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A Cobalt Catalyzed Protocol for the Synthesis of Substituted β-Phenyl Isoserine Derivatives

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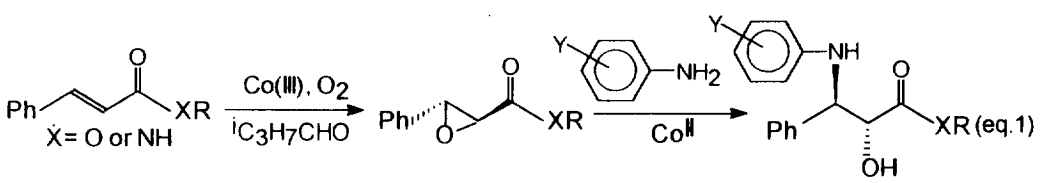
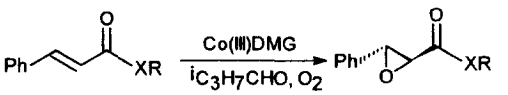
Abstract: *A versatile Cobalt Catalysed protocol for the epoxidation of α-β unsaturated esters or amides followed by its cleavage with aniline and its derivatives to afford substituted β-phenyl isoserine derivative has been developed.*

β-Phenyl isoserine plays a very important role as the C-13 side chain in taxol[1] and related derivatives, as it is known that this side chain i.e. the N-benzoyl (2R,3S-) 3-phenyl isoserine moiety, is crucial for the strong antitumor activity of these diterpenes. Various research groups are involved in the modification of the C-13 side chain of taxol to produce drugs with better bioavailability and potency. Accordingly, it seems quite attractive to investigate the structure activity relationship for the C-13 side chain analogs of taxol with some modification of the *baccatin* moiety in order to find more effective anticancer agents with improved pharmacological properties. Apart from this, the presence of an α-hydroxy β-amino amide or ester moiety is also found to be present in a large number of molecules which act as efficient enzyme-inhibitors e.g. bestatin which contains this unit is a potent amino peptidase inhibitor.[2] In view of the importance of β-phenyl isoserine and its derivative, we have developed an efficient methodology to access this unit by a cobalt catalyzed protocol . Earlier studies from our group have demonstrated[3] that cobalt complexes act as efficient catalysts during the aerobic epoxidation of various alkenes . In another study we have also demonstrated[4] that epoxides can be opened in a regioselective manner with aniline and its derivatives in the presence of a catalytic amount of cobalt chloride. We now demonstrate a versatile cobalt catalyzed protocol by employing a combination of epoxidation, followed by its opening with aniline and derivatives, to afford a variety of substituted β-phenyl isoserine derivatives (eq. 1).



Our initial studies were directed at developing an efficient catalytic system for the epoxidation of α,β-unsaturated carbonyl compounds. We discovered that α,β-unsaturated esters and amides can be epoxidised by a Co(III)DMG[5] catalyzed reaction involving 2-methylpropanal and molecular oxygen under ambient conditions. Ethyl cinnamate **1a** and α,β-unsaturated amides **2-4** derived from cinnamic acid were oxidised in moderate to good yields by employing these conditions to afford the corresponding epoxides **1a-4a** respectively (Scheme 1).

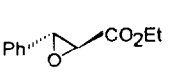
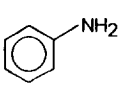
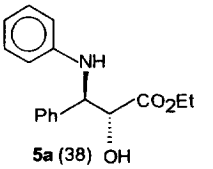
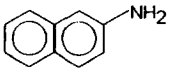
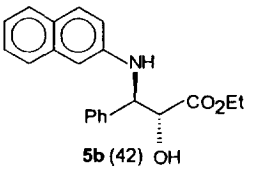
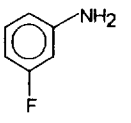
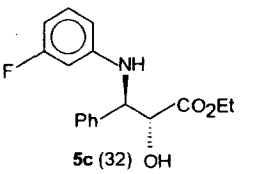
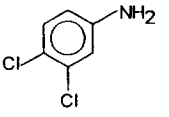
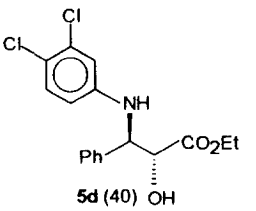
Scheme 1



X = O, R = Et(**1**) **1a**(45%)
X = NH, R= C_6H_5(**2**) **2a**(52%)
X = NH, R = -$CH_2C_6H_5$(**3**) **3a**(61%)
X = NH, R = $^{c}C_6H_{11}$(**4**) **4a**(66%)

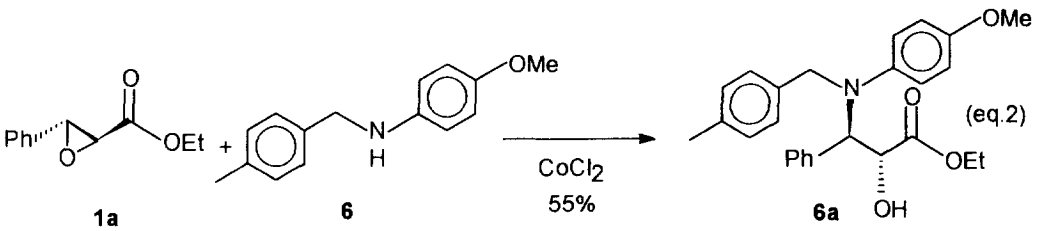
We next explored the cobalt chloride catalyzed opening of epoxides **1a-4a** with aniline and its derivatives

Table1. Cobalt(II) Chloride Catalysed opening of ethyl epoxy cinnamate with anilines.

Entry	Epoxide	Aniline	Product(Yield%)[a]
1.	 **1a**		 **5a** (38)
2.	**1a**		 **5b** (42)
3.	**1a**		 **5c** (32)
4.	**1a**		 **5d** (40)

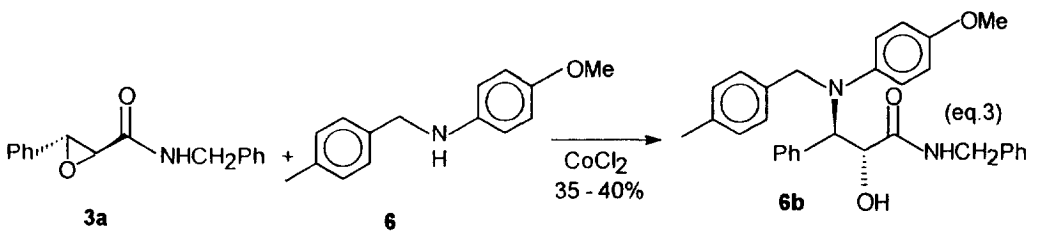
a) Yield of the purified product based on epoxide

and accordingly the epoxide from ethyl cinnamate (15 mmol) was stirred with one equivalent of aniline or its derivatives in acetonitrile (20 mL) in the presence of catalytic amount of cobalt chloride (5mol%) for 5 to 10 h. at ambient temperature to afford substituted β -phenyl isoserine derivatives (Table 1). Thus, the epoxide of ethyl cinnamate **1a** can be converted to the corresponding α-hydroxy β-amino ester **5a** using aniline (Table 1, entry 1). Similarly β-naphthylamine, m-fluoroaniline, and 3,4-dichloroaniline were used to convert efficiently this epoxide to the corresponding α-hydroxy β-amino derivatives **5b-5d** . (Table 1, entries, 2-4). It is interesting to note that the stereochemistry of **5a-5d** was found to be mainly *anti*, however, a small amount of the corresponding *syn* product was also observed in the reaction mixture. Similarly the secondary amine **6** derived from *p*-methoxy aniline efficiently transformed the epoxy cinnamate **1a** to the corresponding *anti* derivatives of β-phenyl isoserine in excellent yields (eq. 2).



1a **6** **6a**

It is noteworthy, though not particularly surprising , that these cobalt catalyzed openings didn't afford the other regioisomers. The cobalt catalyzed opening of epoxy amides **2a-4a** with anilines also proceeded smoothly to provide the corresponding *anti* α-hydroxy β-amino amide **7a-c** derivatives in good to excellent yields. Thus epoxy amides **2a** and **4a** could be transformed to the corresponding *anti* α-hydroxy β-amino amide **7a** and **7c** respectively on reaction with aniline in good yields (Table 2 entries, 1 & 3). Similarly the epoxy amide **3a** could be efficiently opened with *p*-bromoaniline to afford the corresponding *anti* diastereomer **7b** in good yields (Table 2, entry 2).

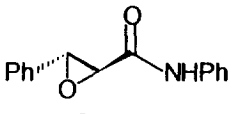
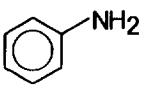
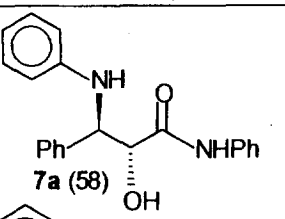
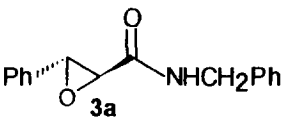
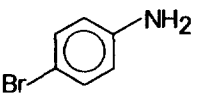
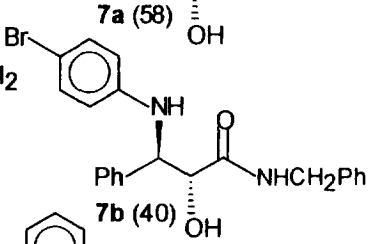
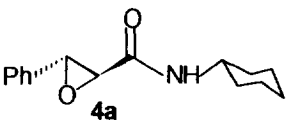
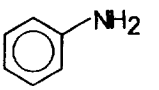
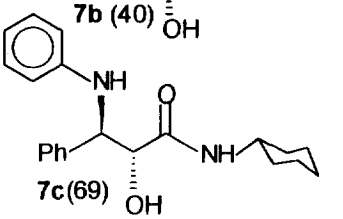


3a **6** **6b**

These reactions were accompanied by small amounts of *syn*-diastereomers. It is also interesting to note

that the secondary amine **6** also efficiently transformed the epoxy amide **3a** to the corresponding α-hydroxy β-amino amide **6b** mainly as the *anti* diastereomer in good yields (eq. 3)

Table2. Cobalt(II) chloride catalysed opening of α,β epoxy amides with anilines.

Entry	epoxy amides	Anilines	Product(Yield%)[a]
1.	 **2a**		 **7a** (58)
2.	 **3a**		 **7b** (40)
3.	 **4a**		 **7c**(69)

a) Yield based on starting α,β–unsaturated amide

In conclusion we have developed a versatile cobalt catalyzed protocol for the synthesis of β-phenyl isoserine derivatives which are potentially useful as enzyme inhibitors. We are currently pursuing the studies on the enantioselective synthesis of these derivatives.

References

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5 Bagchi, I.; *MSc. Project Report*, **1996**, IITKanpur. We thank Dr. Vibha Khanna for performing some experiments in the initial stages of this work.

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