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Reverse Turn Induced π-Facial Selectivity during Polyaniline-Supported Cobalt(II) Salen Catalyzed Aerobic Epoxidation of *N*-Cinnamoyl L-Proline Derived Peptides

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A novel chemo- and diastereoselective aerobic epoxidation of the *N*-cinnamoyl peptides catalyzed by polyaniline-supported cobalt(II) salen (PASCOS) is described. The *N*-cinnamoyl proline derived peptides **1** show a high π-facial selectivity during these epoxidations. The origin of this diastereoselectivity in **1** has been attributed to (i) the propensity of the *N*-cinnamoyl proline amide to exist predominantly as trans rotamer in $CDCl_3$, DMSO-d_6, and CH_3CN medium and (ii) existence of these peptides as organized structures (γ- and β-turns) due to the presence of intramolecular hydrogen bonds. An extensive solution NMR and MD simulation study on **1d** and **1f** indicates that the origin of the high π-facial selectivity is due to the well-defined γ- and β-turns which result in the hindrance of one face of the cinnamoyl double bond in the transition state of the epoxidation reaction.

Introduction

After extensive work on the development of homogeneous cobalt catalysts for biomimetic aerobic oxidation of various functionalized/unfunctionalized hydrocarbons and epoxidation of a diverse range of olefinic systems,[1] we introduced polyaniline-supported cobalt acetate as a simple and novel heterogeneous epoxidation catalyst in which a low-cost, easily synthesizable polyaniline was used for the first time as the polymeric support to generate a heterogeneous epoxidation catalyst.[2] Earlier, polyaniline was used as a polymeric support to palladium for generation of a heterogeneous catalyst for hydrogenation of alkenes,[3] but there was no report of it being used as a heterogeneous support to a catalyst that acted as an oxo-transfer agent to olefins. The polyaniline-supported cobalt acetate catalyst was recyclable, resistant to decomposition in organic solvents as well as in aqueous medium, and applicable for epoxidation on a wide variety of olefins including chalcone and α,β-unsaturated amides with good to excellent yields. Moreover, unlike most of the epoxidation catalysts known in the literature, this catalyst did not require any peroxo or any other hazardous oxygen-rich compound as an oxo source. Reactions were carried out in the presence of isobutyraldehyde and simply in ambient oxygen pressure (using an oxygen balloon), using molecular oxygen as the oxo source. Soon after the successful introduction of polyaniline as a support for an epoxidation catalyst, cobalt-salen was attached to it to develop another heterogeneous epoxidation catalyst, which came out to be equally as robust as polyaniline-supported cobalt acetate and effected the epoxidation reactions on cinnamoyl amide derivatives in excellent yields.[4] The most significant difference between other polymer-linked catalysts and polyaniline-supported cobalt(II) salen (PASCOS) is that in this case the polymer itself may coordinate to the central metal ion, which will make the catalyst very stable and less prone to leaching of the polymer from the catalyst. A tentative structural arrangement of cobalt(II) salen in the polyaniline matrix is shown in Figure 1.

Recently it has been shown from our group that *N*-cinnamoyl amides **1** can be converted to β-phenylisoserine derivatives **3** via a tandem polyaniline-supported cobalt(II) salen (PASCOS) catalyzed aerobic epoxidation and amination protocol (Scheme 1). The intermediate

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(1) (a) Punniyamurthy, T.; Bhatia, B.; Iqbal, J. *J. Org. Chem*. **1994**, *59*, 850. (b) Punniyamurthy, T.; Iqbal, J. *Tetrahedron Lett*. **1994**, *35*, 4003 and 4007. (c) Reddy, M. M.; Punnyamurthy, T.; Iqbal, J. *Tetrahedron Lett*. **1995**, *36*, 159. (d) Reddy, M. M.; Punnyamurthy, T.; Iqbal, J. *Tetrahedron Lett*. **1995**, *36*, 159. (e) Punnyamurthy, T.; Reddy, M. M.; Kalra, S. J. S.; Iqbal, J. *J. Pure Appl. Chem*. **1996**, *68*, 619. (f) Punnyamurthy, T.; Kalra, S. J. S.; Iqbal, J. *Tetrahedron Lett*. **1995**, *36*, 8497. (g) Punnyamurthy, T.; Asthana, P.; Kalra, S. J. S.; Iqbal, J. *Proc. Indian Acad. Sci*. **1996**, *107*, 335. (h) Mandal, A. K.; Khanna, V.; Iqbal, J. *Tetrahedron Lett*. **1996**, *37*, 3769. 17.

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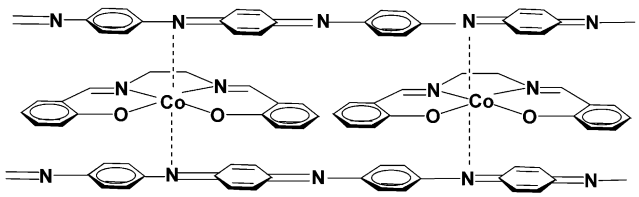


FIGURE 1.

cinnamoyl epoxide **2** undergoes a stereoselective S_N2 type opening with several aromatic amines leading to a highly selective synthesis of the *anti* diastereomer of the *β*-phenylisoserine derivatives.

Thus, epoxidation of the cinnamoyl amides, followed by opening of the epoxides with amines in the same pot, catalyzed by polyaniline-supported cobalt salen, led to the formation of vicinal amino alcohols which are *β*-phenylisoserne deivatives, a novel class of unnatural *β*-amino acid residues. This is an excellent example of protecting group functionalization where *N*-cinnamoylated peptides are used as synthons to generate novel *β*-amino acid residues in a very selective manner. PASCOS is a very specific catalyst for epoxidaion of cinnamoyl double bonds. Allyl and crotonyl amides remain unaffected under the same reaction conditions. To achieve a stereoselective outcome of the two-step process, both steps (that is, the epoxidation and the opening) have to be stereoselective in nature. It already has been established[5b] that the ring opening in glycidyl peptides proceeds via an S_N2 pathway, giving only the *anti* diastereomers as the products under these reaction conditions. To achieve an overall chiral synthesis of *β*-phenylisoserine peptides, we attempted stereoselective epoxidation on a number of *N*-cinnamoylated peptides using cobalt salen polyaniline as catalyst and also conducted a detailed study to find out the origin of this diastereoselectivity, which is described in the following section.

Results and Discussions

To achieve a chiral synthesis of these derivatives we have attempted a diastereoselective aerobic epoxidation of *N*-cinnamoyl-L-proline derivatives. The findings are listed in Table 1, which indicates that the epoxidation of methyl-*N*-cinnamoyl L-prolinate **1a** exhibits very poor diastereoselectivity during epoxidation; however, the corresponding allylic amide **1b** showed better selectivity in formation of the corresponding epoxide **2b** than the former. Interestingly, the diastereoselectivity increases for substrates having an additional C-terminal amino acid residue in **1a**. Thus, PASCOS catalyzed aerobic epoxidation of dipeptides **1c**−**e** afforded the corresponding epoxides **2c**−**e,** respectively, with higher diastereoselectivities. The ratio in favor of the major enantiomer was found to be >70:<30.

The absolute stereochemistry for the major enantiomer of epoxides **2a**−**e** was assigned as 2*R*,3*S*, which was established by following a correlation with the epoxide obtained by Sharpless's epoxidation procedure.[5] Thus the cinnamoyl alcohol was subjected to Sharpless's epoxidation by using (+)-DET to give enantiomerically pure epoxide **4** that was converted to the corresponding carboxylic acid **5** by ruthenium catalyzed oxidation of the primary alcohol group.[6] The carboxylic acid **5** was subsequently transformed to the corresponding peptide **2c** by mixed anhydride coupling with the methyl ester of L-proline-L-leucine dipeptide (Scheme 2). The specific rotation of **2c** prepared by Sharpless's procedure (α_D = −191°) and that by PASCOS catalyzed epoxidation of **1c** were similar in sign and magnitude. Also, the proton NMR of epoxide **2c** obtained by both routes was identical. Thus, based on this correlation, the absolute stereochemistry of epoxide **2c** is assigned 2*R*,3*S*. A similar correlation was also carried out for **2d** and **2e**.

It is noteworthy that the epoxidation of tripeptides **1f**−**h** was found to be more diastereoselective compared with that of peptides **1c**−**e** as they underwent highly selective aerobic epoxidation, leading to corresponding epoxides **2f**−**h** in high yields under the same reaction conditions (Table 2). The ratio in favor of the major diastereomer was found to be >85:<15 (HPLC), and they were separated by column chromatography to afford the epoxide whose purity was ∼90% (chiral HPLC). The absolute stereochemistry of the major diastereomer was assigned to be 2*R*,3*S* by converting diastereomerically pure **2c** (obtained by aerobic epoxidation) to **2f**−**h** (following a sequence of alkaline hydrolysis of **2c** and mixed anhydride coupling with the corresponding amine/esters of amino acids) and comparing with same epoxides obtained by direct epoxidation (Sharpless) of the corresponding olefins.

The moderate yields of the epoxides **2** during PASCOS catalyzed epoxidations and the formation of other oxidized products led us to modify the reaction conditions. We reasoned that buffering the reaction medium might help in reducing the reaction period, which may reduce the side reactions also. Hence the epoxy peptides **2b**, **2c**, **2f, 2i**, and **2j** were obtained with the following epoxidation conditions in high chemical and optical purity (Table 3). To a solution of peptide **1** in acetonitrile was added 2-methylpropanal (3 equiv) and PASCOS catalyst (10 mg), followed by sodium acetate (10 equiv), and the reaction mixture was stirred for 12 h under aerobic condition. Expectedly, **1a** and **1c** underwent complete conversion to the corresponding epoxide **2b** and **2c**, respectively, in excellent yields. On the other hand, an additional amount of aldehyde (2 equiv) and catalyst were required after 12 h to achieve the synthesis of epoxides **2f**, **2i**, and **2j** in excellent conversion and yields during 20−22 h of stirring. It is noteworthy that there was no significant change in the rotation indicating thereby that the diastereoselectivity is not affected as a result of buffering the reaction medium. Thus, buffering the epoxidation reactions with sodium acetate resulted in faster reactions leading to excellent chemical yields, with no adverse effect on the diastereoselectivity of the corresponding epoxides.

Origin of Diastereoselectivity. To understand the cause for the diastereoselectivity during these epoxidations, we have focused on the population of the *cis*/*trans* conformation of the cinnamoyl−*Proline* amide bond which may have a profound role in dictating the *π*-facial selectivity of the cinnamoyl group during epoxidation. It

(5) (a) Das, B. C.; Iqbal, J. *Tetrahedron Lett*. **1997**, *38*, 2903. (b) De, A.; Basak, P.; Iqbal, J. *Tetrahedron Lett*. **1997**, *38*, 8383.

(6) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem*. **1986**, *51*, 1922.

SCHEME 1

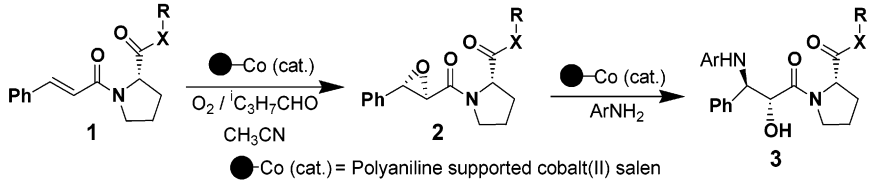
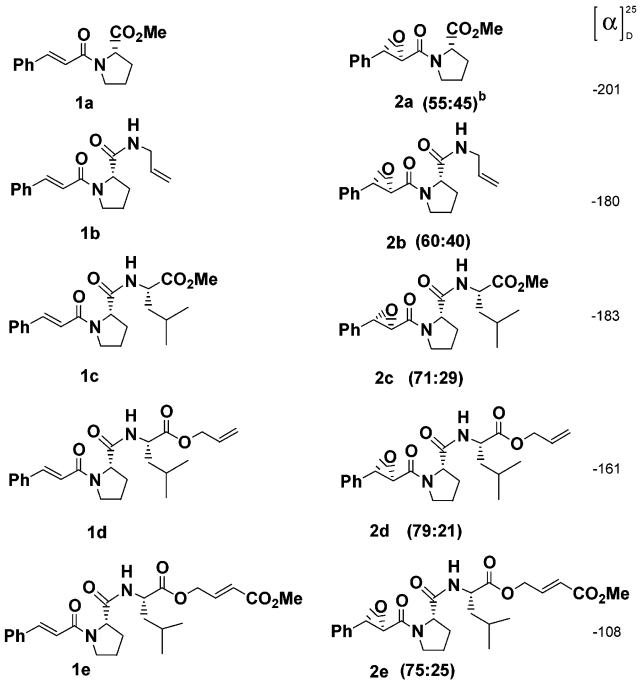
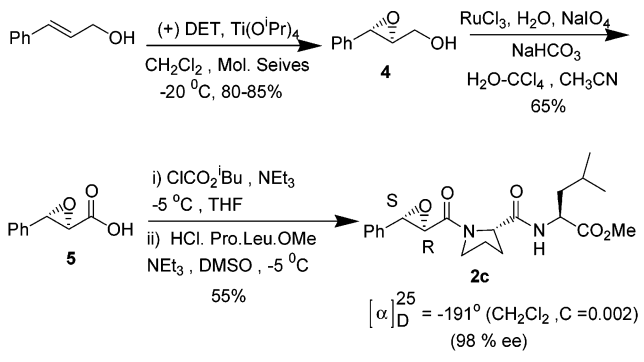


TABLE 1. Polyaniline-Supported Cobalt(II) Salen (PASCOS) Catalyzed Aerobic Epoxidation of *N*-cinnamoyl-L-proline Peptides 1



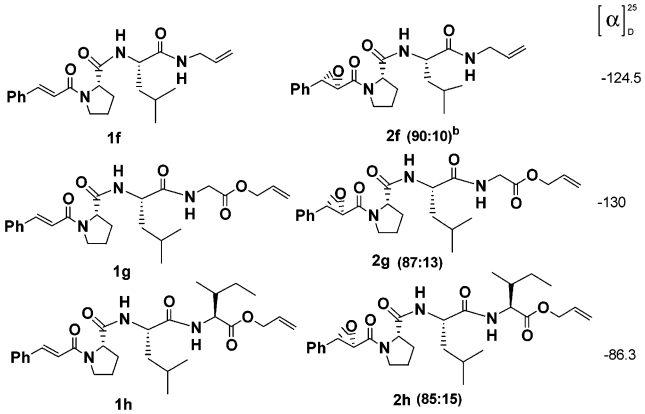
[a] The isolated yields of the epoxides were 80−90% in all the cases. [b] Ratio of the diastereomers determined by chiral HPLC and the absolute configuration (2*R*,3*S*) and specific rotations (in CH_2Cl_2) of the major epoxide are shown in all cases.

SCHEME 2. Assignment of Epoxide Stereochemistry in 2c



is well-known that *Proline* amides are capable of existing as two rotamers and their population is controlled by the polarity of the solvent. The population of the cis/trans ratio is also guided by *Proline*-H_δ and acyl group interaction. For example, population of the cis/trans rotamer ratio in the peptide bond between *Proline* and an α-amino acid will be governed by the noncovalent interaction between the *Proline*-H_δ and the side chain of the α-amino

TABLE 2. Polyaniline-Supported Cobalt(II) Salen (PASCOS) Catalyzed Enantioselective Aerobic Epoxidation of *N*-Cinnamoyl-L-proline Containing Peptides[a]

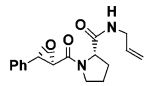
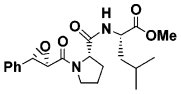
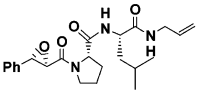
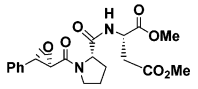
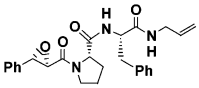


[a] The isolated yields of the epoxides were 75−78% in all the cases. [b] The ratios of the diastereomers were determined by chiral HPLC and the absolute configuration (2*R*,3*S*) and specific rotations (CH_2Cl_2) of the major epoxide is shown in all cases.

acid at the *N*-terminal of *Proline*. It would be interesting to see in our case as the *Proline*-H_δ and the α- or *β*-vinyl proton would be the controlling factor in determining the *π*-facial selectivity during epoxidation. To address that, we have studied the solution NMR spectra of the peptides having the cinnamoyl group in both cis and trans orientations. The possible interactions in cis and trans rotamers in the cinnamoyl *Proline* system are the following (Figure 2).

Two olefin peptides viz. allyl *N*-cinnamoyl-L-*Prolyl*-L-*Leucinate* **1d** and allyl *N*-cinnamoyl-(L)-*Prolyl*-(L)-*Leucine* amide **1f** (differing only in the linkage pattern at the C-terminal of the leucine residue) were chosen for detailed study of their solution NMR spectra. Distinction between the cis and trans rotamers of *Proline* in both the peptides was done by the help of NOESY experiment. The trans isomer was characterized by the presence of NOEs between pro *δ*-H and cinnamoyl α-H whereas the cis isomer showed NOE between *Proline* $C_\alpha H$ and the cinnamoyl $C_\alpha H$ (Figure 3). Both peptides, when they exist with the *trans*-cinnamoyl-*Proline* linkage, have the possibility of forming stable intramolecular hydrogen bonds between the oxygen of the cinnamoyl carbonyl and the amide NH(s), thereby existing as highly organized structures. These kinds of intramolecular hydrogen bonds are salient features of the proteins and dictate the formations of reverse turns (*β*- and *γ*-turns) in the peptide chains which are important motifs of the protein secondary structures. A seven-membered ring in the peptide chain formed due to intramolecular hydrogen boding between the carbonyl of the *i*th residue and the NH of the (*i*+2)nd residue makes a *γ*-turn while similar kinds of hydrogen

TABLE 3. Comparison between Buffered and Unbuffered Reactions Conducted under PASCOS Catalyzed Aerobic Epoxidation of *N*-Cinnamoyl Proline Peptides 1

Epoxide	Without NaOAc		With NaOAc[b]	
	Time	Yield[a]	Time	Yield[a]
 2b	22	48	15	65
 2c	21	53	14	70
 2f	36	56	20	82
 2i	24	55	14	78
 2j	33	64	17	83

[a] Yield of the isolated diastereomer. The ratios of diastereometers were not determined. The purities of the isolated epxodies are in the range of 90−95%. [b] Reaction conditions: To a solution of peptide **1** in acetonitrile was added 2-methylpropanal (3 equiv) and PASCOS catalyst, followed by sodiuim acetate (10 equiv), and the reaction mixture was stirred for 12−20 h under oxygen balloon.

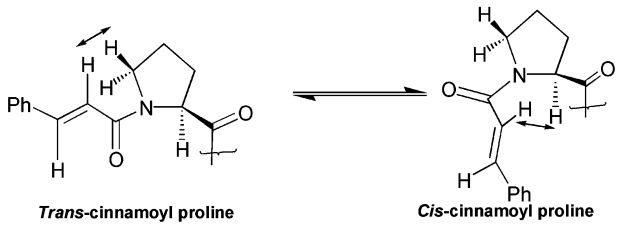


FIGURE 2.

bonding between the carbonyl of the *i*th residue and NH of the (*i*+3)rd residue generate a 10-membered ring known as a *β*-turn. These turns are stable in suitable media and dilution and keep the peptides in highly organized form.[8] Interestingly, it is only the carbonyl of the trans rotamer of the amide linkage between the *i*th and (*i*+1)st residue that can participate in these turns. In the corresponding cis rotamer, this particular carbonyl points in the opposite direction and no intramolecular hydrogen bonding is feasible.

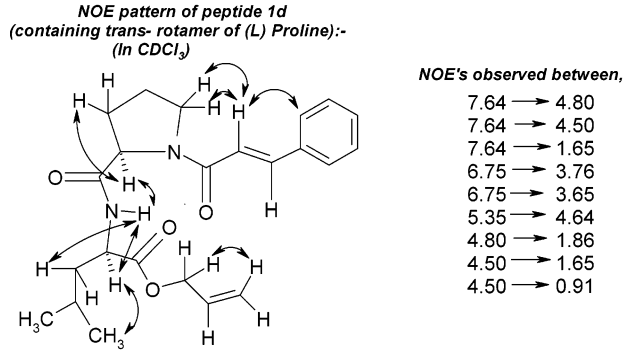


FIGURE 3. NOE's observed in **1d**.

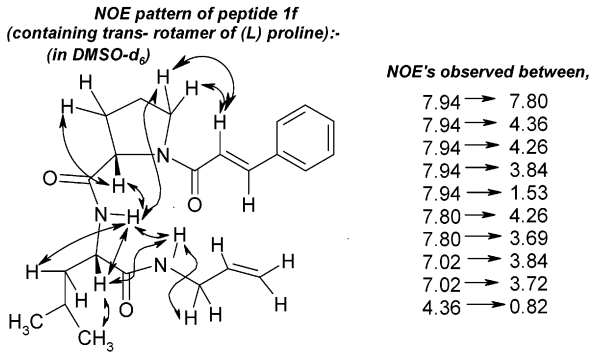


FIGURE 4. NOE's observed in **1f**.

In our case, for both peptides **1d** and **1f**, *Proline* can be considered as occupying the (*i*+1) position, so it is only the *trans*-cinnamoyl−*Proline* bond that can promote the formation of the turns in both cases. For peptide **1d**, a seven-membered ring (*γ*-turn) can form due to intramolecular hydrogen bonding between the cinnamoyl carbonyl and the NH of the *Leucine* residue (Figure 3) while for peptide **1f** there are possibilities for the formation of both a 7-membered ring, i.e. a *γ*-turn (due to similar kind of bonding as in **1d**), as well as a 10-membered ring (*β*-turn) due to intramolecular hydrogen bonding between the cinnamoyl carbonyl and the NH of the allyl amide (Figure 3). The solution NMR of **1f** in DMSO-d_6 shows two sets of signals in the ratio of 45:55 due to cis and trans rotamers, respectively, about the *Proline*−amide bond. Detailed analysis of NMR spectra was undertaken for both isomers and the spectral data for **1f** with trans and cis rotamers of *Proline* are presented in Tables 4 and 5, respectively.

To probe the existence and extent of intramolecular hydrogen bonding, variable-temperature NMR experiments are a very useful tool. The low magnitude of the chemical shift/temperature coefficient ($\Delta\delta/\Delta T$) for the amide proton is an indicator of its participation in H-boding. The ($\Delta\delta/\Delta T$) values for the cis isomer of **1f** have a large magnitude (ca. −6 ppb/°C) for both the NHs (Table 4) while it is moderately small (Table 3) for the trans isomer ($\Delta\delta/\Delta T = -3.4$ ppb/°C for allyl NH and −4.5 ppb/°C for Leu NH). It suggests that a sizable fraction of the trans isomer has allyl NH participating in H-bonding. The presence of such an H-bond coupled with the existence of NOESY peaks between *Leu* NH/allyl NH and strong *Proline* C_αH/*Leucine* NH suggest the preference of a *β*-turn around the *Proline-Leucine* residue (Figure 4).

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(8) For *β*-turn see: (a) Ball, J. B.; Hughes, R. A.; Alewood, P. L.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467 and references therein. (b) Haubner, R.; Finsinger, D.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1374. (c) Kim, K.; Germanas, J. P. *J. Org. Chem*. **1997**, *62*, 2853. (d) Jones, I. G.; Jones, W.; North, M. *J. Org. Chem*. **1998**, *63*, 1505. (e) Krauthauser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719.

TABLE 4. Chemical Shifts (ppm), Coupling Constants (Hz),[a] and Temperature Coefficients (ppb/°C) (DMSO-d_6) for Compound 1f (Trans)

protons	Pro	Leu	allyl
NH		7.94 (d) ($J_{NH-\alpha H} = 8.5$)	7.80 (t) ($J_{NH-\alpha H} = 5.6$)
CαH	4.36 (dd) ($J_{\alpha-\beta 1} = 4.0$, $J_{\alpha-\beta 2} = 8.5$)	4.26 (m) ($J_{\alpha-\beta(\text{pro S})} = 5.0$, $J_{\alpha-\beta(\text{pro R})} = 9.8$)	3.69 (m)
Cβ1H	2.13 (m)	1.5−1.6 (m)[b]	5.78 (m)
Cβ2H	2.10 (m)		($J_{\beta-\gamma-cis}$ =10.5, $J_{\beta-\gamma-trans} = 17.2$, $J_{\alpha 1-\beta} = 5.0$, $J_{\alpha 2-\beta} = 5.0$)
Cγ1H	1.92 (m)	1.5−1.6 (m)	5.13 (m) ($J_{\alpha-\gamma} = 1.7$, $J_{\gamma-\gamma} = 1.7$)
Cγ2H	1.83 (m)		5.02 (m)
Cδ1H	3.84 (m)	0.87 (d) (CH_3, $J_{\gamma-\delta(\text{pro R})} = 6.3$)	
Cδ2H	3.72 (m)	0.82 (d) (CH_3, $J_{\gamma-\delta(\text{pro S})} = 5.9$)	
others: 7.47 (d, $J = 15.5$, cinnamoyl βH), 7.02 (d, $J = 15.5$, cinnamoyl αH), 7.46−7.72 (phenyl)			
$\Delta\delta/\Delta T$ (ppb/°C)		−4.5	−3.4

[a] All J values are expressed in Hz. [b] Individual J values for both CβH and Leu residue could not be traced.

TABLE 5. Chemical Shifts (ppm), Coupling Constants (Hz),[a] and Tempareture Coefficients (ppb/°C) (DMSO-d_6) for Compound 1f (Cis)

protons	Pro	Leu	allyl
NH		8.33 (d) ($J_{NH-\alpha H} = 8.5$)	8.11 (t) ($J_{NH-\alpha H} = 5.6$)
CαH	4.71(dd) ($J_{\alpha-\beta 1}$=1.8, $J_{\alpha-\beta 2} = 8.6$)	4.32 (m) ($J_{\alpha-\beta(\text{pro S})} = 5.2$, $J_{\alpha-\beta(\text{pro R})} = 10.2$)	3.65 (m, 2H)
Cβ1H	2.22 (m)	1.45(ddd) ($J_{\beta(\text{pro R})-\beta(\text{pro S})} = 13.3$, $J_{\beta(\text{pro S})-\gamma} = 10.1$)	5.74 (ddt) ($J_{\beta-\gamma-\text{cis}} = 10.5$, $J_{\beta-\gamma-\text{trans}} = 15.4$, $J_{\alpha-\beta} = 5.0$)
Cβ2H	1.92 (m)	1.35 (m)	
Cγ1H	1.91 (m)	1.55 (m)	5.07 (dq, H-trans) ($J_{\alpha 1-\gamma-\text{trans}} = 1.7$, $J_{\gamma-\text{cis},\gamma-\text{trans}} = 1.7$, $J_{\alpha 2-\gamma-\text{trans}} = 1.7$, $J_{\alpha 2-\gamma-\text{cis}} = 1.7$)
Cγ2H	1.81 (m)		5.01 (dq, H-cis) ($J_{\beta-\gamma-\text{cis}} = 11.9$)
Cδ1H	3.55 (m)	0.66 (d) (CH_3, $J_{\gamma-\delta(\text{pro R})} = 6.6$)	
Cδ2H	3.47 (m)	0.61 (m) (CH_3, $J_{\gamma-\delta(\text{pro S})} = 6.3$)	
others: 7.44 (d, $J = 15.5$, cinnamoyl βH), 6.74 (d, $J = 15.5$, cinnamoyl αH), 7.46−7.72 (phenyl)			
$\Delta\delta/\Delta T$ (ppb/ °C)		−6.1	−6.3

[a] All J values are expressed in Hz.

We also observed that in both cis and trans isomers the *Leucine* side chain is fairly rigid. For the cis isomer the coupling constants $J_{\alpha-\beta(\text{pro R})} = 10.2$ Hz, $J_{\chi-\beta(\text{pro S})} = 5.2$ Hz, $J_{\beta(\text{pro R})-\gamma} = 4.7$ Hz, and $J_{\beta(\text{pro S})-\gamma} = 10.1$ Hz and strong NOE peaks between *Leucine* C_αH-*Leucine* C_δH-(pro *S*) and *Leucine* NH-*Leucine* β (pro *R*) support such conclusion. The values show that a very large fraction of rotamers (∼70%) have an N−C_α−C_β−C_γ angle about −60°(g⁻) and about 70% of the rotamers about the C_β−C_γ bond have an anti relationship between βH (pro *S*) and γH in both isomers. However, observations suggest very similar behavior of the *Leucine* side chain for both the cis and trans isomers (Tables 3 and 4). The NMR study was also performed by dissolving **1f** in a comparatively less polar solvent ($CDCl_3$), where it showed a preponderance of the trans isomer to a large extent (of ∼90%). Intramolecular hydrogen bonds are generally more stable in solvents with lower polarity. So, it can be safely assumed that a similar kind of structural organization as in DMSO-d_6 prevails in $CDCl_3$ also for compound **1f**.

For the olefin **1d**, in addition to studying the solution NMR of both rotamers in $CDCl_3$ we studied the NMR in DMSO-d_6 solvent also where the spectrum shows the presence of cis and trans isomers in equal proportion. NOSEY/TOCSY experiments were used in assigning the resonances to both isomers. The $\Delta\delta/\Delta T$ for the *Leucine* NH (in DMSO-d_6) has a large magnitude, which rules out the presence of intramolecular H-bonding in **1d**. Experiments were then performed in $CDCl_3$ solution where a majority of the population of the molecules in **1d** (∼80%) are found to possess trans conformation. The *Leucine* NH appeared at a low field with a δ value of 7.64 ppm, which indicates its possible participation in H-bonding (Table 6).

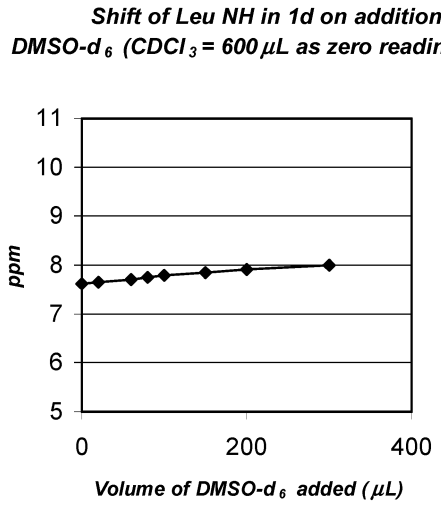
Additional support for such an H-bond in **1d** was gained from solvent titration as the addition of up to 33% DMSO (v/v) shifted the resonance signal by only 0.4 ppm (Chart 1). The most likely acceptor would be the carbonyl of the cinnamoyl group. A strong *Proline*$_\alpha$H/*Leucine* NH NOESY peak in addition to the above-mentioned H-bonding implies the propensity of a γ-turn in the mol-

TABLE 6. Chemical Shifts (ppm), Coupling Constants (Hz),[a] and Temperature Coefficients (ppb/°C) ($CDCl_3$) for Compound 1d (Trans)

protons	Pro	Leu	allyl
NH		7.64 (d, $J_{NH-\alpha H} = 7.4$)	
CαH	4.78 (dd) ($J_{\alpha-\beta1} = 1.9$, $J_{\alpha-\beta2} = 8.0$)	4.50 (m)	4.63 (dq) ($J_{\alpha1-\beta} = 3.2$, $J_{\alpha1-\alpha2} = 11.2$, $J_{\alpha1-\gamma} = 1.6$) 3.62 (dq) ($J_{\alpha2-\beta} = 3.2$, $J_{\alpha2-\gamma} = 1.6$)
Cβ1H	2.49 (m)	1.6−1.7 (m)	5.91 (m) ($J_{\beta-\gamma-trans} = 17.2$, $J_{\beta-\gamma-cis} = 10.5$)
Cβ2H	1.86 (m)	1.6−1.7 (m)	
Cγ1H	2.18 (m)	1.6−1.7 (m)	5.35 (m)
Cγ2H	2.05 (m)		5.24 (m)
Cδ1H	3.76 (m)	0.88 (d)	
Cδ2H	3.64 (m)	0.914 (d) (CH_3, $J_{\gamma-\delta} = 6.1$)	
others: 7.75 (d, $J = 15.5$, cinnamoyl CβH), 6.75 (d, $J = 15.5$, cinnamoyl CαH), 7.3−7.6 (phenyl)			
$\Delta\delta/\Delta T$ (ppb/°C)		−4.0	

[a] All J values are expressed in Hz.

CHART 1. ^{1}H NMR Titration Study on 1d in $CDCl_3$-DMSO-d_6



ecule. The NOE pattern for **1d** is described in Figure 4. The observations obtained from NMR studies are consistent with Molecular Dynamics (MD) calculation studies discussed subsequently.

Molecular dynamics (MD) calculations for compounds **1d** and **1f** were carried out with the Cerius[2] program on a Silicon graphics Indigo[2] workstation. Charges were calculated by using the charge-equilibration method and the CFF9 force field with default parameters were used throughout the simulations. To understand the conformational freedom, Simulated Annealing Molecular Dynamics calculations were carried out. The temperature was varied between 300 and 1200 K in steps of 50 K for 100/150 cycles. The molecules were allowed to equilibrate for 0.5 ps for every change in temperature. Minimizations were done first with steepest descent, followed by conjugate gradient methods for a maximum of 1000 iterations each or a root-mean-sauare deviation of 0.01 kcal/mol, whichever was earlier. The energy-minimized structures were then subjected to MD simulations. Various conformers obtained in each MD run were minimized by using the above-mentioned minimization protocol. The majority of peptides having trans conformations at the *Proline* residue in $CDCl_3$ indicate the propensity of β- or

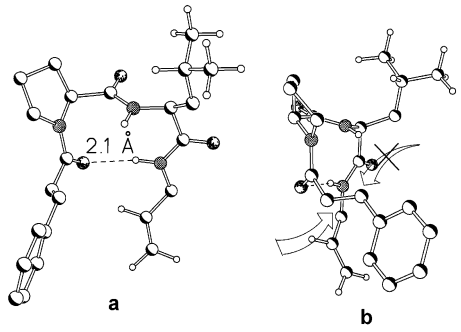
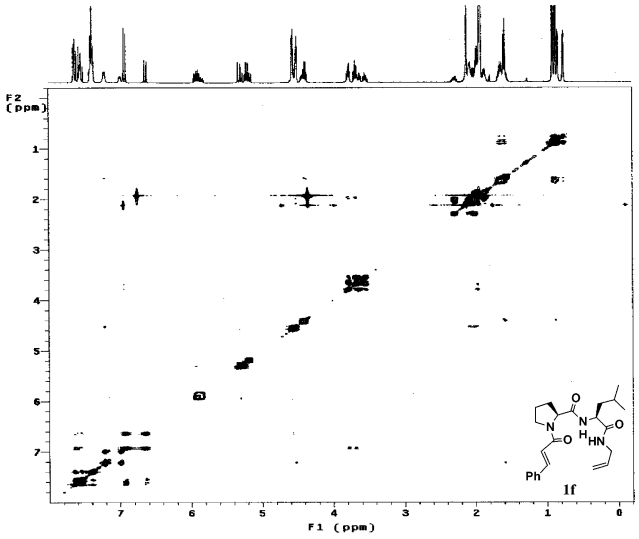


FIGURE 5. (a) The hindrance of one of the π-faces in **1f** due to formation of a β-turn. (b) The crossed arrow points out the hindered face of the olefin in **1f** while the uncrossed arrow points out the unhindred face and explains the observed stereoselectivity.

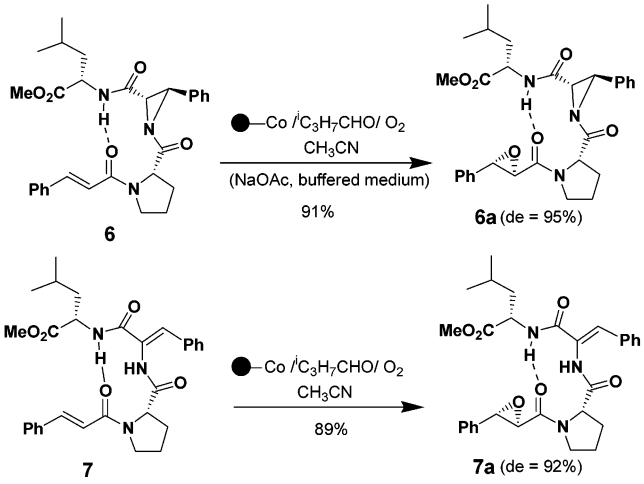
γ-turns in amide **1f** as well as ester **1d**. It is evident from MD study that for olefin **1f**, there is a strong indication for the presence of a β-turn and that this turn is more efficient in inducing selectivity toward epoxidation with very effective hindrance of one of the π-faces of the olefin (Figure 5). The low-energy conformer, which explains this selectivity was chosen from the MD trajectory files in which the hydrogen bond diststance (between *Leucine* NH and cinnamoyl carbonyl) of 2.1 Å is indicative of the presence of a β-turn around the *Proline-Leucine* system (Figure 5). Again, it is clear from the diagram that the structural organization due to the presence of this β-turn in the peptide renders only one face of the olefin free for the approach of the oxygen during epoxidation to give rise to the observed diastereoelectivity (2*R*,3*S*).

The NMR studies in $CDCl_3$ and DMSO-d_6 clearly indicate that these peptides are existing as organized structures in solution. It is interesting to note that even in a highly polar solvent like DMSO and considerably polar solvent like $CDCl_3$ the peptides **1d** and **1f** exhibit the presence of γ- and β-turns, respectively. Furthermore, we have carried out NMR studies in CD_3CN, which also happens to be the medium for these epoxidation reactions. The trans:cis ratios of the *Proline* rotamers in CD_3CN for both peptides (**1d** and **1f**) are ∼9:1 which clearly support that the majority of the peptides exist with the trans rotamer of *Proline* (the NOESY spectrum of **1f** in

CHART 2. NOESY Spectra of 1f in CD_3CN



SCHEME 3



CD_3CN is shown in Chart 2). The presence of such highly organized structures in acetonitrile medium suggests that the transition state geometries of these molecules during epoxidation may be controlled by the formation of intramolecular hydrogen bonds leading to organized γ- or β-turns.

Hence, the 2D solution NMR of the olefins (**1d** and **1f**) and their MD simulation studies clearly suggest that the epoxidations may be occurring on preorganized structures formed due to the presence of γ- or β-turns. Thus, the high facial selectivity in epoxidation of **1c**−**e** can be explained by invoking the possibility of these reactions taking place on preorganized structures resulting from the formation of γ- and β-turns due to intramolecular H-bonding. The tripeptides **1c**−**e** can adopt a seven-membered γ-turn thereby forcing the cinnamoyl group to exist with trans, s-cis geometry (Figure 6, A) as the corresponding s-trans geometry will be disfavored due to nonbonding interactions. The seven-membered γ-turn will render only one face of the cinnamoyl double bond exposed and thus epoxidation via such organized structures will be facially selective. A similar explanation can be offered for the high enantioselectivity during epoxidation of **1f**−**h,** which would take place on well-organized

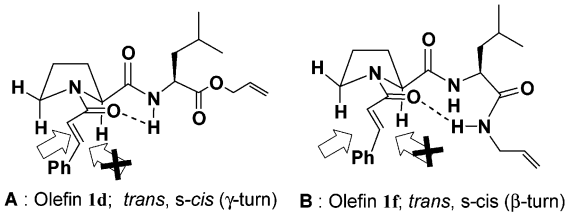


FIGURE 6. The structural organization in **1d** and **1f** that explains the observed diastereoselectivity.

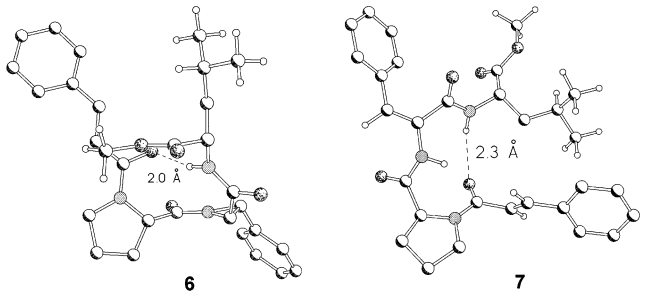


FIGURE 7. Hindrance of one of the π-faces of the cinnamoyl bond in **6** and **7** due to the formation of a β-turn.

β-turn conformations (Figure 6B) and will render such epoxidations facially selective.

That the high enantioselectivity is dictated by the β-turn is again seen during the epoxidation of *N*-cinnamoyl peptides **6** and **7**, which are constrained to have an intramolecular ten-membered hydrogen bond (Scheme 3). The constraint present due to aziridine and dehydrophenylalanine residues in **6** and **7**, respectively, is responsible for coaxing the carbonyl group of the cinnamoyl and amino group of the *Leucine* residue to adopt a geometry, which encourages the intramolecular hydrogen bond, whose presence is also established by NMR titrations.[8] This intramolecular hydrogen bonding pre-organizes[9] the cinnamoyl group to undergo facially selective aerobic epoxidation under catalysis of polyaniline-supported cobalt salen to give predominantly diastereomers **6a** and **7a**, respectively, with a de >90, as indicated by HPLC. The absolute configuration for **6a** and **7a** is assigned as 2*R*,3*S* by analogy with epoxides **2f**−**h**.

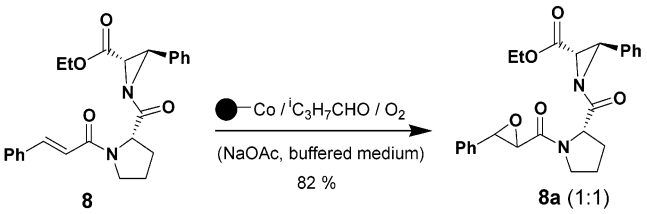
The selected low-energy conformers of **6** and **7** from the MD trajectory files are shown in Figure 7. It is evident from these figures that both structures are preorganized as β-turns due to the presence of intramolecular hydrogen bonds.

The hydrogen bond distances in these structures are typical (2.3−2.0 Å). The structures clearly show that one of the π-faces of the cinnamoyl double bond in both cases of aziridine peptide **6** and dehydrophenylalanine derived tripeptide **7** is hindered by the ester part and the side chain of the *Leucine* residue, respectively. The diastereoselectivity of the epoxidations is expected to be achieved from the less hindered side of the cinnamoyl double bond. The NMR, MD studies clearly vindicate the diastereoselectivity observed during epoxidation of these tripeptides.

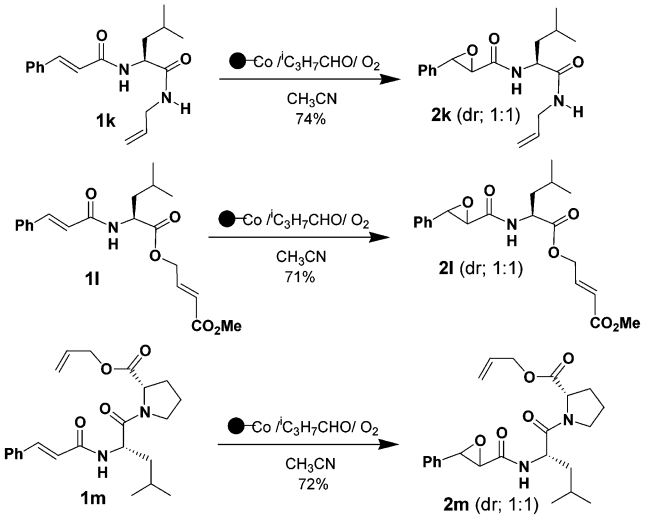
Interestingly, optically pure aziridine peptide **8**, which also does not have features to preorganize itself forming

(9) Prabhakaran, E. N.; Nandy, J. P.; Shukla, S.; Tewari, A.; Das, S. K.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6461.

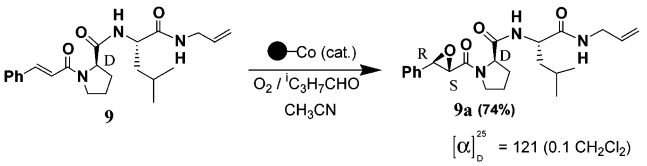
SCHEME 4



SCHEME 5



SCHEME 6



a turn, also undergoes a nondiastereoselective epoxidation at its cinnamoyl end under the same reaction conditions giving an ~1:1 mixture of diastereomeric epoxides **8a** (Scheme 4).

It is noteworthy, though not particulary surprising, that PASCOS catalyzed diastereoselectivity is very specific to the presence of *Proline* residue in the *i*+1 position as any other amino acid in this place does not exercise any control on the facial selectivity. This is amply clear from the epoxidation of peptides **1k**, **1l**, and **1m** (*Proline* in the *i*+2 position), which showed no diastereoselectivity during PASCOS catalyzed oxidation, as a diastereomeric mixture of the corresponding epoxides **2k**, **2l**, and **2m**, respectively, was obtained in good yields (Scheme 5). The ^{1}H NMR studies on **1k**, **1l**, and **1m** revealed the absence of intramolecular hydrogen bonds in these peptides.

It is also interesting to note here that the chirality of the *Proline* residue controls the diastereoselectivity in **1** as replacing the L-*Proline* in **1f** with D-*Proline* gives rise to **9** whose epoxidation under polyaniline catalyzed reaction leads to the corresponding epoxide **9a**. The sign and magnitude of optical rotation ($[\alpha]_D$ +121; CH_2Cl_2) of **9a** indicates that the epoxide stereochemistry in it is opposite to that present in **1f** (Scheme 6). This result further confirms the role of γ- or β-turn in structural preorganization of the *N*-cinnamoyl-L-proline derived peptides during the epoxidation reaction.

In conclusion, we have developed a novel diastereoselective aerobic epoxidation of the cinnamoyl peptides, catalyzed by polyaniline-supported cobalt salen. The origin of this diastereoselectivity has been attributed to the propensity of the *N*-cinnamoyl *Proline* amide to exist predominantly as the trans rotamer in CH_3CN medium. Existence of these peptides as organized structures (γ- and β-turns) is due to the presence of intramolecular hydrogen bonds. By extensive solution NMR and MD simulation studies we have concluded that the origin of the high facial selectivity is due to the well-defined γ- and β-turns which result in the hindrance of one face of the cinnamoyl double bond in the transition state of the epoxidation reaction. The proposal is finally supported by carrying out a highly diastereoselective epoxidation on peptides, which are constrained to form intramolecular hydrogen bonding leading to a β-turn.

Experimental Section

Materials and Methods. Acetonitrile, ethyl acetate, hexane, THF, and all other solvents were purified by standard procedures. All the amino acids were purchased from Spectrochem, India Limited and used as such. Polyaniine supported Co(salen) was prepared according to the procedure developed in our laboratory. Column chromatography was performed on ACME silica gel eluant. TLC was performed on ACME silica-G coated glass plates that were irradiated with iodine or Kieselgel 60 GF_{254} coated glass plates that were irradiated with a UV lamp. ^{1}H NMR spectra were recorded using JEOL PMX-60, Bruker WP-80, JEOL 300 FT NMR, JNM-LA 400 FTNMR Varian Gemini 2000 NMR, or JEOL 200 FT NMR machines in $CDCl_3$ or in DMSO-d_6. Chemical shifts are given relative to TMS in ppm (δ). Multiplicity is indicated by the following abbreviations: singlet (s); br s (broad singlet); doublet (d); dd (doublet of a doublet); dt (doublet of a triplet); td (triplet of a doublet); ddd (doublet of a doublet of a doublet); q (quartet); and m (multiplet). The FAB mass spectra were recorded on a JEOL SX 102/DA 6000 mass spectrometer data system using argon (6 kV, 10 mA) as the FAB gas and on Hewlett-Packard, 5989A mass spectrometer and PE SICEX API 300 LC-MS machines with isobutane as the gas. IR spectra were recorded on a Perkin-Elmer 683 spectrophotometer and a Perkin-Elmer 1650 spectrophotometer using either a neat sample or a solution in $CDCl_3$/CH_2Cl_2 and solids were examined as KBr pellets and the values are reported in ν_{max} (cm^{-1}). HPLC analyses were done with a Rainin system fitted with a Dynamax SD-200 pump and detected with a Groton PDA solonet Diode Array Detector.

Preparation of Polyaniline. Freshly distilled aniline (10 mL, 109.5 mmol) was dissolved in 125 mL of 1.5 M HCl and a solution of ammoniumpersulfate (54.8 mmol) in 1.5 M HCl (125 mL) was added to it at 0 °C. Since aniline polymerization is strongly exothermic, the oxidant was added slowly over a period of 1 h. After the addition of the oxidant was over the reaction mixture was stirred for an additional 4 h. The polyaniline hydrochloride precipitated and was separated by filtration and rinsed consecutively with water (3 × 30 mL), methanol (2 × 25 mL), and diethyl ether (2 × 15 mL) to remove the oligomers and any possible side products. The polymer was then vacuum-dried until constant mass. Deprotonation of polyaniline hydrochloride was achieved with aqueous ammonia (3 wt %). Deprotonated polymer was again washed with water, methanol, and diethyl ether and dried until constant mass (~3 g). Polyaniline is quiet stable in air and can be stored indefinitely in closed glass vials.

Preparation of Polyaniline-Supported Cobalt(II) Salen (PASCOS). Cobalt(II) salen (200 mg) and polyaniline (200 mg) were added to a solution of acetic acid (25 mL) in acetonitrile (25 mL) and the mixture was stirred at ambient temperature

for 36 h. The resultant catalyst was filtered off and washed first with acetic acid (3 × 10 mL) and then thoroughly with acetonitrile until the filterate was colorless. The resulting residue was dried in an air oven at 110 °C for 2 h to afford the black (or blakish brown) catalyst (325 mg). The presence of cobalt(II) species in this catalyst was confirmed by UV and EPR spectroscopy. PASCOS is stable to atmosphere and can be stored indefinitely in closed vials.

Synthesis of Methyl-*N*-cinnamoyl (L)-Prolinate (1a). To a stirring, ice-cold solution of cinnamic acid (1.15 g, 10 mmol) and triethylamine (1.4 mL, 10 mmol) in THF (15 mL) was added isobutyl chloroformate (1.29 mL, 10 mmol) and the mixture was stirred vigorously for 1 min, after which a solution of the methyl-(L)-prolinate hydrochloride (1.82 g, 11 mmol) in DMSO (4−5 mL) was added followed by triethylamine (3.1 mL, 22 mmol) dissolved in THF (15 mL). The reaction vessel was allowed to warm to room temperature and vigorously stirred for an additional 3−4 h. Triethylamine hydrochloride was filtered off on a sintered funnel under suction and washed with THF. Removal of solvent from the filtrate in vacuo yielded a residue, which was taken in EtOAc (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic layer was isolated and dried over anhydrous Na_2SO_4 and after evaporation of solvent in vacuo the resulting mass was subjected to column chromatography (EtOAc:hexane 1:2) to afford **1a** as a crystalline solid (mp 58 °C) in good yields (74%).

^{1}H NMR ($CDCl_3$, 60 MHz): δ 7.55 (d, J = 14.6 Hz, 1H); 7.2−7.11 (m, 5H); 6.6 (d, J = 14.8 Hz, 1H); 4.6−4.5 (m, 1H); 3.68 (br s, 3H); 3.52−3.41 (m, 2H); 2.2−1.8 (m, 4H).

Synthesis of Allyl-*N*-cinnamoyl (L)-Proline Amide (1b). To a stirring ice cold solution of *N*-cinnamoyl-proline (2.45 g, 10 mmol) and triethylamine (1.4 mL, 10 mmol) in THF (15 mL) was added isobutylchloroformate (1.29 mL, 10 mmol) and the mixture was stirred vigorously for 50−60 s, after which a solution of allyl amide (1.2 mL, 15 mmol) in THF (10 mL) was added followed by triethylamine (2.1 mL, 15 mmol) dissolved in THF (10 mL). The reaction vessel was allowed to warm to room temperature and vigorously stirred for further 3−4 h. Triethylamine hydrochloride was filtered off on a sintered funnel under suction and solvent was removed in vacuo. The resulting residue was taken in EtOAc (40 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL), water (2 × 10 mL), and brine (1 × 10 mL). Drying the organic layer (anhyd. Na_2SO_4) and concentration in vacuo yielded a thick residue that was further purified by column chromatography (Silicagel-EtOAc:hexane 1:1.5) to yield allyl-*N*-cinnamoyl-proline amide **1b** in good yield (81%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, J = 15.4 Hz, 1H); 7.56−7.53 (m, 2H); 7.49 (br s, 0.8H); 7.40−7.38 (m, 3H); 6.76 (d, J = 15.4 Hz, 1H); 6.27 (m, 0.2H); 5.88−5.79 (m, 1H); 5.18 (dd, J = 17.9, 1.2 Hz, 1H); 5.11 (d, J = 8.56 Hz, 1H); 4.76 (d, J = 7 Hz, 1H); 3.93−3.84 (m, 2H); 3.81−3.74 (m, 1H); 3.66−3.61 (m, 1H); 2.54−2.51 (m, 1H); 2.18 (dt, J = 18.3, 9.3 Hz, 1H); 2.08−2.04 (m, 1H); 1.91−1.81 (m, 1H).

Synthesis of Methyl-*N*-cinnamoyl-(L)-proline-(L)-leucinate (1c). A stirring solution of *N*-cinnamoyl-(L)-proline (2.45 g, 10 mmol) and triethylamine (1.4 mL, 10 mmol) in THF (15 mL) was cooled to −10 °C in an ice-salt bath and to it was added isobutylchloroformate (1.29 mL, 10 mmol) with vigorous stirring for 50−60 s. Then a solution of methyl-(L)-leucinate hydrochloride (2.00 g, 11 mmol) in DMSO (0.5 mL) was added followed by a solution of triethylamine (3.1 mL, 22 mmol) in THF (15 mL). The mixture was warmed to room temperature by removal of the ice bath and vigorously stirred for further 4 h. Triethylamine hydrochloride was filtered off on a sintered funnel under suction and washed twice with THF. Removal of solvent from the filtrate in vacuo yielded a residue, which was dissolved in EtOAc (30 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). Drying (Na_2SO_4) and evaporation of solvent in vacuo yielded the crude product, which was further purified by column chromatography (EtOAc: Hexane = 1:1.5) to yield methyl-*N*-cinnamoyl-(L)-proline-(L)-leucinate **1c** as a solid (mp 110−11 °C) in good yield (80%); $[\alpha]^{25}_D$ −170.5° (c = 0.01, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 15.3 Hz, 1H), 7.65 (d, J = 7.32 Hz, 1H), 7.56−7.53 (m, 2H), 7.39−7.35 (m, 3H), 6.76 (d, J = 15.6 Hz, 1H), 4.78 (d, J = 6.84 Hz, 1H); 4.57−4.47 (m, 2H); 3.73 (s, 3H); 3.71−3.59 (m, 2H); 2.51−2.46 (m, 1H); 2.06−2.03 (m, 1H); 2.21−2.12 (m, 1H); 1.89−1.81 (m, 3H); 1.67−1.56 (m, 2H); 0.91 (d, J = 5.6 Hz, 3H); 0.88 (d, J = 5.6 Hz, 3H). FT-IR (CH_2Cl_2): 3278, 3059, 2956.5, 2872.7, 1744.8, 1649.6, 1598.1, 1542.1, 1498.0, 1425.3 cm^{-1}.

Synthesis of Allyl-*N*-cinnamoyl-(L)-proline-(L)-leucinate (1d). To a solution of *N*-cinnamoyl-(L)-proline-(L)-leucine (1.25 g, 3.5 mmol) in acetone (20 mL) was added K_2CO_3 (0.351 g, 3.85 mmol) and allyl bromide (0.47 g, 3.85 mmol) and the reaction mixture was set to reflux for 8 h, at which point complete conversion had taken place. The inorganic salt was filtered off and solvent was removed in vacuo. The resulting residue was subjected to purification by column chromatography (Silica gel-EtOAc:hexane 40:60) to afford **1d** in good yield (84%).

^{1}H NMR data (500 MHz) for compound **1d** in DMSO-d_6 are presented in Table 5 for the trans rotamer of the proline residue.

Synthesis of Methyl-4-*N*-cinnamoyl- (L)-proline-(L)-leucinyl)-crotonate (1e). To a solution of *N*-cinnamoyl-(L)-proline-(L)-leucine (0.54 g, 1.5 mmol) in acetone (7.5 mL) was added K_2CO_3 (0.23 g, 1.65 mmol) and methyl-4-bromocrotonate (0.27 g, 1.5 mmol) and the reaction mixture was set to reflux for 8 h during which time the reaction is almost complete. The inorganic salts were filtered off on a sintered funnel under suction and solvent was removed in vacuo. The resulting residue was taken up in EtOAc (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). Drying the organic layer (anhyd. Na_2SO_4) and concentration in vacuo yielded a thick residue that was further purified by column chromatography (EtOAc in hexane, 40%) (TLC: R_f = 0.5; hexane:ethyl acetate 1:1) to yield methyl-4-(*N*-cinnamoyl-(L)-proline-(L)-leucinyl)-crotonate **1e** as a white solid (mp 92 °C) in good yield (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.3 Hz, 1H); 7.75 (d, J = 15.5 Hz, 1H); 7.56−7.53 (m, 2H); 7.41−7.39 (m, 3H); 6.94 (td, J = 15.9, 4.64 Hz, 2H); 6.78 (d, J = 15.6 Hz, 1H); 6.08 (td, J = 15.9, 1.9 Hz, 1H); 4.79 (dd, J = 4.9, 1.9 Hz, 2H); 4.64 (d, J = 3.2 Hz, 1H); 4.51 (dd, J = 12.9, 5.6 Hz, 1H); 3.79−3.74 (m, 1H); 3.75 (s, 3H); 3.68−3.61 (m, 1H); 2.53−2.48 (m, 1H); 2.29−2.28 (m, 1H); 2.18−2.02 (m, 1H); 1.91−1.81 (m, 1H); 1.70−1.62 (m, 3H); 0.93 (d, J = 5.8 Hz, 3H); 0.89 (d, J = 5.8 Hz, 3H).

Synthesis of Allyl-*N*-cinnamoyl-(L)-proline-(L)-leucine Amide (1f). To a stirring ice-cold solution of *N*-cinnamoyl-(L)-proline-(L)-leucine (1.79 g, 5 mmol) and triethylamine (0.7 mL, 5 mmol) in THF (10 mL) was added isobutyl chloroformate (0.65 mL, 5 mmol) and the mixture was stirred vigorously for 50−60 s, after which a solution of allylamine (0.6 mL, 7.5 mmol) in THF (10 mL) was added followed by triethylamine (1.1 mL, 8 mmol) dissolved in THF (10 mL). The reaction mixture was allowed to come to room temperature and further stirred for 3−4 h. Inorganic salt was filtered off followed by removal of the solvent in vacuo. The residue then was taken up in EtOAc (35 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by column chromatography (Silicagel-EtOAc−hexane 2:3) to afford allyl-*N*-cinnamoyl-(L)-proline-(L)-leucine amide **1f** as a crystalline solid (mp 123−24 °C) in excellent yield (88%).

^{1}H NMR data (500Mz) for compound **1f** in DMSO-d_6 are presented in Table 3 and Table 4 for trans and cis rotamers of proline residue, respectively.

Synthesis of Allyl-*N*-cinnamoyl-(L)-proline-(L)-leucine-glycinate (1g). To a solution of *N*-cinnamoyl-(L)-proline-(L)-leucine-glycine (0.83 g, 2 mmol) in acetone (15 mL) was added K_2CO_3 (0.455 g, 3.3 mmol) and allyl bromide (0.268 g, 2.2 mmol) and the reaction mixture was set to reflux for 8 h, at which point complete conversion had taken place. The inorganic salt was filtered off and solvent was removed in vacuo. The resulting residue was subjected to purification by column chromatography (Silica gel-EtOAc:hexane 45:55) to afford **1g** in good yield (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 15.4 Hz, 1H); 7.55−7.53 (m, 2H); 7.39−7.27 (m, 3H); 6.84 (d, J = 8.6 Hz, 1H); 6.75 (d, J = 15.4 Hz, 1H); 5.90 (ddd, J = 22.9, 11.7, 5.8 Hz, 1H); 5.33 (dd, J = 17.5, 1.4 Hz, 1H); 5.24 (dt, J = 10.5, 1.2 Hz, 1H); 4.74 (d, J = 6.1 Hz, 1H); 4.63 (d, J = 5.6 Hz, 2H); 4.48−4.45 (m, 1H); 4.14 (dd, J = 8.1,, 5.5 Hz, 1H); 3.97 (dd, J = 18.1, 5.5 Hz, 1H); 3.81−3.79 (m, 1H); 3.70 (dd, J = 8.8, 7 Hz, 1H); 2.37−2.24 (m, 1H); 2.14−1.99 (m, 3H); 1.83−1.81 (m, 1H); 1.59−1.52 (m, 2H); 0.89 (d, J = 6.1 Hz, 3H); 0.86 (d, J = 6.1 Hz, 3H).

Synthesis of Allyl-*N*-cinnamoy-(L)-proline-(L)-leucine-(L)-isoleucinate (1h). To a solution of *N*-cinnamoyl-(L)-proline-(L)-leucine-(L)-isoleucine (1.41 g, 3 mmol) in acetone (15 mL) was added K_2CO_3 (0.455 g, 3.3 mmol) and allyl bromide (0.403 g, 3.3 mmol) and the reaction mixture was set to reflux for 8 h during which time the reaction was almost complete. The inorganic salts were filtered off on a sintered funnel under suction and solvent was removed in vacuo. The resulting residue was taken up in EtOAc (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL) ,and brine (1 × 10 mL). Drying the organic layer (anhyd. Na_2SO_4) and concentration in vacuo yielded a thick residue that was further purified by column chromatography (EtOAc in hexane, 50%) (TLC: R_f = 0.5; hexane:ethyl acetate 1:1) to yield methyl-4-(*N*-cinnamoyl-(L)-proline-(L)-leucinyl)-crotonate **1h** as a white solid in good yield (68%). $[\alpha]^{25}_D$ −171° (*c* 0.0075, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 15.4 Hz, 1H); 7.56−7.49 (m, 2H); 7.41−7.35 (m, 3H); 6.84 (d, J = 8.56 Hz, 1H); 6.74 (d, J = 15.6 Hz, 1H); 5.96−5.85 (m, 1H); 5.33 (td, J = 17.3, 1.5 Hz, 1H); 5.23 (td, J = 9.3, 1.2 Hz, 1H); 4.79−4.74 (m, 1H); 4.64−4.49 (m, 3H); 4.39−4.34 (m, 1H); 3.79−3.76 (m, 1H); 368−3.63 (m, 1H); 2.46−2.41 (m, 1H); 2.17−1.74 (m, 5H); 1.64−1.42 (m, 4H); 0.97−0.80 (m, 12H).

Synthesis of Methyl-*N*-(3-phenylglycidyl)-(L)-prolinate (2a). To a solution of methyl-*N*-cinnamoyl-(L)-prolinate (**1a**) (0.52 g, 2 mmol) in CH_3CN (10 mL) was added 2-methylpropanal (0.365 mL, 4 mmol) and PASCOS (∼0.005 g) and the mixture were stirred under oxygen atmosphere at room temperature for 12 h. After this time, a fresh sample of the catalyst and 2-methylpropanal (0.365 mL, 4 mmol) were added to the reaction mixture and allowed to stir, until complete conversion of the olefin (TLC: R_f = 0.5; hexane:ethyl acetate 1:2). The catalyst was filtered off on a sintered funnel and acetonitrile was removed in vacuo. The resulting residue was taken in EtOAc (25 mL) and washed successively with a saturated solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). Separating the organic phase, drying (Na_2SO_4), and concentration in vacuo yielded the corresponding oxirane containing peptide in high purity and yield (HPLC). This was further subjected to purification by column chromatography (silica gel; EtOAc:hexane 2:3) to afford the pure epoxide **2a** (94%; HPLC) as a gum in 40% yield. $[\alpha]^{25}_D$ −201° (*c* 0.01, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.2 (m, 5H); 4.60 (dd, J = 8.32, 4 Hz, 0.3H); 4.55 (dd, J = 8.32, 4 Hz, 0.7H); 4.14 (d,J = 1.92 Hz, 0.1 H); 4.07 (d, J = 1.88 Hz, 0.7H); 3.98 (d, J = 1.88 Hz, 0.2H); 3.74 (s, 3H); 3.71−3.61 (m, 2H); 3.59 (d, J = 1.9 Hz, 1H); 2.29−1.90 (m, 4H). IR (Neat) ν_{max} 3440−3280 (br), 1790, 1725, 1660, 1520 cm^{-1}.

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline Amide (2b). To a solution of allyl-*N*-cinnamoyl-proline amide (**1b**) (0.426 g, 1.5 mmol) in CH_3CN was added 2-methylpropanal (0.272 mL, 3 mmol) and PASCOS (∼0.005 g) and the mixture was stirred under oxygen atmosphere at ambient temperature for 12 h. After this time, a fresh sample of the catalyst and 2-methylpropanal (0.272 mL, 3 mmol) were added to the reaction mixture and allowed to stir, until (22 h) complete conversion of the olefin (TLC: R_f = 0.5; hexane:ethyl acetate 3:2). The catalyst was filtered off on a sintered funnel and acetonitrile was removed in vacuo. The resulting residue was taken up in EtOAc (30 mL) and washed successively with a saturated solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). Separating the organic phase, drying (Na_2SO_4), and concentration in vacuo yielded the corresponding oxirane containing peptide in high purity and yield (HPLC). This was further subjected to purification by column chromatography (silica gel-EtOAc:hexane 1:1.5) to get the pure epoxide **2b** (40%) as a gum. $[\alpha]^{25}_D$ −180° (*c* 0.01, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J = 7.32 Hz, 0.2H); 7.34−7.36 (m, 2H); 7.32−7.29 (m, 3H); 7.14 (m, 0.8H); 5.85−5.8 (m, 1H); 5.18 (ddd, J = 15.4, 3.4, 1.8 Hz, 1H); 5.11 (ddd, J = 10.2, 4.16, 1.48 Hz, 1H); 4.67−4.65 (m, 1H); 4.1 (d, J = 1.92 Hz, 0.3H); 4.09 (d, J = 2.04 Hz, 0.7 Hz); 3.90−3.78 (m, 2H); 3.69−3.66 (m, 1H); 3.63 (J = 1.8 Hz, 0.8H); 3.61 (d, J = 1.9 Hz, 0.2H); 3.54−3.50 (m, 1H); 2.47−2.4 (m, 1H), 2.22−2.12 (m, 1H); 2.04−1.97 (m, 1H); 1.95−1.84 (m, 1H). MS (*m*/*z*): 301 (M^+), 285, 243, 27, 216, 199, 154.

Synthesis of Methyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucinate (2c). To a solution of the methyl-*N*-cinnamoyl-(L)-proline-(L)-leucinate (**1c**) (0.744 g, 2 mmol) in CH_3CN (10 mL) was added 2-methylpropanal (0.363 mL, 4 mmol) and PASCOS (∼0.005 g) and the mixture was stirred under oxygen atmosphere at room temperature for 12 h. After this time, a fresh sample of the catalyst and 2-methylpropanal (0.363 mL, 4 mmol) were added to the reaction mixture which was allowed to stir until complete (21 h) conversion of the olefin (TLC: R_f = 0.5; hexane:ethyl acetate 1:1). The catalyst was filtered off on a sintered funnel and acetonitrile was removed in vacuo. The resulting residue was taken up in EtOAc (20 mL) and washed successively with a saturated solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). Separating the organic phase, drying, and concentration in vacuo yielded the corresponding oxirane containing peptide in high purity and yield (HPLC). This was further subjected to column chromatography (silica gel; EtOAc:hexane 2:3) purification to afford the pure epoxide **2c** (93%; HPLC) as a solid (45%; mp 89−90 °C). $[\alpha]^{25}_D$ −183° (*c* 0.01, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.20 (m, 5H); 7.12 (d, J = 7.32 Hz, 1H); 4.61−4.57 (m, 1H); 4.44−4.38 (m, 1H); 4.12 (br s, 0.2H); 4.09 (d, J = 1.9 Hz, 0.8H); 3.78−3.71 (m, 1H); 3.73 (s, 3H); 3.60 (d, J = 1.9 Hz, 1H); 3.56−3.47 (m, 1H); 2.42−2.38 (m, 1H); 2.2−2.14 (m, 1H); 2.08−1.84 (m, 5H); 0.95 (d, J = 5.6 Hz, 3H); 0.92 (d, J = 5.6 Hz, 3H). MS (*m*/*z*): 389 (M^+), 339, 307, 281, 269, 244, 216, 209, 181, 154, 136. IR ν_{max}: 3200 (br), 3030, 2910, 2880, 1760, 1655 cm^{-1}

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucinate (2d). To a solution containing allyl-*N*-cinnamoyl-(L)-proline-(L)-leucinate (**1d**) (0.796 g, 2 mmol) in CH_3CN (10 mL) was added 2-methylpropanal (0.363 mL, 4 mmol) and PASCOS (∼0.005 g) and the mixture was stirred under oxygen atmosphere at room temperature for 12 h. After that a fresh sample of catalyst and 2-methylpropanal (0.363 mL, 4 mmol) were added to the reaction mixture and stirring was continued until complete conversion of the olefine to epoxide, the catalyst was filtered off, and solvent was removed. The residue then was taken up in EtOAc (35 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by column chromatography (silica gel-EtOAc−hexane 2:3) to isolate the major diastereomer of allyl-*N*-(3-

phenylglycilyl)-(L)-proline-(L)-leucinate **2d** (40%). $[\alpha]^{25}_D$ −161° (*c* 0.01, CH_2Cl_2).

^{1}H NMR (80 MHz, $CDCl_3$): δ 7.45−7,20 (m, 6H); 5.85−5.80 (m, 1H); 5.30 (d, J = 16 Hz, 1H); 5.10 (d, J = 10 Hz, 1H); 4.9−4.8 (m, 1H); 4.65−4.55 (m, 3H); 4.00 (d, J = 2 Hz, 0.8H); 3.98 (s, 0.2H); 3.75−3.5 (m, 2H); 3.55 (s, 1H); 2.2−1.8 (m, 7H); 0.95 (d, J = 6 Hz, 6H). MS (*m*/*z*): 415 (M^+), 357, 326, 295, 267, 209, 181, 149.

Synthesis of Methyl-4-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucinyl-crotonate (2e). To a solution of methyl-4-*N*-cinnamoyl-(L)-leucinyl-crotonate (**1e**) (0.538 g, 1.5 mmol) in CH_3CN (5 mL/mmol) was added 2-methylpropanal (0.272 mL, 3 mmol) and PASCOS (∼0.005 g) and the mixture was stirred under oxygen atmosphere at room temperature for 12 h. After this time, a fresh sample of the catalyst and 2-methylpropanal (0.272 mL, 3 mmol) were added to the reaction mixture whcih was allowed to stir until complete conversion of the olefin to the epoxide (TLC: R_f = 0.45; hexane:ethyl acetate 1:2.5). The catalyst was filtered off on a sintered funnel and acetonitrile was removed in vacuo. The resulting residue was taken up in EtOAc (20 mL) and washed successively with a standard solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). Separating the organic phase, drying, and concentration in vacuo yielded the corresponding oxirane containing peptide as a crude residue. This crude residue was further subjected to column chromatography (silica gel; EtOAc: hexane 1:2) for purification to get the pure epoxide **2e** (91%; HPLC) in good yield (50%) as a gum. $[\alpha]_D$ −108° (*c* 0.01, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 0.5H); 7.32−7.29 (m, 2H); 7.25−7.20 (m, 3H); 6.86 (td, J = 15.6, 4.6 Hz, 1H); 6.5 (d, J = 8.56 Hz, 0.5H); 5.98 (dd, J = 15.9, 2 Hz, 1H); 4.72 (dd, J = 4.6, 1.96 Hz, 2H); 4.61 (d, J = 8 Hz, 1H); 4.48−4.44 (m, 1H); 3.99 (d, J = 1.7 Hz, 0.8H); 3.96 (s, 0.2H); 3.69 (s, 3H); 3.67−3.59 (m, 2H); 3.54 (d, J = 1.7 Hz, 1H); 2.35−2.29 (m, 1H); 2.17−2.07 (m, 1H); 1.96−1.95 (m, 1H); 1.89−1.84 (m, 1H); 1.60−1.54 (m, 3H); 0.91 (d, J = 4.6 Hz, 3H); 0.87 (d, J = 4.6 Hz, 3H). MS (*m*/*z*): 473 (M^+), 391, 353, 325, 307, 289, 244, 216, 200, 181, 154.

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucine Amide (2f). To a solution containing allyl-*N*-cinnamoyl-(L)-proline-(L)-leucine amide (**1f**) (0.684 g, 1.5 mmol) in CH_3CN (8 mL) was added 2-methylpropanal (0.272 mL, 3 mmol) and PASCOS (∼0.005 g) and the content was stirred under oxygen atmosphere at room temperature for 12 h. After that a fresh sample of catalyst and 2-methylpropanal (0.272 mL, 3 mmol) were added to the reaction mixture and stirring was continued until (36 h) complete conversion of the olefin to epoxide, the catalyst was filtered off, and solvent was removed. The residue then was taken up in EtOAc (35 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by column chromatography (silica gel-EtOAc−hexane 2:3) to isolate allyl-*N*-(3-phenylglycilyl)-(L)-proline-(L)-leucine amide **2f** in good yields (60%). $[\alpha]_D$ =−124.5° (*c* 0.01, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.34 (m, 3H); 7.30−7.28 (m, 2H); 6.96 (d, J = 7.8 Hz, 0.5H); 6.45−6.35 (m, 0.5H); 5.85−5.76 (m, 1H); 5.16 (dd, J = 17.8, 1.44 Hz, 1H); 5.1 (d, J = 10.3 Hz, 1H); 4.59 (dd, J = 8.3, 3.3 Hz, 1H); 4.38−4.32 (m, 1H); 4.10 (s, 0.1H); 4.08 (d, J = 1.76 Hz, 0.8H); 4.06 (d, J = 1.6, 0.1 Hz); 3.86−3.76 (m, 3H); 3.72−3.65 (m, 1H); 3.59 (d, J = 1.74 Hz, 0.9H); 3.44 (d, J = 1.6 Hz, 0.1H); 2.22−2.14 (m, 1H); 2.08−2.02 (m, 1H); 2.00−1.94 (m, 2H); 1.70−1.65 (m, 1H); 1.59−1.48 (m, 2H); 0.87 (dd, J = 6.1, 3.7 Hz 3H); 0.83 (d, J = 5.84 Hz, 1H).

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucine Amide (2f) from 2c. To a stirring solution of $LiOH\cdot H_2O$ (0.046 g, 1.1 mmol) in methanol−water (4:1 ratio, 20 mL) was added **2c** and the mixute was stirred at room temperature for 3 h until the disappearance of starting material. The solvent was removed in vacuo and dichloromethane (10 mL) was added to it followed by a small amount of water (until the phase separation occurred). The pH of the aqueous layer was adjusted to 5 and the aqueous layer was extracted with dichloromethane. Acidification and extraction were continued until the pH remained constant. The combined extract was dried (Na_2SO_4) and taken up into a clean dry flask. Triethylamine (0.2 mL, 1.5 mmol) was added to the reaction vessel and the reaction vessel was cooled to 0 °C. Isobutylchloroformate (0.14 mL, 1 mmol) was added and stirring was continued for 0.5 min. Allylamine (75 μL, 1 mmol) was added to the solution followed by addition of triethylamine (70 μL, 0.5 mmol) and the mixture was stirred vigorously for 3−4 h. Removal of solvent under vacuum yielded a residue, which was taken up in ethyl acetate (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (1 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL) sequentially. The resulting organic layer was dried and concentrated to give a residue, which was subjected to column chromatography to give the pure compound that is chemically and optically identical to **2f** synthesized by aerobic epoxidation of **1f**.

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucine-glycinate (2g). To a solution containing allyl-*N*-cinnamoyl-(L)-proline-(L)-leucine-glycinate (**1g**) (0.546 g, 1.2 mmol) in CH_3CN (10 mL) was added isobutyraldehyde (0.219 mL, 2.4 mmol) and PASCOS (∼0.005 g) and mixture was stirred under oxygen atmosphere at room temperature for 12 h. After that a fresh sample of catalyst and isobyraldehyde (0.219 mL, 2.4 mmol) was added to the reaction mixture and stirring was continued until complete conversion of the olefin to epoxide, the catalyst was filtered off, and solvent was removed. The residue then was taken up in EtOAc (35 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by column chromatography (silica gel-EtOAc−hexane 2:3) to isolate allyl-*N*-(3-phenylglycilyl)-(L)-proline-(L)-leucine-glycinate **2g** in good yield (61%). $[\alpha]_D$ −130° (*c* 0.01, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.8 Hz, 1H); 7.66−7.23 (m, 5H); 6.9 (br s, 1H); 5.92−5.84 (m, 1H); 5.29 (dd, J = 17.5, 1.5 Hz, 1H); 5.22 (dd, J = 9.3, 1.5 Hz, 1H); 4.62−4.65 (m, 4H); 4.15−3.96 (m, 2H); 4.08 (s, 1H); 3.78−3.69 (m, 22H); 3.60 (d, J = 1.92 Hz, 0.8H); 3.58 (s, 0.2H); 2.28−1.74 (m, 4H); 1.66−1.51 (m, 3H); 0.95−0.85 (m, 6H).

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucine-glycinate (2g) from 2c. To a stirring solution of $LiOH\cdot H_2O$ (0.046 g, 1.1 mmol) in methanol−water (4:1 ratio, 20 mL) was added **2c** and the mixture was stirred at room temperature for 3 h until the disappearance of starting material. The solvent was removed in vacuo and dichloromethane (10 mL) was added to it followed by a small amount of water (until the phase separation occurred). The pH of the aqueous layer was adjusted to 5 and the aqueous layer was extracted with dichloromethane. The combined extract was dried (Na_2SO_4) and taken up into a clean dry flask. Triethylamine (0.2 mL, 1.5 mmol) was added to the reaction vessel and the reaction vessel was cooled to 0 °C. Isobutyl chloroformate (0.14 mL, 1 mmol) was added and stirring was continued for 0.5 min. A solution of allyl-glycinate hydrochloride (0.15 g, 1 mmol) in DMSO (0.5 mL) was added to the solution followed by addition of triethylamine (140 μL, 1 mmol) and the mixture was stirred vigorously for 3−4 h. Removal of solvent under vacuum yielded a residue, which was taken up in ethyl acetate (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (1 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL) sequentially. The resulting organic layer was dried and concentrated to give a residue, which was subjected to column chromatography to give the pure compound that is chemically and optically identical to **2g** synthesized by aerobic epoxidation of **1g**.

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucine-(L)-isoleucinate (2h). To a solution of allyl-*N*-cinnamoyl-(L)-proline-(L)-leucine-(L)-isoleucinate (**1h**) (0.760 g, 1.5 mmol) in CH_3CN (7.5 mL) was added 2-methylpropanal (0.272 mL, 3 mmol) and PASCOS (~0.005 g) and the mixture was stirred under oxygen atmosphere at room temperature for 12 h. After this time, a fresh sample of the catalyst and 2-methylpropanal (0.272 mL, 3 mmol) were added to the reaction mixture that was allowed to stir until complete conversion of the olefine (TLC: $R_f = 0.5$; hexane:ethyl acetate 3:2). The catalyst was filtered off on a sintered funnel and acetonitrile was removed in vacuo. The resulting residue was taken up in EtOAc (30 mL) and washed successively with a saturated solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). Separating the organic phase, drying (Na_2SO_4), and concentration in vacuo yielded the corresponding oxirane containing peptide in high purity and yields (HPLC). This was further subjected to column chromatography (silica gel; EtOAc:hexane −1:1) for purification to get the pure epoxide **2h** in good yield (59%) as a gum. $[\alpha]_D$ −86.3° (*c* 0.01, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.8 Hz, 0.5H); 7.60 (d, J = 7.56 Hz, 1H); 7.36−7.27 (m, 5H); 7.12 (d, J = 8.56 Hz, 0.5H); 5.92−5.84 (m, 1H); 5.32 (d, J = 17.3 Hz, 1H); 5.22 (d, J = 10.2 Hz, 1H); 44.63−4.54 (m, 5H); 4.09 (s, 0.4H); 4.07 (s, 0.6H); 3.84−3.80 (m, 1H),;3.69−3.67 (m, 1H); 3.65−3.59 (m, 1H); 2.20−1.8 (m, 3H); 1.75−1.55 (m, 2H); 1.5−1.35 (m, 1H); 1.29−1.15 (m, 1H); 0.95−0.84 (m, 12H).

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-leucine-(L)-isoleucinate (2h) from 2c. To a stirring solution of $LiOH·H_2O$ (0.046 g, 1.1 mmol) in methanol−water (4:1 ratio, 20 mL) was added **2c** and the mixture was stirred at room temperature for 3 h until the disappearance of starting material. The solvent was removed in vacuo and dichloromethane (10 mL) was added to it followed by a small amount of water (until the phase separation occurred). The pH of the aqueous layer was adjusted to 5 and the aqueous layer was extracted with dichloromethane. Acidification and extraction were continued until the pH remained constant. The combined extract was dried (Na_2SO_4) and taken up into a clean dry flask. Triethylamine (0.2 mL, 1.5 mmol) was added to the reaction vessel and the reaction vessel was cooled to 0 °C. Isobutyl chloroformate (0.14 mL, 1 mmol) was added and stirring was continued for 0.5 min. A solution of allyl-leucinate hydrochloride (0.21 g, 1 mmol) in DMSO (0.5 mL) was added to it followed by addition of triethylamine (140 μL, 1 mmol) and the mixture was stirred vigorously for 3−4 h. Removal of solvent under vacuum yielded a residue, which was taken up in ethyl acetate (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (1 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL) sequentially. The resulting organic layer was dried and concentrated to give a residue, which was subjected to column chromatography to give the pure compound that is chemically and optically identical with **2h** synthesized by aerobic epoxidation of **1h**.

Synthesis of Methyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-aspartate (2i). To a solution containing methyl-*N*-cinnamoyl-(L)-proline-(L)-aspartate (78 mg, 0.2 mmol) in CH_3CN (2 mL) was added 2-methylpropanal (30 mg, 0.4 mmol) and PASCOS (~0.005 g) followed by addition of solid anhydrous sodium acetate (131 mg, 1.6 mmol) and the mixture was stirred under oxygen atmosphere at room temperature for 14 h. After that a fresh sample of catalyst and 2-methylpropanal (86 μL, 0.95 mmol) and anhydrous sodium acetate (0.311 g, 10 mmol) were added to the reaction mixture and stirring was continued until complete conversion of the olefin to epoxide (TLC: R_f = 0.41; EtOAc:hexane 3:1.5). The catalyst and the inorganic salt were filtered off and solvent was removed. The residue then was taken up in EtOAc (10 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) and brine (1 × 5 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by flash column chromatography (silica gel-EtOAc−hexane 40:60) to afford **2i** in good yield (78%) as a gum. $[\alpha]_D$ −106° (*c* 0.002, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.3 Hz, 1H), 7.35−7.32 (m, 5H), 4.85 (dd, J = 8, 4.1 Hz, 1H), 4.62 (t, J = 3.6 Hz, 1H), 4.14 (d, J = 5.7 Hz, 0.5H), 4.08 (d, J = 5.7 Hz, 0.5H), 3.82 (dt, J = 9.8, 4.2 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.65−3.61 (m, 1H), 3.58 (d, J = 5.7 Hz, 1H), 2.92 (dd, J = 20, 15.1 Hz, 2H), 2.36−2.33 (m, 1H), 2.27−2.19 (m, 1H), 2.15−2.10 (m, 1H), 1.90 (br s, 1H). IR ν_{max}: 3030 (br), 2789, 1762, 1610, 1587 cm^{-1}

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(L)-proline-(L)-phenylalanine Amide 2j. To a solution containing allyl-*N*-cinnamoyl-(L)-proline-(L)-phenylalanine amide (648 mg, 1.5 mmol) and X (0.20 g, 0.38 mmol) in CH_3CN (7.5 mL) was added 2-methylpropanal (216 mg, 3 mmol) and PASCOS (~0.005 g) followed by addition of solid anhydrous sodium acetate (0.311 g, 10 mmol) and the mixture was stirred under oxygen atmosphere at room temperature for 17 h. After that a fresh lot of catalyst and 2-methylpropanal (86 μL, 0.95 mmol) and anhydrous sodium acetate (0.311 g, 10 mmol) was added to the reaction mixture and stirring was continued until complete conversion of the olefin to epoxide (TLC: R_f = 0.45; EtOAc:hexane 3:2). The catalyst and the inorganic salt were filtered off and solvent was removed. The residue then was taken up in EtOAc (25 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by flash column chromatography (silica gel-EtOAc−hexane 43:57) to afford **2j** in good yield (83%) as a solid (mp 96−97 °C). $[\alpha]_D$ −96° (*c* 0.001, CH_2Cl_2).

Author: Please identify the missing component (X) in the above.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.35 (m, 3H); 7.30−7.25 (m, 3H); 7.22−7.18 (m, 4H); 7.09 (d, J = 8.2 Hz, 1H); 6.91 (t, J = 5.5 Hz, 1H); 5.73 (ddd, J = 22.7, 10.3, 54 Hz, 1H); 5.06 (td, J = 26.2, 1.5 Hz, 1H); 5.05 (dd, J = 2.6, 1.4 Hz, 1H); 4.52 (dd, J = 7.8, 3.2 Hz, 1H); 4.00 (d, J = 2 Hz, 1H); 3.79 (dd, J = 7.6, 1.7 Hz, 2H); 3.65−3.50 (m, 2H); 3.55 (d, J = 2 Hz, 1H); 3.23 (dd, J = 13.9, 6.1 Hz, 1H); 3.01 (dd, J = 13.9, 6.1 Hz, 1H); 2.05−2.02 (m, 1H); 1.97−1.88 (m, 2H); 1.84−1.79 (m, 1H); MS (*m*/*z*) 448 (M^+), 141, 328, 302, 244, 216, 200, 154, 136; IR ν_{max}: 3300−3030 (br), 2880, 1760, 1600, 1575 cm^{-1}.

Synthesis of 3-Phenyl-(2*S*,3*S*)-oxy-propanol (4). A mixture of activated molecular sieves (0.9 g) and 50 mL of DCM was cooled to −10 °C. L-(+)-Diethyl tertarate (0.5 g, 2.4 mmol), $Ti(O^iPr)_4$ (0.45 g, 1.6 mmol), and ^{t}BuOOH (7.8 mL, 48 mmol 6.2 M in CH_2Cl_2) were added sequentially. After 10 min, the mixture was cooled to −20 °C and cinnamyl alcohol (4.35 g, 32.5 mmol in 10 mL of CH_2Cl_2) was added with stirring over a time period of 15 min. Stirring was continued for 45 min at −20 °C at which point the reaction mixture was allowed to come to 0 °C and quenched with water (10 mL) and was allowed to come to room temperature. To this was added 2.5 mL of a 30% aqueous solution of sodium hydroxide saturated with sodium chloride and the mixture was were stirred for 10 min, which led to clear separation of the aqueous and organic layers. The organic phase was removed and combined with two extracts of the aqueous phase (CH_2Cl_2, 2 × 10 mL). The combined organic phases were dried over Na_2SO_4 and filtered through Celite to give a clear colorless solution. Concentration followed by chromatography gave pure (94%; HPLC) 3-phenyl-(2*S*,3*S*)-oxy-propanol **4** (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.20 (m, 5H); 4.01 (dd, J = 12.7, 2.9 Hz, 1H); 3.90 (d, J = 2.2 Hz, 1H); 3.74 (dd, J = 12, 6.8 Hz, 1H); 3.21 (td, J = 4.1, 2.2 Hz, 1H); 2.71 (br s, 1H). $[\alpha]^{25}_D$ −49° (*c* 0.01, CH_2Cl_2).

Synthesis of 3-Phenyl-(2*R*,3*S*)-glycidic Acid (5). $Ru^{III}Cl_3·H_2O$ (0.0075 g, 33 μM) was added to a stirring biphasic mixture of epoxy alcohol **4** (0.15 g, 1 mmol), sodium periodate (0.642 g, 3 mmol), and sodium bicarbonate (0.42 g, 5 mmol) in

CCl_4 (2 mL), acetonitrile (2 mL), and water (3 mL). After 42 h of stirring, additional amounts of $RuCl_3$ (0.0076 g, 34 μM) and sodium periodate (0.157 g, 0.72 mmol) were added and the stirring was continued for 1 h to complete the reaction. Then dichloromethane (8 mL) was added followed by a small amount of water (until phase separation occurred). The pH of the water layer was adjusted to 4 and the aqueous layer was extracted with dichloromethane. Acidification and extraction were repeated until the pH remained constant. The combined layer was dried over Na_2SO_4 and after evaporation of solvent compound **5** was characterized for the presence of the carboxylic group by IR (3457 cm^{-1}) and used immediately for further coupling without complete characterization due to its poor stability.

Synthesis of Methyl-*N*-cinnamoyl-(L)-leucine-(L)-prolinate (1m). A stirring solution of *N*-cinnamoyl-(L)-leucine (1.30 g, 5 mmol) and triethylamine (0.7 mL, 5 mmol) in THF (10 mL) was cooled to 0 °C and to it was added isobutylchloroformate (0.65 mL, 5 mmol) with vigorous stirring for 50 s. After that, a solution of methyl-(L)-prolinate hydrochloride (0.916 g, 5.5 mmol) in DMSO (2 mL) was added followed by a solution of triethylamine (1.6 mL, 11 mmol) in THF (10 mL). The reaction mixture was allowed to come to room temperature and further stirred for 3−4 h. Inorganic salt was filtered off followed by removal of the solvent in vacuo. The residue then was taken up in EtOAc (35 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 15 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue that was dried over Na_2SO_4 and subjected to purification by column chromatography (silica gel-EtOAc−hexane 1:1.5) to isolate methyl-*N*-cinnamoyl-(L)-leucine-(L)-prolinate **1m** as a gum in modest yield (61%).

^{1}H NMR ($CDCl_3$, 60 MHz): δ 7.72 (d, J = 16 Hz, 1H); 7.52 (d, J = 8.9 Hz, 1H); 7.50−7.16 (m, 5H); 6.47 (d, J = 16 Hz. 1H); 4.8−4.7 (m, 1H); 4.58−4.50 (m, 1H); 3.75 (s, 3H); 3.74−3.59 (m, 2H); 2.20−2.10 (m, 1H); 2.10−1.99 (m, 3H); 1.76−1.49 (m, 3H); 0.96 (d, J = 5.6 Hz, 6H).

Synthesis of Methyl-*N*-(3-phenylglycidyl)-(L)-leucine-(L)-prolinate (2m). To a solution of methyl-*N*-cinnamoyl-(L)-leucine-(L)-prolinate (**1m**) (0.558 g, 1.5 mmol) in CH_3CN (8 mL) was added 2-methylpropanal (0.272 mL, 3 mmol) and PASCOS (∼0.005 g) and the mixture was stirred under oxygen atmosphere at room temperature for 12 h. After this time, a fresh sample of the catalyst and 2-methylpropanal (0.272 mL, 3 mmol) were added to the reaction mixture and allowed to stir until complete conversion of the olefine (TLC: R_f = 0.5; hexane: ethyl acetate 3:2). The catalyst was filtered off on a sintered funnel and acetonitrile was removed in vacuo. The resulting residue was taken up in EtOAc (20 mL) and washed successively with a saturated solution of $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). Separating the organic phase, drying (Na_2SO_4), and concentration in vacuo yielded the corresponding oxirane containing an equal diastereomeric mixture of peptide **2m** in high chemical yields (72%) as a gum.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36−7.32 (m, 3H); 7.29−7.22 (m, 2H); 4.54−4.52 (m, 1H); 4.2−4.12 (m, 1H); 3.95 (d, J = 1.92 Hz, 0.4H); 3.92 (s, 0.2H); 3.74 (s, 1.8H); 3.72 (s, 1.2 H); 3. 67 (d, J = 1.84 Hz, 0.4H); 3.69−3.55 (m, 2H); 3.52 (d, J = 1.96 Hz, 0.4H); 3.47 (d, J = 1.84 Hz, 0.4H); 3.40 (d, J = 1.96 Hz, 0.2H); 2.21−2.09 (m, 1H); 2.07−1.96 (m, 2H); 1.82−1.62 (m, 2H); 1.58−1.52 (m, 2H); 0.99 (d, J = 6 Hz, 3H); 0.95 (dd, J = 9, 3 Hz, 3H).

Synthesis of Methyl-*N*-(cinnamolyl-(L)-prolyl)-3-phenylaziridine-2-(L)-leucinate (6). To an ice-cooled stirred solution of methyl-*N*-(*N*-cinnamolyl-(L)-prolyl)-3-phenylaziridine-2-carboxylic acid (0.16 g, 0.41 mmol) in CH_2Cl_2 (5 mL) was added HOBt hydrate (0.055 g, 0.41 mmol) and triethylamine (0.06 mL, 0.41 mmol) followed by addition of a solution of (L)-leucine methyl ester hydrochloride (0.074 g, 0,41 mmol) and triethylamine (0.06 mL, 0.41 mmol) in CH_2Cl_2 (2.5 mL). Stirring was continued for 10 min at 0 °C. After that, another solution of DCM (2.5 mL) containing DCC (0.084 g, 0.41 mmol) was added to the reaction mixture, the solution was allowed to come to room temperature, and stirring was continued at ambient condition for 16 h. The solvent was evaporated and the resulting mass was directly subjected to purification by column chromatography (silica gel-ethyl acetate:hexane 38:62) to obtain methyl-*N*-(*N*-cinnamolyl-(L)-prolyl)-3-phenylaziridine-2-(L)-leucinate **6** in good yield (68%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (d, J = 15.4 Hz, 1H); 7.65 (d, J = 7.32 Hz, 1H); 7.55−7.53 (m, 4H); 7.39−7.36 (m, 6H); 6.77 (d, J = 15.4 Hz, 1H); 4.78 (d, J = 6.6 Hz, 1H); 4.49 (d, J = 7.8 Hz, 1H); 3.80−3.76 (m, 1H); 3.73 (s, 3H); 3.71 (s, 0.4 H); 3.67 (br s, 0.6H); 3.65 (m, 0.5H); 3.63 (m, 0.5H); 3.61 (br s, 0.1H); 3.55 (br s, 0.7H); 3.39 (br s, 0.2H); 2.25−2.46 (m, 1H); 2.31−2.14 (m, 2H); 2.06−1.98 (m, 1H); 1.91−1.82 (m, 1H); 1.71−1.56 (m, 2H); 1.25 (br s, 1H); 0.90 (d, J = 6.08 Hz, 3H); 0.88 (d, J = 6.08 Hz, 3H).

Synthesis of Methyl-*N*-(*N*-3′-phenylglycidyl-(L)-prolyl)-3-phenylaziridine-2-(L)-leucinate (6a). To a solution containing methyl-*N*-(*N*-cinnamolyl-(L)-prolyl)-3-phenylaziridine-2-(L)-leucinate (**7**) (0.20 g, 0.38 mmol) in CH_3CN (8 mL) was added 2-methylpropanal (86 μL, 0.95 mmol) and PASCOS (∼0.004 g) followed by addition of solid anhydrous sodium acetate (0.311 g, 10 mmol) and the mixture was stirred under oxygen atmosphere at room temperature for 12 h. After that a fresh sample of catalyst and 2-methylpropanal (86 μL, 0.95 mmol) and anhydrous sodium acetate (0.311 g, 10 mmol) was added to the reaction mixture, stirring was continued until complete conversion of the olefine to epoxide, the catalyst and the inorganic salt were filtered off, and solvent was removed. The residue then was taken up in EtOAc (25 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by column chromatography (silica gel-EtOAc−hexane 43:57) to isolate methyl-*N*-(*N*-glycidyl-(L)-prolyl)-3-phenylaziridine-2-(L)-leucinate **6a** in good yield (91%). Spectral data for the major diastereomer are given below.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29−7.12 (m, 10H); 4.60 (d, J = 7.56 Hz, 1H); 4.43−4.41 (m, 1H); 4.10 (br s, 0.1H); 4.02 (br s, 0.9H); 3.73−3.69 (m, 3H); 3.66 (s, 3H); 3.54 (br s, 0.9H); 3.49 (br s, 0.8H); 3.44 (s, 0.2H); 3.40 (s, 0.1H); 2.34−2.32 (m, 1H); 2.09−2.07 (m, 1H); 1.94−1.57 (m, 4H); 1.18 (br s, 2H); 0.89−0.86 (m, 6H). MS (m/z): 519 $(M + 1)^+$.

Synthesis of Methyl-*N*-cinnamoyl-(L)-proline-dehydrophenylalanine-(L)-leucinate (7). To an ice-cooled stirred solution of *N*-cinnamoyl-(L)-proline-dehydrophenylalanine (0.16 g, 0.41 mmol) in CH_2Cl_2 (5 mL) was added HOBt hydrate (0.055 g, 0.41 mmol), (L)-leucine methyl ester hydrochloride (0.074 g, 0,41 mmol), and triethylamine (0.12 mL, 0.82 mmol), and stirring was continued for 10 min at 0 °C. After that, a solution of DCC (0.084 g, 0.41 mmol) in CH_2Cl_2 (2.5 mL) was added to the solution and the reaction mixture was allowed to come to room temperature. Stirring was continued at ambient condition for 16 h. The solvent was evaporated and the resulting mass was directly subjected to purification by column chromatography (silica gel-ethyl acetate:hexane 38:62) to obtain methyl-*N*-cinnamoyl-(L)-proline-dehydrophenylalanine-(L)-leucinate **7** in pure (92%; HPLC) form with good yield (78%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (s, 0.75H); 7.67 (d, J = 15.4 Hz, 1H); 7.54−7.26 (m, 11H); 6.73 (d, J = 15.4 Hz, 1H); 4.76−4.69 (m, 1H); 4.58 (dd, J = 7.32, 4.60 Hz, 1H); 3.86−3.80 (m, 1H); 3.75−3.59 (m, 4H); 2.30−1.99 (m, 4H); 1.78−1.60 (m, 3H); 1.26−1.22 (br s, 8H); 0.89 (d, J = 6.08 Hz, 3H); 0.85 (d, J = 6.08 Hz, 3H). MS (m/z): 519 $(M + 1)^+$, 502, 374, 348, 260, 228, 200, 172, 131.

Synthesis of Methyl-*N*-(3-phenylglyidyl)-(L)-proline-dehdrophenyalanine-(L)-leucinate (7a). To a solution containing methyl-*N*-cinnamoyl-(L)-proline-dehydrophenylalanine-(L)-leucinate (**Y**) (0.20 g, 0.38 mmol) in CH_3CN (8 mL) was added 2-methylpropanal (86 μL, 0.95 mmol) and PASCOS (∼0.004 g) and the mixture was stirred under oxygen atmos-

phere at room temperature for 12 h. After that a fresh sample of catalyst and 2-methylpropanal (86 μL, 0.95 mmol) was added to the reaction mixture and stirring was continued until complete conversion of the olefine to epoxide, the catalyst was filtered off, and solvent was removed. The residue then was taken up in EtOAc (25 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by column chromatography (silica gel-EtOAc−hexane 2:3) to isolate methyl-*N*-(3-phenylglyidyl)-(L)-prolyl-dehdrohenyalanine-(L)-leucinate **7a** in good yield (89%). Experimental data for the major diastereomer are given below.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 0.6H); 7.92 (s, 0.4H); 7.50−7.20 (m, 11H); 4.74−4.70 (m, 1H); 4.55−4.51 (m, 1H); 4.08 (d, J = 1.92 Hz, 0.4H); 4.05 (d, J = 1.6 Hz, 0.6H); 3.74 (s, 1.2H); 3.71(s, 1.8H); 3.60 (d, J = 1.98 Hz, 0.4H), 0.4H); 3.59 (d, J = 1.68 Hz, 0.6H) 2.30−1.99 (m, 4H); 1.78−1.60 (m, 3H); 1.26 (br s, 1H); 0.89 (d, J = 6.08 Hz, 3H); 0.85 (d, J = 6.08 Hz, 3H).

Synthesis of Ethyl-*N*-(*N*-3′-phenylglycidyl-(L)-prolyl)-3-phenylaziridine-2-carboxylate (8a). To a solution containing ethyl-*N*-(*N*-3′-phenylglycidyl-(L)-prolyl)-3-phenylaziridine-2-carboxylate (**9**) (0.164 g, 0.39 mmol) in CH_3CN (10 mL) was added 2-methylpropanal (86 μL, 0.98 mmol) followed by the addition of solid anhydrous sodium acetate (0.311 g, 10 mmol) and PASCOS (∼0.004 g) and the mixture was stirred under oxygen atmosphere at room temperature for 12 h. After that a fresh sample of catalyst and 2-methylpropanal (88 μL, 0.98 mmol) and solid anhydrous sodium acetate (0.311 g, 10 mmol) were added to the reaction mixture, stirring was continued until complete conversion of the olefine to epoxide, the catalyst and the inorganic salt were filtered off, and solvent was removed. The residue then was taken up in EtOAc (30 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) and brine (1 × 10 mL). The organic layer was separated and concentrated in vacuo to a residue, which was dried over Na_2SO_4 and subjected to purification by column chromatography (silica gel-EtOAc−hexane 2:3) to isolate the diastereomers of ethyl-*N*-(*N*-3′-phenylglycidyl-(L)-prolyl)-3-phenylaziridine-2-carboxylate **8a** in good yield (92%). Experimental data for one of the pure diastereomers of **9a** are given below.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41−7.20 (m, 10H); 6.82 (d, J = 6.32 Hz, 1H); 4.77 (dd, J = 7.8, 3.4 Hz, 1H, 0.5H); 4.61 (dd, J = 3.64, 8.52 Hz, 0.5H); 4.30−4.12 (m, 2H); 4.06 (d, J = 1.68 Hz, 0.3H); 4.00 (d, J = 1.96 Hz, 0.7H); 3.95 (d, J = 1.72 Hz, 0.6 H); 3.73−3.61 (m, 1H); 3.67 (d, J = 1.96 Hz, 0.3H); 3.52−3.42 (m, 1H); 3.50 (d, J = 1.96 Hz, 0.4H); 3.15 (d, J = 1.92 Hz, 0.6H); 3.12 (d, J = 2.2 Hz, 0.7H); 2.87 (d, J = 1.96 Hz, 0.3H); 2.40−1.87 (m, 4H); 1.30 (dt, J = 7.08, 3.68 Hz, 3H); MS (m/z): 435 (M^+), 419, 280, 269, 241, 228, 216, 200.

Synthesis of Allyl-*N*-(3-phenylglycidyl)-(D)-proline-(L)-leucine Amide (9a). This epoxide was prepared according to the procedure followed for **2f** in 74% yield and 91% (HPLC) purity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.36 (m, 3H); 7.35−7.34 (m, 2H); 6.37 (d, J = 7.75 Hz, 1H); 5.92−5.86 (m, 1H); 5.21 (dd, J = 17.5, 1.5 Hz, 1H); 5.18 (d, J = 10.5 Hz, 1H); 4.62 (dd, J = 8.5, 3.5 Hz, 1H); 4.40−4.33 (m, 1H); 4.16 (s, 0.2H); 4.12 (d, J = 1.76 Hz, 0.6H); 4.16 (d, J = 1.5 Hz, 0.2 H); 3.82−3.765 (m, 3H); 3.63−3.56 (m, 1H); 3.65 (d, J = 1.7 Hz, 0.8H); 3.50 (d, J = 1.6 Hz, 0.2H); 2.19−2.11 (m, 1H); 2.13−2.08 (m, 1H); 2.05−1.21 (m, 2H); 1.68−1.59 (m, 1H); 1.51−1.49 (m, 2H); 0.85 (dd, J = 6.1, 3.7 Hz 3H); 0.81 (d, J = 5.84 Hz, 1H).

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Supporting Information Available: Spectra data **1d**, **1f**, **2c**, **2f**, **2l**, **6**, **6a**, **7**, and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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