The Juliá-Colonna Type Asymmetric Epoxidation Reaction Catalyzed by Soluble Oligo-L-leucines Containing an α-Aminoisobutyric Acid Residue: Importance of Helical Structure of the Catalyst on Asymmetric Induction

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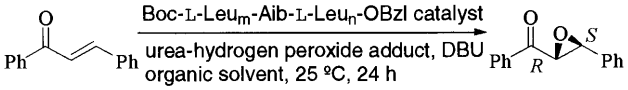
Length-defined organic solvent soluble oligo-L-leucines containing an Aib residue were prepared by stepwise elongation and fragment condensation methods, and were used as catalysts in the Juliá–Colonna asymmetric epoxidation reaction. The yield and enantioselectivity rose by increasing the number of amino acid units in the catalyst. The enantioselectivity was very sensitive to the reaction solvent. The IR characteristic bands (the amide I region) in CH_2Cl_2 indicated the soluble catalysts to be of helical structure in solution.

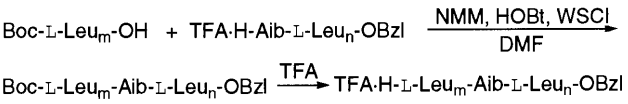
Epoxides are a widely used group of compounds in organic synthesis.[1] For this reason several approaches for enantioselective epoxidation have been developed.[2] Juliá-Colonna asymmetric epoxidation which utilizes poly-L-leucine as catalyst has been established as a highly selective method of epoxidizing enones[2d,3] and has found application in natural product synthesis.[4] Our interest in the chemistry of small ring compounds[5] has attracted us to this very intriguing reaction, of which mechanistically little has been uncovered. The primary problem concerning mechanistic examinations has been the insolubility of the catalyst in ordinary solvents. One advance has been the introduction of cross-linked aminomethylpolystyrene support.[6] This paved the way for preparation of polymer-bound length-defined catalysts, from which it was deduced that the chirality of the *N*-terminus dictates the stereochemistry of the product and that a certain number of consecutive amino acids of the same chirality at this end are required for reasonable levels of asymmetric induction.[7] Still here, however, the state of the catalysts has hampered spectroscopic examinations, and thus has complicated speculations about the mechanism of the asymmetric induction.

In their early work, Juliá and Colonna had already suggested that α-helical structure might be important for asymmetric induction in the epoxidation reaction under tri- and biphasic conditions,[8] unfortunately they could not produce evidence to back it up. Our observation of IR spectra of length-defined oligo-L-leucines in the solid state agreed with their suggestion.[9] Based on the report that the presence of even only a single α-aminoisobutyric acid (Aib) residue placed in the mid-section of oligo-L-amino acid chains promotes helix formation and greatly improves the solubility of the oligomers towards organic solvents,[10] we prepared several length-defined oligo-L-leucines containing an Aib residue, and have carried out the first examination of the Juliá–Colonna asymmetric epoxidation reaction with soluble catalysts. Herein we disclose our results.

The protected oligo-L-leucines (Boc-L-Leu_m–Aib–L-Leu_n-OBzl) were prepared by the fragment condensation of Boc-L-Leu_m-OH and TFA·H-Aib-L-Leu_n-OBzl as shown in Scheme 2 by modifying reported procedures.[10] The oligo-L-leucines were fully characterized by MS (MALDI-TOF), ^{1}H NMR and IR spectra. All the Boc-L-Leu_m–Aib–L-Leu_n-OBzl peptides prepared here were soluble in a variety of organic solvents.



Scheme 1. Juliá-Colonna asymmetric epoxidation using soluble oligo-L- leucine catalysts.



Scheme 2. Preparation of Boc-L-Leu_m-Aib-L-Leu_n-OBzl and Free NH_2 catalysts: NMM = N-methylmorpholine; HOBt = hydroxybenzotriazole; WSCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; TFA = trifluoroacetic acid.

Epoxidation reactions of chalcone with the urea-hydrogen peroxide adduct and DBU in the presence of soluble catalysts (Boc-L-Leu_m–Aib–L-Leu_n-OBzl and TFA·H–L-Leu_m–Aib–L-Leu_n-OBzl oligomers) were investigated at room temperature in organic solvents.[11] Table 1 shows the stereoselectivity in the epoxidation catalyzed by Boc-L-Leu_m–Aib–L-Leu_n-OBzl (m = 4, 6 and n = 4, 6) in THF and some *N*-deprotected oligomers having a free NH_2 group. Both Boc-L-Leu_m–Aib–L-Leu_n-OBzl and TFA·H–L-Leu_m–Aib–L-Leu_n-OBzl oligomers were effective as catalysts from the viewpoint of both chemical yield and stereoselectivity. The general trend was that the longer catalyst gave better results, a tendency similarly observed in the epoxidation reaction under tri- or biphasic conditions.[7,8,9] Contrary to previous observations under heterogeneous tri- and biphasic conditions where protection of the *N*-terminus as amides[8] and carbamates[9] lead to significant deterioration in reactivity, our protected catalysts furnished comparable results with corresponding unprotected catalysts. Coupled with the fact that NMe_2 (in the place NH_2) is also compatible,[7,8] neither the hydrogen-bonding ability of the hydrogen atom attached to nitrogen nor the basicity of the nitrogen atom are involved in the stereo-determining step, and thus the role of the *N*-terminus seems to be minimal. The negative results with previous carbonyl protected catalysts[8,9] could be due to unfavorable catalyst conformations induced by the groups.

The solvent effect on the enantioselectivity is shown in Table 2. The stereoselectivity was very sensitive to the reaction solvent. The highest enantioselectivity was observed in THF. In $CHCl_3$ solution, very low enantioselectivity was observed although the epoxide was obtained in comparable yield. Since

Table 1. Boc-L-Leu$_m$–Aib–L-Leu$_n$-OBzl and TFA·H-L-Leu$_m$–Aib–L-Leu$_n$-OBzl catalyzed epoxidation in THF

Entry	Catalyst	yield /%	% ee[a]
1	Boc-L-Leu$_4$–Aib–L-Leu$_4$-OBzl[b]	50	61
2	TFA·H-L-Leu$_4$–Aib–L-Leu$_4$-OBzl	61	68
3	Boc-L-Leu$_4$–Aib–L-Leu$_6$-OBzl	60	78
4	TFA·H-L-Leu$_4$–Aib–L-Leu$_6$-OBzl	54	73
5	Boc-L-Leu$_6$–Aib–L-Leu$_4$-OBzl	89	85
6	Boc-L-Leu$_6$–Aib–L-Leu$_6$-OBzl	73	94

[a] Estimated by HPLC using a chiral OD column. [b] Known compound.

Table 2. Solvent effect in Boc-L-Leu$_6$–Aib–L-Leu$_6$-OBzl catalyzed epoxidation

Entry	Solvent	yield /%	% ee[a]
1	THF	73	94
2	Toluene	47	84
3	CH_2Cl_2	41	76
4	$CHCl_3$	72	15

[a] Estimated by HPLC using a chiral OD column

IR measurements indicated the homogeneous catalyst to be helical even in $CHCl_3$, this experimental result can be ascribed to the presence of a relatively fast background uncatalyzed epoxidation process.[12]

Examination of the IR spectra of Boc-L-Leu$_6$–Aib–L-Leu$_6$-OBzl, which exhibited the highest selectivity, showed a weak band at 3424 cm^{-1} (w, free N-H stretching), and strong bands at 3324 (s, hydrogen bonding N-H stretching) and 1661 cm^{-1} (s, C=O stretching) in CH_2Cl_2 solution, which can be assigned to helical structure.[13]

We have demonstrated that soluble oligo-L-leucine catalysts that show a high degree of helical conformational structure give results comparable to those of insoluble catalysts. Therefore, we draw the conclusion that in general the segment of the catalysts in the Juliá-Colonna reaction involved in the asymmetric induction process assumes helical conformation. This improvement in solubility of the catalyst brings in a new dimension to the Juliá-Colonna reaction and should lead to further understanding of the reaction.

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11 General method: To a mixture of chalcone 25 mg (0.12 mmol), catalyst 0.030 mmol, urea-hydrogen peroxide adduct 12.5 mg (0.16 mmol) and 1 ml of THF, 0.1 ml of DBU (0.67 mmol) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. The resulting mixture was extracted with CH_2Cl_2. The combined extracts were washed with aqueous $Na_2S_2O_3$, water and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by preparative TLC [silica gel, petroleum ether : ether = 10 : 1 (v/v)]. As the reaction progresses, the turbidity caused by the lowly soluble urea-hydrogen peroxide adduct decreases.

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