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Polyaniline Supported Cobalt(II) Salen Catalysed Synthesis of Pyrrolidine Containing α-Hydroxyamide Core Structures as Inhibitors for HIV Proteases

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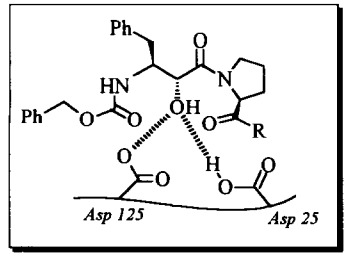
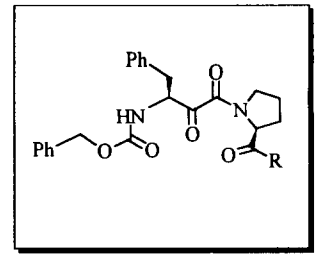
Abstract: A novel synthesis of pyrrolidine containing α-hydroxyamide core structures as inhibitors for HIV protease is developed by employing polyaniline supported cobalt (II) salen catalysed formation of the epoxide from cinnamoylamides of L-proline followed by its opening with anilines at ambient condition. © 1997 Published by Elsevier Science Ltd.

The generation of libraries of small drug like molecules[1] coupled with high through-put screening technologies has paved way for the discovery and optimization of lead compounds for new drugs in the pharmaceutical industry. As a result of this much interest is being focused by organic chemists on the generation of chemically and functionally diverse libraries of small organic molecules using solution phase or polymer support techniques. Wong and coworkers have demonstrated[2] that pyrrolidine-containing α-hydroxy or α-ketoamide core structures function as the mechanism based inhibitors of HIV proteases. Their studies have shown that increasing the hydrophobicity around terminal nitrogen enhances the binding of such core structures with the active site of HIV proteases. Similarly, the α-hydroxyamide moiety has been shown to hydrogen bond **1** (Scheme 1) with *Aspartate 25* and *125* of the HIV proteases. The α-ketoamide core structure **2** (Scheme 1) was shown to be more active than the corresponding α-hydroxyamide. In view of the importance of these core structures, we have developed a general route to α-hydroxyamide containing dipeptide isosteres from *L*-proline and β-phenylisoseriene derivatives. In order to introduce the hydrophobic environment around terminal nitrogen, we have carried out a general polyaniline supported cobalt(II) catalysed opening of the epoxy amide from *L*-proline with substituted aniline derivatives (Eq. 1).

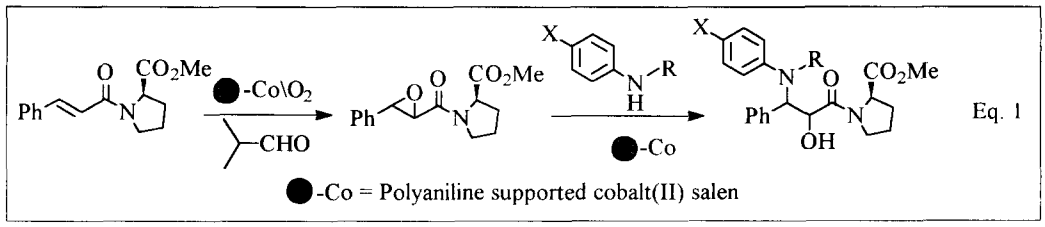


1



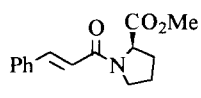
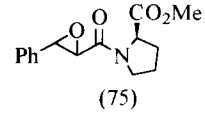
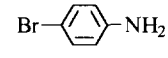
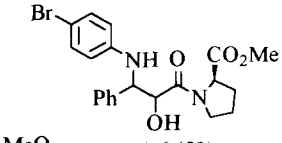
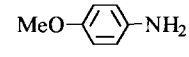
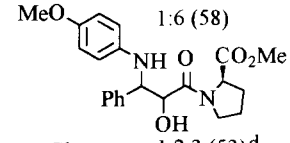
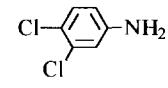
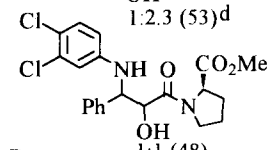
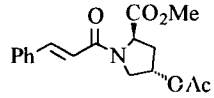
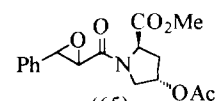
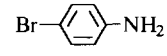
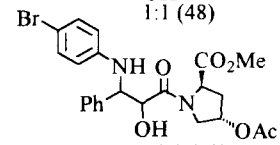
2

Scheme 1



Our earlier studies have indicated[3] that polyaniline supported cobalt(II) complex catalyzes the epoxidation of various alkenes under dioxygen at ambient condition. We now demonstrate that polyaniline supported cobalt(II) salen complex[4] can be used to perform dual role in which it first catalyzes the epoxidation of cinnamoyl amide of *L*-proline and subsequently promotes the opening of the epoxide with aniline and its derivatives.

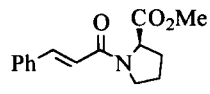
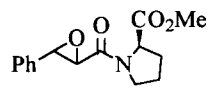
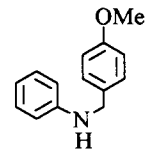
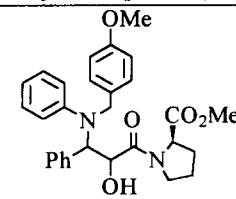
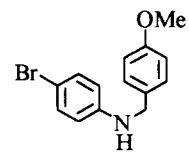
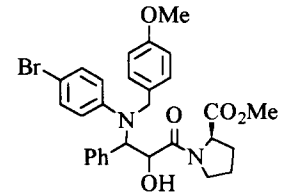
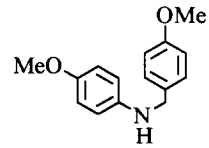
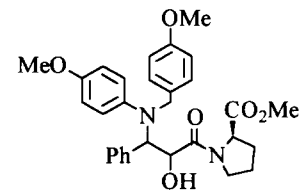
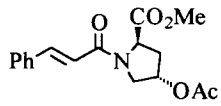
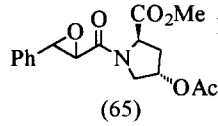
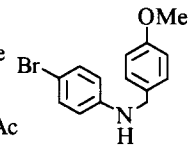
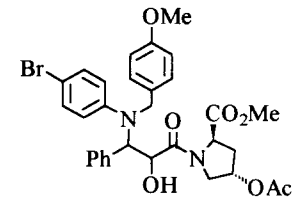
Table 1. Cobalt(II) Salen-Polyaniline Catalysed Synthesis of α-Hydroxyamides from Primary Amines

Entry	Alkene	Epoxide (yield, %)	Amine	Products Syn:Anti (yield,%) a,b,c
1		 (75)		 1:6 (58)
2				 1:2.3 (53)d
3				 1:1 (48)
4		 (65)		 1:3 (42)

[a]Diastereomeric ratio determined from 400 MHz ^1H NMR. [b]Isolated yield based on epoxide. [c]No attempts were made to ascertain the optical purity of the diastereomers. [d]$CoCl_2$ was used as the catalyst.

Typically, cinnamoyl amide derived from *L*-proline methyl ester (1 mmol) was dissolved in CH_3CN (10 mL) and 2-methylpropanal (5 mmol) was added to it and the resulting mixture was stirred in the presence of catalytic amount of cobalt(II) salen-polyaniline complex (15-20 mg) under dioxygen balloon at ambient temperature for 20-22 h. The catalyst was filtered and CH_3CN was removed under vacuuo. The residue was

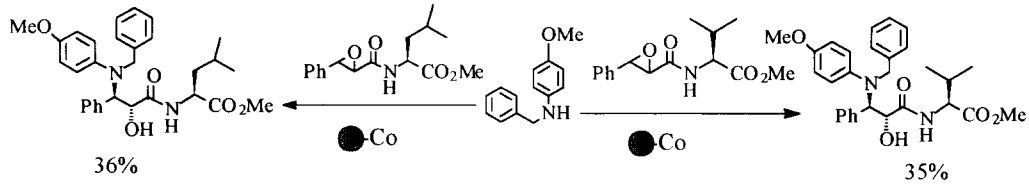
Table 2. Cobalt(II) Salen-Polyaniline Catalysed Synthesis of α-Hydroxyamides from Secondary Amines

Entry	Alkene	Epoxide (yield, %)	Amine	Product(s) Syn:Anti (yield, %) [a,b,c]
1		 (75)		 1:2 (45)
2				 1:2 (42)
3				 1:3 (42)
4		 (65)		 1:1.5 (41)

[a]Diastereomeric ratio determined from 400 MHz ^1H NMR. [b]Isolated yield based on epoxide. [c]No attempts were made to ascertain the optical purity of the diastereomers.

dissolved in ethyl acetate (20 mL) and the organic layer was successively washed with $NaHCO_3$ solution (3 x 10 mL) and brine solution (3 x 10 mL). Drying (Na_2SO_4) and removal of ethyl acetate under vacuuo provided the epoxide. The crude epoxide (1 mmol) was then reacted with aniline or its derivatives (1.2 mmol) in the presence of catalytic amount of cobalt(II) salen-polyaniline complex (15-20 mg) in CH_3CN (10 mL) at ambient temperature for 12-16 h. The usual work-up followed by silica gel column chromatography afforded the β-phenylisoserine-proline dipeptide derivatives in good yields. The generality of these reactions was demonstrated by converting the epoxides from cinnamoyl amides of *L*-proline and *trans*-4-acetoxy-*L*-proline

methyl esters with several primary and secondary amines derived from anilines to the corresponding dipeptide derivatives. It is noteworthy that the opening of epoxide with *para* substituted anilines resulted in the formation of *anti*-diastereomer as the major product and among these reactions, the high *anti*-selectivity was observed during the opening with *p*-bromoaniline (Table 1, entry 1). However, the opening of the epoxide from *trans*-4-acetoxy-*L*-proline with *p*-bromoaniline resulted in low *anti*-selectivity as compared to the reaction with the corresponding *L*-proline epoxide (Table 1, entry 4). Interestingly, the opening reactions with secondary amines derived from aniline were controlled by the *para* substituent on aniline ring. Thus, with *p*-methoxy substituent the *anti*-diastereomer was found to be the major product whereas opening with the corresponding *p*-bromo substituent resulted in moderate *anti*-selectivity (Table 2, entries 2 and 3). Similarly, opening with unsubstituted aniline derivative gave a moderate *anti*-selectivity (Table 2, entry 1), whereas nearly an equal ratio of *syn* and *anti*-diastereomers were obtained by the reaction of *p*-bromoaniline derivative with the cinnamoyl epoxide of *trans*-4-acetoxy-*L*-proline methyl ester (Table 2, entry 4). A similar effect of the *p*-methoxy group on the opening of cinnamoyl epoxides from *L*-valine and *L*-isoleucine derivatives were also observed as opening of these epoxides with secondary amines having a *p*-methoxyaniline derivatives resulted in the formation of *anti*-diastereomer as the major product (Scheme 2). The corresponding *syn*-diastereomer was observed in trace amounts only.



Scheme 2

In conclusion, polyaniline supported cobalt(II) salen catalysed conversion of cinnamoyl amide of *L*-proline methyl ester to the corresponding α-hydroxy-*L*-proline amide provides a general and efficient protocol to potentially useful inhibitors of HIV proteases.

References and Notes

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3. Das, B.C.; Iqbal, J. *Tetrahedron Lett.* **1997**, in press.
4. A mixture of polyemeraldine[5] (100 mg) and cobalt(II) salen[6] (100 mg) was stirred in CH_3CN (20 mL) at ambient temperature for 36 h. Filtration and washing with CH_3CN and CH_3COOH followed by drying (110° C) afforded the polyaniline supported cobalt(II) salen complex (180 mg) as a crystalline solid.
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