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Revisiting the Juliá-Colonna enantioselective epoxidation: supramolecular catalysis in water

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Christopher Bérubé[a†], Xavier Barbeau[b†], Patrick Lagüe[b] and Normand Voyer[a]

We describe an efficient epoxidation process leading to chiral epoxyketones using the reusable homo-oligopeptide poly-L-Leucine (PLL) in pure water, without any organic co-solvent. A range of substituted epoxyketones can be accessed with good conversions and high enantioselectivities. Based on the experimental results and computational studies, we propose a mechanism that demonstrates the importance of both the α-helical structure and the presence of a hydrophobic groove of the homo-oligopeptide catalyst for reactivity and selectivity.

Developing new bioinspired catalytic systems as green and scalable processes that use environmentally friendly reagents under mild conditions is an exciting area of research. As with enzymes, performing efficient reactions in pure water without organic solvents could reduce chemical wastes by 85% in large scale processes, which is both economically and environmentally appealing.[1] However, achieving efficient organic enantioselective transformations in pure water brings some challenges of solubility, reactivity, and selectivity.[2] Towards solving these problems, the use of peptide catalysts has attracted considerable attention.[3] Probably the best example, reported in the early 1980s by Juliá and Colonna, is the asymmetric epoxidation of electron-deficient enones to useful enantioenriched epoxyketones[4] in high yields and optical purities catalyzed by homo-oligopeptides.[5] This supramolecular catalytic process, initially described as a triphasic system, requires an aqueous oxidant phase, an organic immiscible solvent, and an insoluble homo-oligopeptide as a catalyst and chirality source. Over the years, the Juliá-Colonna epoxidation has been studied and further improved, notably as a biphasic system,[4a,6] under homogenous conditions,[6h,7] on solid-support[8] and in phase-transfer[9] conditions. Despite this significant progress, all the systems developed so far with natural homo-oligopeptides require the use of miscible or immiscible organic solvents for efficiency. Interestingly, mechanistic investigations have provided insights on the process. A mechanism has been proposed, supported by significant data.[10] It requires an α-helical structure and terminal hydrogen bonding groups, which serve to maintain the substrates in a chiral environment. Still, the proposed mechanism cannot explain all the data observed and certain aspects remain elusive.[6f,10b]

Herein, we describe an ecofriendly process to prepare chiral α,β-epoxyketones by the utilization of homo-oligopeptides in pure water for the Juliá-Colonna asymmetric epoxidation. We also describe mechanistic investigations that demonstrate the supramolecular origin of catalysis and enantioselectivity of the process, which involve both the hydrophobic and conformational features of the oligopeptide catalyst.

We chose to investigate poly-L-leucine (PLL) and poly-L-alanine (PLA), as they gave the highest yields and enantioselectivities in the classic Juliá-Colonna epoxidation.[5b] We also evaluated poly-L-isoleucine (PLI) and poly-L-valine (PLV) to study the importance of conformation and hydrophobicity for the reaction. These two oligopeptides bear a substituent on the β-carbon of their side chain. They prefer to adopt a β-structure rather than a helical one in solution and in the solid-state. Homo-oligopeptides are readily available from the corresponding amino acids *N*-carboxyanhydrides.[11] These activated amino acids can be polymerized readily with 1,3-diaminopropane as a nucleophilic initiator, leading to PLL, PLA, PLI and PLV in good overall yields and with a sufficient degree of polymerisation (DPn = 19, 18, 17, 16 for PLL, PLA, PLI and PLV) respectively by MALDI mass sprectrometry.[11-12] Also, NMR studies showed no detectable peaks other than those of the homo-oligopeptides.[11]

[a] *Département de Chimie and PROTEO, Université Laval, Faculté des sciences et de génie, 1045 avenue de la Médecine, Québec, QC, G1V OA6, Canada. E-mail : normand.voyer@chm.ulaval.ca*
[b] *Département de biochimie, microbiologie et bioinformatique and PROTEO, Université Laval, Faculté des sciences et de génie, 1030 avenue de la Médecine, Québec, QC, G1V OA6*
†These authors contributed equally to manuscript.
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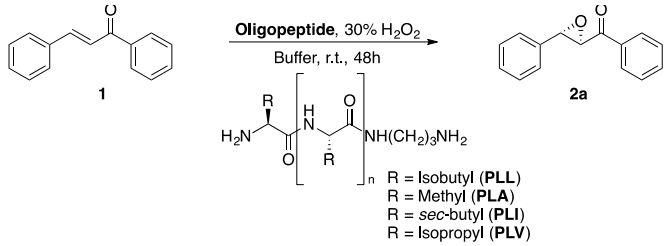
Table 1 Optimisation of reaction conditions[a]



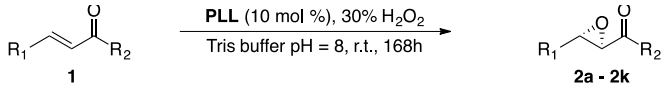
Entry	Catalyst (mol %)	Buffer	Yield (%)[b]	ee (%)[b]
1	-	8	<5	0
2	-	10	18	0
3	-	12	10	0
4	PLL (1)	8	38	95
5	PLL (1)	10	48	80
6	PLL (1)	12	53	75
7	PLL (2.5)	8	48	96
8	PLL (5)	8	61	96
9	PLL (10)	8	97	97
10	PLA (10)	8	<5	0
11	PLI (10)	8	<5	0
12	PLV (10)	8	<5	0

[a] Unless otherwise note, the reaction performed using **1** (0.1 mmol) and PLL in 1 mL of buffer solution and 30% H_2O_2 for 48 hours.
[b] Determined by chiral HPLC.

The process investigated is shown in Table 1 and uses hydrogen peroxide which is a mild oxidant, safe to handle, atom-efficient, and produces water and oxygen as byproducts. Results are reported in Table 1. First, the background reaction, without oligopeptides, led to very low conversion of **2a** at pH 8, 10 and 12, although the reaction is more important at the two highest pH tested (Table 1, entries 1-3). Then, we investigated 1 mol% of PLL at the same three pH (Table 1, entries 4-6). Surprisingly, we observed 38% yield and 95% ee of (*2R,3S*)-epoxychalcone **2a** at pH 8, even though the solubility of both the oligopeptide and the substrate is almost negligible. This result represents the first example of Julia-Colona epoxidation of electron-deficient olefins in pure water with a high enantiomeric excess. It suggests that PLL acts as both chiral source and solubilizing agent for the substrate in absence of organic co-solvent. At the same catalyst loading (Table 1, entries 4-6), increasing the pH increased the yields from 38% to 48% and 53%. However, the enantioselectivity dropped from 95% to 80% and 75%, respectively. This phenomenon can be attributed to the enhanced background reaction occurring at higher pH. It is also possible that the lower enantioselectivities obtained using more alkaline aqueous solutions could be due to a slow degradation of PLL;[5c,6a] pH has a significant influence on the yield and the enantioselectivity of the process.. Having identified pH 8 as the optimal pH, we verified the catalyst loading up to 10 mol% (Table 1, entries 7-9). Higher catalyst loadings maintain high enantioselectivity and significantly increase the chemical yield. The use of 10 mol % of PLL provides highest enantioselectivities and quantitative conversion of (*2R,3S*)-epoxychalcone **2a** (97%). Noteworthy of mention, using these optimized conditions with PLA, PLI, and PLV did not provide **2a** in any significant yield. Clearly, PLL possesses specific characteristics conveying unique catalytic activity. We studied the reusability of the PLL in our water process. The insoluble PLL in the buffer solution was easily recovered between each run by a simple filtration. The recovered PLL was then reused under the same conditions in the epoxidation of **1**. After the first recycling experiment, PLL showed very good reusability: up to 96% conversion and 96% ee of **1** were obtained, with 94% of the original PLL mass recovered. For the second and third recycling experiments, PLL showed good reusability where enantiomeric excesses remained almost the same (93% and 87% ee) with a decrease of conversion (30% and 10%) of the starting material. The decrease in conversion is most probably due to the loss of PLL and partial unfolding.

Using the optimized conditions, we explored the generality of the process with different α,β-unsaturated ketones. The results are summarized in Table 2. Using optimized conditions with an electron-withdrawing chloro group on the β-phenyl moiety led to a 42% yield and 90% ee of (*2R,3S*)-epoxide **2b** (Table 2, entry 2). We also verified the effect of a *para*-fluoro and *para*-trifluoro substitution on the α-phenyl moiety of the chalcone. Reactions with these substrates led to high yields (87% and 91%) and high enantioselectivities such as 96% and 90% of (*2R,3S*)-epoxides **2c** and **2d** respectively (Table 2, entries 3,4). Comparable results were obtained with chalcone having a *para*-fluoro substitution on the β-phenyl moiety, leading to both a high yield (83%) and enantioselectivities, such as 93% of (*2R,3S*)-epoxide **2e** (Table 2, entry 5). Bi-substituted enones led to a lower yield (53%), but high enantioselectivity (94%) of (*2R,3S*)-epoxide **2f** (Table 2, entry 6). It is possible that the presence of two electon-withdrawing groups deactivates the substrates. Substitutions at different positions on the β-phenyl moiety with the strong electron-withdrawing nitro group led to variable results (Table 2, entries 7-9). Comparable enantioselectivities were obtained with *para* and *meta* substitutions leading to 75% and 79% of (*2R,3S*)-epoxide **2g** and **2h,** respectively. However, the yield and enantioselectivity are lower in the case of the *ortho*-nitro substituted **2i** (Table 2, entry 9). In this case, both electronic

Table 2 Substrate scope in the epoxidation process catalyzed by PLL



Entry	R_1	R_2	No	Yield (%)[b]	ee (%)[b]
1	Ph	Ph	**2a**	97	97
2	*p*-Cl-Ph	Ph	**2b**	42	90
3	*p*-F-Ph	Ph	**2c**	87	96
4	*p*-CF_3-Ph	Ph	**2d**	91	90
5	Ph	*p*-F-Ph	**2e**	83	93
6	*p*-F-Ph	*p*-CH_3-Ph	**2f**	53	94
7	*p*-NO_2-Ph	Ph	**2g**	58	75
8	*m*-NO_2-Ph	Ph	**2h**	28	79
9	*o*-NO_2-Ph	Ph	**2i**	17	50
10	*p*-OMe-Ph	Ph	**2j**	13	75

[a] Unless otherwise noted, the reactions are performed using electron-deficient enones (0.05 mmol) and PLL in 1 mL of buffer solution and 30% H_2O_2 for one week. [b] Determined by chiral HPLC

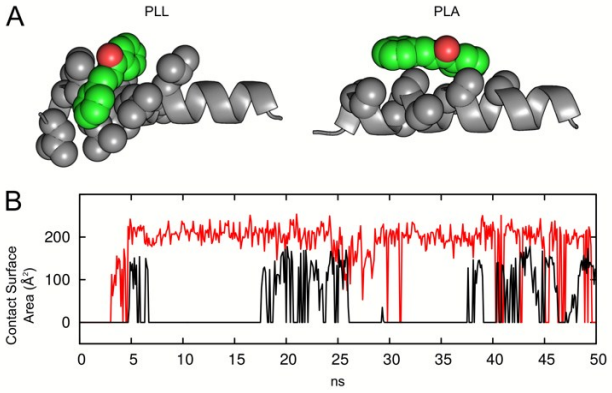


Fig. 1 A) Interaction of *trans*-chalcone **1** with PLL and PLA. PLL and PLA are represented in gray cartoon. Leucine side chains interacting with *trans*-chalcone **1** are represented as spheres. B) Contact surface area (Å) between *trans*-chalcone **1** and PLL (red) or PLA (black).

and steric effects can be evoked to explain the significant decrease in reactivity. Predictably, substitution with a *para*-methoxy electron-donating group on the β-phenyl moiety afforded (*2R,3S*)-epoxide **2j** with a very low conversion (13%),probably due to enone lower electrophilicity. However, the reaction proceeded with good enantioselectivity (75%) (Table 2, entry 10). Again, steric and electronic effects are probable factors that led to the poor reactivity in this case. In summary, studies with different substrates strongly suggest that both steric hindrance and electronic factors of chalcones play a crucial role in the outcomes of the process, especially on the chemical yields. On the other hand, the well-established mechanism described in the literature for the triphasic system cannot explain the results obtained here in pure water. Indeed, Kelly and Roberts proposed that hydrogen bonding of the three terminal amidic N-H groups, near the *N*-terminus, acts as an oxy-anion hole for the resonance-stabilized hydroperoxide enolate intermediate.[10d] Considering that PLA presents a high percentage of α-helical conformation in the solid-state and in an aqueous suspension,[12] there should have been a certain level of enantioselectivity in the reaction. Furthermore, hydrogen bonding interactions are minimized in pure water. Clearly, hydrophobic interactions must be involved somehow in favouring the transformation, and other factors must therefore being considered to explain the results obtained in the actual process. Using computational tools, we modelled PLL and PLA oligomers of 20 residues with an α-helical conformation, their preferred conformation based on ATR-FTIR results.[12] PLL with a helical conformation creates nice hydrophobic chiral grooves, regularly distributed along the helical axis. MD Simulations, used to study the interactions of *trans*-chalcone **1** with PLL and PLA, showed that *trans*-chalcone **1** fits perfectly within the PLL groove, as illustrated in Figure 1A. 50 ns trajectories were recorded for each peptide in the presence of one *trans*-chalcone **1** molecule, contact was observed 88% of the time between *trans*-chalcone **1** and PLL, and only 33% of the time between *trans*-chalcone **1** and PLA. Figure 1B shows the surface of contact between *trans*-chalcone **1** and PLL or PLA. The contacts between *trans*-chalcone **1** and PLA were transient and lead to a stable and defined supramolecular complex. By contrast, contacts between *trans*-chalcone **1** and PLL were lasting and lead to a

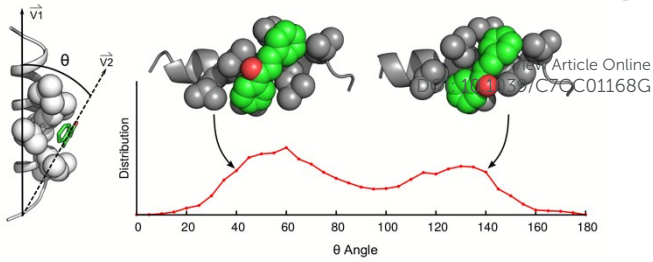


Fig. 2 Angular distribution of angle θ between *trans*-chalcone **1** (green) carbonyl (red) and PLL helix. The angle between the PLL helix axis and the *trans*-chalcone **1** carbonyl vector was calculated from the inverse cosine of the scalar product of these two vectors. PLL is represented in gray cartoon. Leucine side chains interacting with *trans*-chalcone **1** are represented as spheres.

stable complex where the *trans*-chalcone **1** inserts in the non-polar groove formed by the leucine side chains and the alpha helix main chain (Figure 1A). A short video presenting the interaction of *trans*-chalcone **1** with PLL and PLA is available in the supplementary information.[12] To further characterize the interaction between *trans*-chalcone **1** and PLL, we calculated the orientation of **1** with respect to the PLL helix. The angular distribution is presented in Figure 2 and shows that *trans*-chalcone **1,** when bound to PLL, adopts a wide range of orientations, with no preference for the side exposed to the solvent and accessible to the nucleophilic species (Fig. 2). Thus, the enantioselectivity observed from the experimental results does not appear to result from nucleophilic attack of a loose hydroperoxide anion coming from the solvent; a ratio close to 50% of each epoxide enantiomer would be observed if that was the case. Rather, we suggest a mechanism where the hydroperoxide anion would be concentrated at the *N*-terminal of the PLL. The *trans*-chalcone **1** would slide in the leucine side chain's hydrophobic groove until it reaches the *N*-terminal to react with the hydroperoxide anion. This "groove sliding" mechanism would lead to a reactive supramolecular complex formed by the PLL, the *trans*-chalcone **1** and the hydroperoxide, as represented in Figure 3. Depending on the orientation of **1** with respect to the PLL, four different complexes are possible. To test this assumption, the four complexes were built and energy-minimized using quantum mechanics calculations.[12] The resulting structures are represented in Figure 3. Of the four supramolecular complexes, only the complex depicted in Figure 3A has a distance of 2.5 Å and an angle of 98° between the hydroperoxide anion and *trans*-chalcone **1** reactive atoms, corresponding to reactive *trans*-chalcone **1** which leads to the

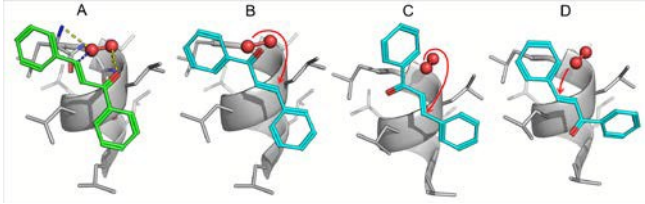


Fig.3 Supramolecular complexes proposed for the "groove sliding" mechanism. *Trans*-chalcone **1** and PLL are represented in sticks and ribbon respectively. Hydroperoxide is in red spheres. Only the complex depicted in A has a distance of 2.5 Å and a 98° angle between the hydroperoxide and trans-chalcone 1 reactive atoms.

corresponding (*2R,3S*)-epoxide **2a** obtained experimentally. Based on the experimental results described above and the computational results of previous pertinent mechanistic studies, we propose that in pure water, both a helical conformation and hydrophobic interactions are responsible for the chiral catalytic effect of PLL. Interestingly, more hydrophobic and less hindered enones demonstrate higher yields and enantioselectivity ratios than those with larger polar substituents, which have a lower affinity for the hydrophobic groove of PLL. These results are in agreement with the proposed mechanistic hypothesis.

We demonstrated that PLL acts as an efficient biomimetic supramolecular catalyst in water, solubilizing and complexing in a predictable manner the substrate, leading to high yields and enantioselectivities in the epoxidation of α,β-conjugated enones in pure water, without an organic co-solvent. Although the outcomes of the process vary with the structure of the substrates, PLL efficiently catalyzes the epoxidation of a variety of electron-deficient enones, leading to high enantioselectivities. Both the conformation and hydrophobic nature of oligopeptide catalysts are essential in order to act as efficient biomimetic catalyst. This new process in water opens the way to easily and rapidly access a variety of chiral epoxyketones through environmentally benign enantioselective processes.

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