Pergamon

Tetrahedron Letters 42 (2001) 333–337

TETRAHEDRON LETTERS

π-Facial selectivity in polyaniline supported cobalt catalysed aerobic epoxidation of *N*-cinnamoyl proline derivatives

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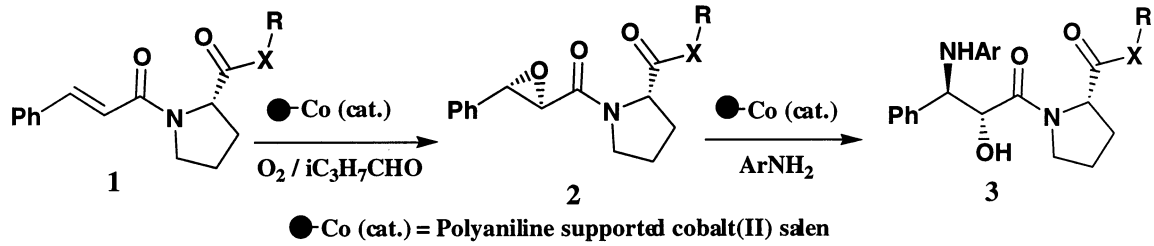
Received 4 August 2000; revised 23 October 2000; accepted 2 November 2000

Abstract—Polyaniline supported cobalt salen catalyses the facially selective aerobic epoxidation (oxygen/2-methylpropanal) of *N*-cinnamoyl proline derived peptides. A high diastereoselectivity is observed for peptides which are able to adopt a γ- or β-turn due to intramolecular hydrogen bonding.

We have recently shown[1] that *N*-cinnamoyl amides **1** can be converted to the corresponding β-phenylisoserine derivatives **3** via a tandem polyaniline supported cobalt(II) salen catalysed aerobic epoxidation and amination protocol (Scheme 1). The intermediate cinnamoyl epoxides **2** underwent a stereoselective S_N2 type of opening with several aromatic amines leading to a highly selective synthesis of the *anti* diastereomer of the β-phenylisoserine derivatives. In order to achieve a chiral synthesis of these derivatives, we have attempted a diastereoselective aerobic epoxidation of *N*-cinnamoyl L-proline derivatives and our findings are described below.

Typically, *N*-cinnamoyl L-proline containing peptides **1** (5 mmol) were dissolved in acetonitrile (10 mL) and the solution was stirred in the presence of polyaniline supported cobalt(II) salen (catalyst) and 2-methylpropanal (4 equiv.) under an oxygen balloon at ambient conditions for 15–20 h. The cobalt catalyst was filtered off and the solvent removed to give a residue, which was dissolved in dichloromethane and washed successively with a saturated solution of sodium bicarbonate and water. Drying and evaporation of the solvent gave a residue which was chromatographed over silica gel to afford the corresponding epoxides in high purity. The purities of these epoxides were determined by chiral HPLC to be ~85–90%. The results for these epoxidations are compiled in Tables 1 and 2. *It is noteworthy that these reactions are chemospecific as only the cinnamoyl double bond is epoxidized under these conditions.* The results in Table 1 indicate that the epoxidation of *N*-cinnamoyl L-proline methyl ester **1a** exhibits very poor diastereoselectivity (**2a**) during these epoxidations, however, the corresponding allylic amide **1b** showed better selectivity (**2b**) than the former. Interestingly, the diastereoselectivity increases for substrates having an additional C-terminal amino acid residue in **1a**. Thus the polyaniline supported cobalt(II) salen catalysed aerobic epoxidation of dipeptides **1c**–**1e** afforded the corresponding epoxides **2c**–**2e**, respectively, with higher diastereoselectivities. The ratio in favour of the major



Scheme 1.

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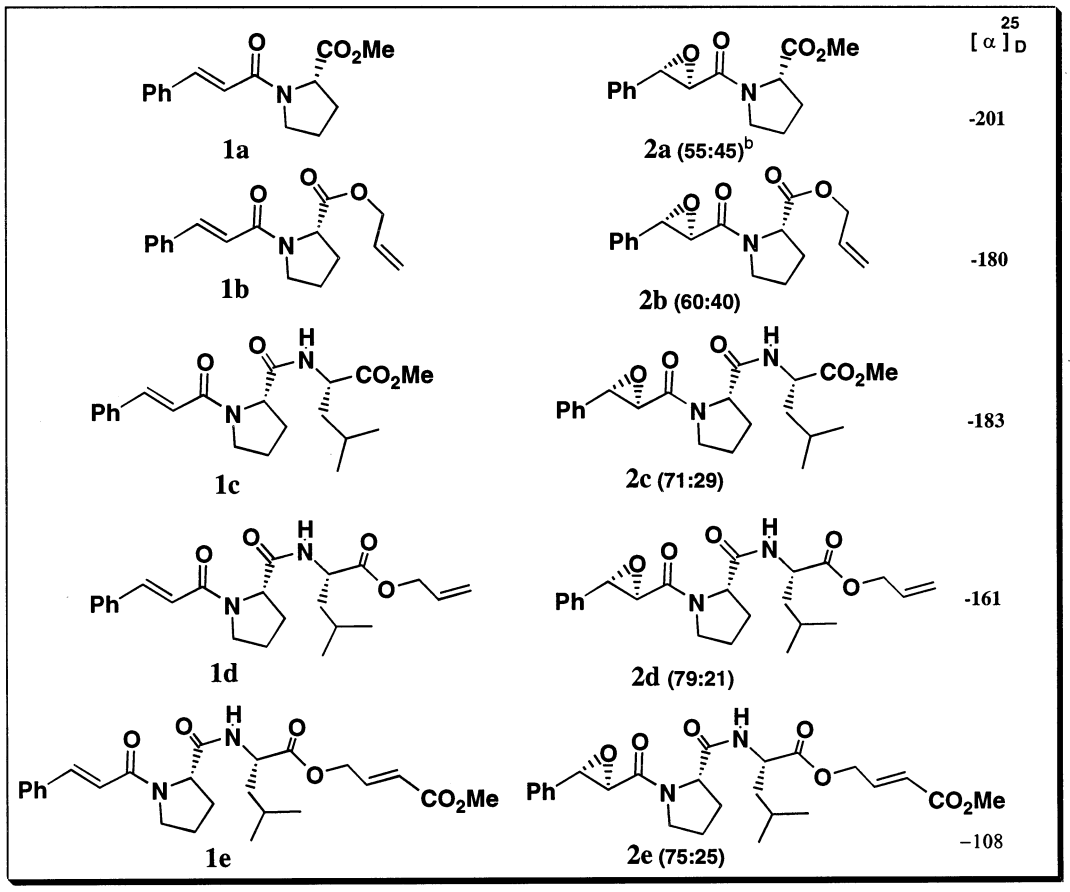
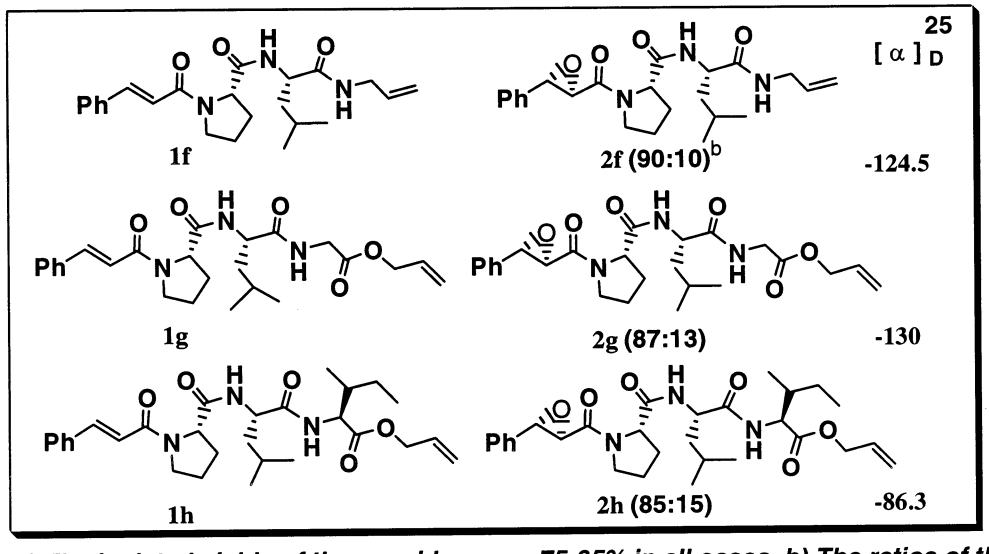
0040-4039/01/$ - see front matter
PII: S0040-4039(00)01949-3

Table 1. Polyaniline supported cobalt(II) salen catalysed aerobic epoxidation of *N*-cinnamoyl L-proline peptides[a]

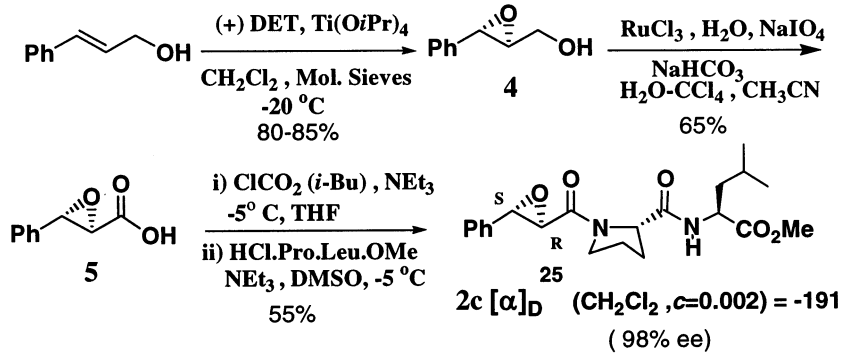


a) The isolated yield of the epoxides were 80-90% in all the cases. b) Ratio of the diastereomers determined by chiral HPLC and the absolute configuration (2R,3S) and specific rotaion (CH_2Cl_2) of the major epoxide is shown for all the cases.

Table 2. Polyaniline supported cobalt(II) salen catalysed enantioselective aerobic epoxidation of *N*-cinnamoyl L-proline containing tripeptides[a]



a) The isolated yields of the epoxides were 75-85% in all cases. b) The ratios of the diastereomers were determined by chiral HPLC and the absolute configuration (2R,3S) and specific rotation (CH_2Cl_2) of the major epoxide is shown for all cases.



Scheme 2.

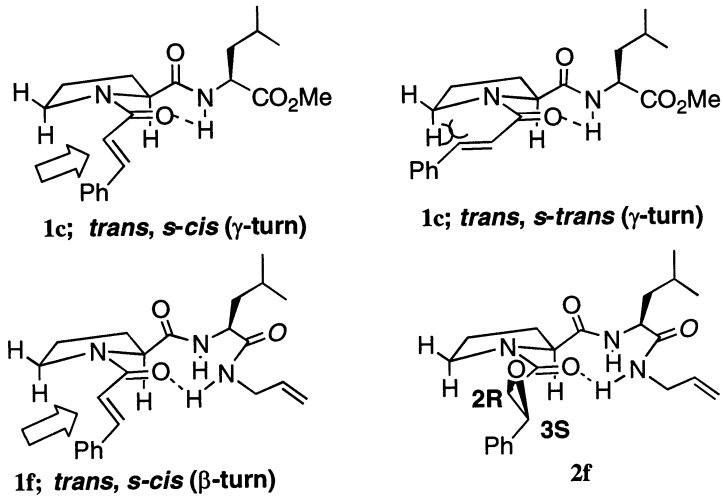
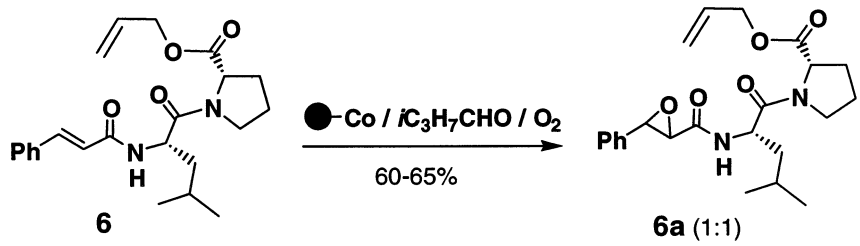


Figure 1.

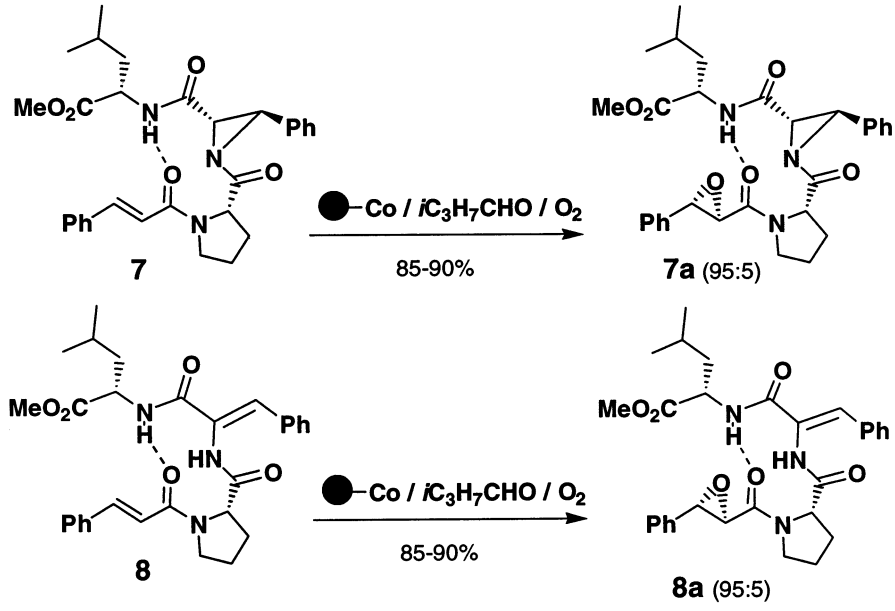
~90%. The absolute stereochemistry for the major enantiomer of epoxides **2a**–**e** were assigned as 2*R*,3*S* which was established by following a correlation with the epoxide obtained by Sharpless epoxidation.[2] Thus cinnamoyl alcohol was subjected to Sharpless' epoxidation using (+)-DET to give the enantiomerically pure epoxide **4** which was converted to the corresponding carboxylic acid **5** by ruthenium catalysed oxidation[3] of the primary alcohol group. 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 the Sharpless procedure ($\alpha_D = -191$) and by polyaniline supported cobalt(II) salen catalysed epoxidation of **1c** ($\alpha_D = -183$) were similar in sign and magnitude. Also, the proton NMR of the epoxide **2c** obtained by both routes (i.e. the Sharpless procedure and the cobalt catalysed aerobic protocol) were identical. Thus based on this correlation, the absolute stereochemistry of the epoxide **2c** is assigned 2*R*,3*S*. A similar correlation was also carried out for epoxides **2d** and **2e**.

It is noteworthy that the epoxidation of tripeptides **1f**–**h** were found to be highly diastereoselective[4] compared with the peptides **1b**–**e** as they underwent highly selective aerobic epoxidation, leading to the corresponding epoxides **2f**–**h** in high yields (Table 2). The ratio in favour of the major diastereomer was found to be >85:<15 (HPLC) and they were separated by column chromatography to afford epoxides whose purity was ~90% (Chiral HPLC). The absolute stereochemistry for the major diastereomer was assigned to be 2*R*,3*S* by converting **2c** (obtained by aerobic epoxidation) to **2f**–**g** using the procedure[5] described earlier and comparing these compounds. The high facial selectivity in epoxidation of **1b**–**h** may be explained by invoking the possibility of these reactions taking place on organized structures resulting from intramolecular hydrogen bonding and such structures,[6] known as γ- and β-turns, are invariably responsible for the secondary structures in peptides and proteins. Interestingly, the tripeptides **1b**–**e** can adopt a seven-membered γ-turn thereby forcing the cinnamoyl group to exist with the *trans*, *s-cis* geometry (Fig. 1, **1c**), as the corresponding *trans*, *s-trans* geometry will be disfavoured due to non-bonding interactions. This 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 enan-



Scheme 3.



Scheme 4.

tioselectivity during the epoxidation of **1f**–**h** which will take place on well-organized β-turn conformations (Fig. 1, **1f**), which will render such epoxidations facially selective (Fig. 1, **2f**). The presence of intramolecular hydrogen bonding[7] in **1c**–**h** has been observed by using proton NMR studies in a mixture of $CDCl_3$ and DMSO-d_6. The role of a γ- or β-turn in promoting high diastereoselectivity is evident from the fact that the peptide **6** undergoes a non-diastereoselective oxidation of the cinnamoyl double bond to afford a 1:1 mixture of the corresponding monoepoxide **6a** (Scheme 3) owing to the absence of the intramolecular hydrogen bonding features responsible for a γ- or β-turn. That the high enantioselectivity is dictated by the β-turn is seen during the epoxidation of the *N*-cinnamoyl peptides **7** and **8** which,[8] are constrained to have an intramolecular 10-membered hydrogen bond. The constraint present due to the aziridine and dehydrophenylalanine residues in **7** and **8**, respectively, is responsible for coaxing the carbonyl groups of the cinnamoyl and the amino groups of the leucine residue to adopt a geometry which encourages the intramolecular hydrogen bond whose presence is established[7] by proton NMR studies (Scheme 4). This intramolecular hydrogen bonding preorganizes the cinnamoyl group to undergo facially selective aerobic epoxidation under the conditions described above to give predominantly one diastereomer **7a** and **8a**, respectively, (95:5) as indicated by the chiral HPLC. The absolute configuration for **7a** and **8a** is assigned as 2*R*,3*S* by analogy with the epoxides **2f**–**h**.

In conclusion, polyaniline supported cobalt(II) salen catalysed reaction of *N*-cinnamoyl L-proline derived peptides in the presence of oxygen and 2-methylpropanal leads to a highly diastereoselective epoxidation of the cinnamoyl double bond. The high facial selectivity for these epoxidations may be explained by assuming that the reactions are taking place on well-organized γ- or β-turns formed by the substrates.

Acknowledgements

We thank DST, New Delhi for the financial support to this work.

References

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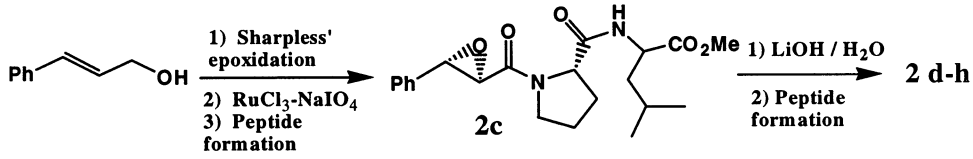
2. Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
3. **Synthesis of methyl 3-phenyl-(3*S*,2*R*)-oxy-glycyl-L-proline-L-leucinate 2c:** $Ru(III)Cl_3 \cdot H_2O$ (7.5 mg, 33 μM) was added to a stirring biphasic mixture of epoxy alcohol **4** (150 mg, 1 mmol), sodium periodate (643 mg, 3 mmol) and sodium bicarbonate (420 mg, 5 mmol) in CCl_4 (2 mL), acetonitrile (2 mL) and water (3 mL). After 42 h of stirring, additional amounts of $RuCl_3$ (7.6 mg, 34 μM) and sodium periodate (157 mg) 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 layers were dried (Na_2SO_4) and taken in a clean dry flask. Triethylamine (0.2 mL, 1.5 mmol) was added and the reaction vessel was cooled to −5°C. Isobutyl chloroformate (0.13 mL, 1 mmol) was added and stirred for 0.5 min. A solution of methyl L-proline-L-leucinate hydrochloride (0.418 mg, 1.5 mmol) in DMSO (0.5 mL) was added and the mixture stirred vigorously for 3–4 h. Removal of solvent under vacuum yielded a residue which was taken up in EtOAc and washed with a saturated aqueous solution of $NaHCO_3$, water and brine. The resulting organic layer was dried and concentrated to give a residue which was subjected to column chromatography to yield the required product **2c** as a solid in moderate yields (31%, mp = 105–107°C). $[\alpha]_D^{25} = -191$ (CH_2Cl_2, *c* 0.002). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.36–7.26 (m, 5H), 4.66 (m, 1H), 4.49 (m, 1H), 4.09 (s, 1H), 3.73 (s, 3H), 3.61 (s, 1H), 3.56 (m, 2H), 2.39–2.11 (m, 4H), 1.98–1.88 (m, 3H), 0.96 (m, 6H). **FT-IR** (CH_2Cl_2): 3286.2, 3063.3, 2965.3, 2872.6, 1743.5, 1648.5, 1541.7, 1449.9. **Mass (*m*/*z*)**: 389 $(M+1)^+$ (80%), 269 (75%), 244 (60%), 209 (80%), 154 (90%), 136 (100%).
4. For a recent study on the epoxidation of *N*-cinnamoyl pyrrolidine derivatives, see: Meth-Cohn, O.; Chen, Y. *Tetrahedron Lett.* **1999**, *40*, 6069.
5. The absolute stereochemistry for **2d–h** was correlated according to the following protocol. The key intermediate **2c** (obtained by Sharpless' procedure) was transformed to the respective epoxypeptides by base hydrolysis and mixed anhydride coupling with the corresponding amines/esters of amino acids.



6. For β-turns see: (a) Ball, J. B.; Hughes, R. A.; Alewood, P. L.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467 and references cited 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. (f) For turn-inducing role of proline in the cyclization of small peptides, see: Sager, C.; Mutter, M.; Dumy, P. *Tetrahedron Lett.* **1999**, *40*, 7987.
7. The presence of intramolecular hydrogen bonds was proved by the standard protocol mentioned in References 6c and 6e by FT-IR and by recording the proton NMR spectrum of **1**, **7** and **8** dissolved in various concentrations of DMSO-d_6 in the $CDCl_3$. The amide protons are generally characterized by the appearance of signal between 6 and 9 ppm. The chemical shift of the amide proton did not change appreciably with increasing concentration of DMSO-d_6 thereby indicating the presence of an intramolecular hydrogen bond in **1**, **7** and **8**.
8. The manuscript describing the synthesis and reverse turn properties of **6**, **7** and **8** will be submitted for the publication in *J. Org. Chem.*