand we continued with an assessment of the catalytic activity. The polymersomes were employed in a test reaction between styrene and ethyl diazoacetate at a 10 mol% copper concentration. Reaction times were limited to 10 minutes, which was sufficient to reach a maximum conversion, while polymersome precipitation occurring after prolonged reaction times, was prevented. After an extraction with CH_2Cl_2 the cyclopropane products could be recovered in a yield of 54% (Table 1, entry 2). This result could not be obtained with non-functionalised polymersomes, indicating that the observed activity is due to the presence of the copper-bis(oxazoline) catalyst (entry 4). To optimise the catalytic performance of the polymersomes, two different catalysts **C2** and **C3** were synthesised. Despite the slightly lower yield of polymersomes loaded with catalyst **C2**, the enantioselectivity significantly improved, making this catalyst superior to catalysts **C1** and **C3** (entries 5, 6). These results are in correspondence with previous studies, in which the activity of the different catalysts in organic solvents was investigated.[1b] To evaluate the effect of the catalyst loading in the polymersomes, we prepared block copolymers **P2** and **P3** in which 5% and 20%, respectively, of the styrene monomers were functionalised with an azide handle. Applying both polymers in a catalytic assay between styrene and ethyl diazoacetate did not lead to an increase in conversion nor in enantioselectivity (entries 7, 8). This made us decide to continue further experiments with catalyst **C2** and polymer **P1**.

Table 1. Asymmetric cyclopropanation reaction of styrene derivatives and ethyl diazoacetate.[a]



entry	R	solvent	rxn time (min)	load.[b] (mol%)	catalyst	polymer	conv.[c,d] (%)	*trans*/*cis*[d]	ee *trans*[e] (%)
1	H	H_2O	120	10	**C1**	**P1**	50[f]	73/27	60
2	H	H_2O	10	10	**C1**	**P1**	54	74/26	60
3	H	H_2O	10	2	**C1**	**P1**	12	72/28	60
4	H	H_2O	10	0	-	**P1**	0	-	-
5	H	H_2O	10	10	**C2**	**P1**	39	68/32	84
6	H	H_2O	10	10	**C3**	**P1**	43	59/41	34[g]
7	H	H_2O	10	10	**C2**	**P2**	31	70/30	85
8	H	H_2O	10	10	**C2**	**P3**	29	71/29	87
9	H	CH_2Cl_2	10	10	**C2**	-	40	70/30	86
10	H	H_2O	10	10	**C2**	-	9	67/33	35
11	H	CH_2Cl_2	10	10	**C1**	-	53	72/28	64
12	H	H_2O	10	10	**C1**	-	12	72/28	26
13	OMe	H_2O	10	10	**C2**	**P1**	93[k]	68/32	59[h]
14	Cl	H_2O	10	10	**C2**	**P1**	32[k]	75/25	53[h]
15	tBu	H_2O	10	10	**C2**	**P1**	67[k]	67/33	71
16[l]	COOH	H_2O	10	10	**C2**	**P1**	3	nd	nd
17	NH_2	H_2O	10	10	**C2**	**P1**	0	nd	nd

[a] Reactions were carried out in Milli-Q or CH_2Cl_2 (3.0 mL) at room temperature using styrene (0.46 mmol, 5.0 equiv) and ethyl diazoacetate (0.092 mmol, 1.0 equiv). [b] Catalyst loading in mol%. [c] Conversion of ethyl diazoacetate into cyclopropane product. [d] Determined by ^{1}H-NMR spectroscopy of crude product, using triethylene glycol dimethyl ether as an internal standard. [e] Determined by chiral GC. [f] Polymersomes started to precipitate after 15 min. [g] Configuration of product was (1*S*,2*S*). [h] Determined by chiral HPLC. [k] Isolated yields. [l] Substrate was solubilised by addition of Et_3N (0.46 mmol, 5.0 equiv).

To put these results into perspective we performed a study in which the catalytic activity of our catalytic polymersomes was compared with the activity of catalyst **C2** in Milli-Q and CH_2Cl_2. Much to our satisfaction, the conversion we obtained for the catalytic polymersomes was comparable with the conversion of the parent catalyst in CH_2Cl_2 (entry 9), even when this last reaction was allowed to stir for two hours. However, employing catalyst **C2** in Milli-Q provided cyclopropane product **1** in a much lower yield (entry 10). Furthermore, under these reaction conditions the enantioselectivity decreased significantly to 35% while this was not the case for our catalytic polymersomes. A similar study with catalyst **C1** yielded comparable results (entries 11, 12). These observations indicate that the catalyst inside the polymersomes is surrounded by a hydrophobic environment from which water is excluded, since water is affecting both the conversion and the enantioselectivity of the asymmetric cyclopropanation reaction.

In order to investigate the scope of our catalytic polymersomes we screened a series of alkenes for the asymmetric cyclopropanation reaction (Table 1, entries 13-17). According to our expectations the yield increased when a more activated alkene was used (entry 13), while it dropped when a more electron-deficient alkene was applied (entry 14). The presence of a bulky substituent did not hamper the reaction, but led to a higher yield instead (entry 15). A remarkable effect was observed when we changed the hydrophilicity of the alkene. 4-Vinylbenzoic acid did virtually not produce any cyclopropane product, even when it was solubilised with triethylamine (entry 16). To prove that the low yield could not be ascribed to the electron-poor nature of the alkenes, we performed an asymmetric cyclopropanation reaction with 4-aminostyrene. The intrinsic electron-donating property of the amino moiety would theoretically enhance the reaction rate of the reaction. Nevertheless, only starting material could be recovered after work-up (entry 17).

We explain this substrate selectivity by the hydrophobic concentrator effect.[5,15] The hydrophobicity of styrene (logP = 3.05) leads to an increased local concentration around the catalyst and therefore to higher reaction rates. However, the introduction of a hydrophilic functionality on the alkene increases the solubility in water. This lowers the driving force towards the hydrophobic domain of the polymersome bilayer and thus diminishes the conversion rate of the asymmetric cyclopropanation reaction.

Conclusions

In conclusion, we have developed a polymersome nanoreactor that can catalyse asymmetric cyclopropanation reactions in water with conversions and enantioselectivities that are comparable to the performance of the free catalyst in organic solvent. Immobilisation of a Cu-bis(oxazoline) catalyst inside the polymersome membrane *via* a CuAAC reaction allowed for stability and a good control over the catalyst loading. Furthermore, the hydrophobic environment around the catalyst was demonstrated by substrate selectivity. Hydrophobic substrates were readily converted into the corresponding cyclopropane products, while hydrophilic substrates did not undergo any reaction. This makes these catalytic polymersomes a promising alternative for the asymmetric cyclopropanation reaction of hydrophobic alkenes in organic solvents. We envision that encapsulating enzymes inside the lumen of these polymeric vesicles will extend this methodology and produce multifunctional nanoreactors, capable of performing cascade reactions in a tandem manner.

Notes and references

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