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A Remarkable Stereocontrol During Cobalt(II) chloride Catalysed Opening Of Cinnamoyl Epoxides With N - Substituted Anilines

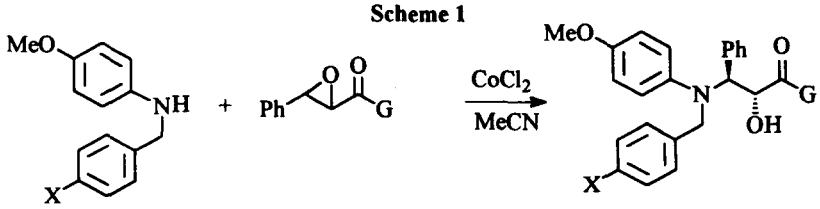
Asit De, Shubhajit Ghosh and Javed Iqbal*
Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

Abstract: The stereochemistry of the cobalt(II) chloride catalysed opening of cinnamoyl epoxides with N-substituted anilines is controlled by the *para* substituent of the aromatic ring attached to nitrogen atom. Thus the secondary amine having a *para* methoxy group cleaves the epoxide to afford the corresponding *anti* amino alcohol as the major product whereas amines containing *para* chloro, bromo, methyl or hydrogen substituents afford the *syn* amino alcohols as the major diastereomer. © 1997 Elsevier Science Ltd.

We have recently developed[1] a cobalt catalysed methodology for the synthesis of vicinal amino alcohols from cinnamoyl epoxide and substituted aniline derivatives. Cobalt(II) chloride catalyses the opening of the cinnamoyl epoxide with aniline or *para* substituted anilines to afford the corresponding *anti* amino alcohols and this methodology has been exploited in generating a library of compounds possessing core structures present in various enzyme inhibitors. We now show that N-substituted anilines exhibit an interesting *para*-substituent effect on the stereochemistry of amino alcohols during cobalt(II) chloride catalysed opening of the cinnamoyl epoxides.

The reaction of cinnamoyl epoxide with N-substituted aniline in the presence of cobalt(II) chloride affords the corresponding amino alcohols in good yields. The stereochemistry of the amino alcohols is dependent upon the *para* sustituent of the aromatic ring attached to the nitrogen atom. The opening of the cinnamoyl epoxide with N-substituted aniline having a *para* methoxy group gives the corresponding *anti*

Scheme 1

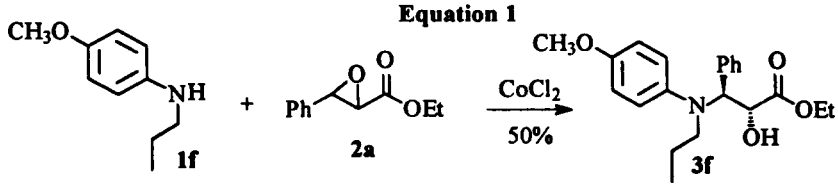


1a) X = H	2a) G = OEt	3a) 58%
1b) X = Cl	2a) G = OEt	3b) 40%
1c) X = OCH_3	2a) G = OEt	3c) 53%
1d) X = CH_3	2a) G = OEt	3d) 55%
1e) X = H	2b) G = $NHCH_2Ph$	3e) 49%

amino alcohol as the major product in high yields and only a trace of the *syn* diastereomer was observed in the reaction mixture. Thus the reaction[2] of secondary amines **1a-d** with *anti* epoxide of ethyl cinnamate **2a** in the presence of catalytic cobalt(II) chloride afforded the *anti* amino alcohol **3a-d** as the major product in good isolated yields (**Scheme 1**). Similarly the epoxy amide **2b** was transformed on treatment with **1e** to the corresponding *anti* amino alcohol **3e** as a single diastereomer.

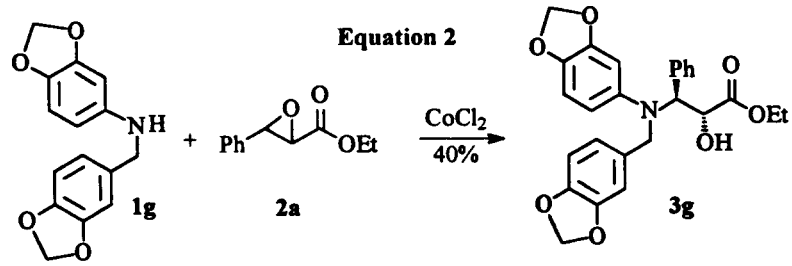
The stereochemistry of the amino alcohols obtained on opening with *para* methoxy aniline derivatives is not affected by the substituents in N-benzyl group and in each case the corresponding *anti* diastereomer is obtained as the main product (**Scheme 1, 3a-d**). Similarly the N-propyl aniline derivative **1f** reacted with **2a** to afford the corresponding *anti* amino alcohol **3f** under these reaction conditions **(Equation 1)**.

Equation 1



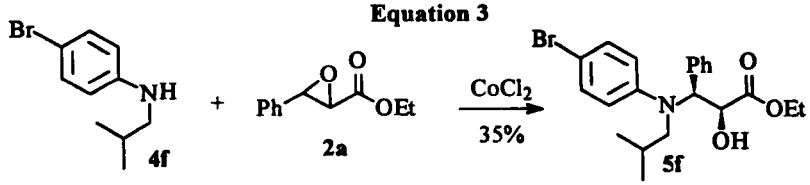
The aniline derivative **1g** having a methylene dioxo group also afforded the corresponding *anti* amino alcohol **3g** (**Equation 2**) as the major product . This observation suggests that the strong electron donating groups in the *para* position of the ring directly attached to nitrogen atom is responsible for the high *anti* selectivity of the epoxide opening. *It is noteworthy that the moderate yields obtained in these reactions is due to the low conversion of amine to amino alcohol as the corresponding unreacted amine is recovered from the reaction mixture .*

Equation 2



On the other hand the reaction of N-substituted anilines having a *para* substituent like hydrogen, methyl, chloro, or bromo with *anti* cinnamoyl epoxides in the presence of cobalt(II) chloride affords the

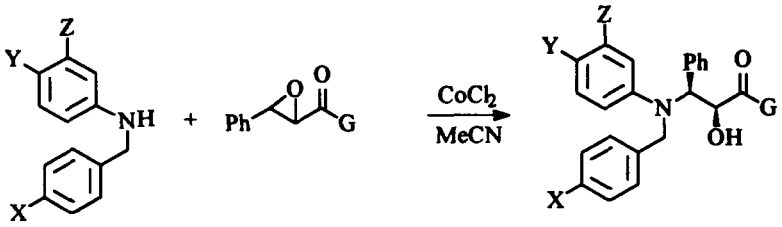
Equation 3



corresponding *syn* diastereomer as the main product. Thus the cobalt catalysed opening of the *anti* epoxide of cinnamic ester **2a** or amide **2b** with N-substituted anilines **4a-e** resulted in the formation of *syn* amino

alcohol **5a-e** as the main diastereomer (**Scheme 2**). The crude reaction mixture showed the presence of minor amounts of the corresponding *anti* diastereomer and as observed earlier the *para* substituent of the N-benzyl group did not have any effect on the stereoselectivity of the opening of epoxide. The opening of **2a** with N-alkylated aniline **4f** also resulted in the formation of the corresponding *syn* diastereomer **5f** as the major product (**Equation 3**).

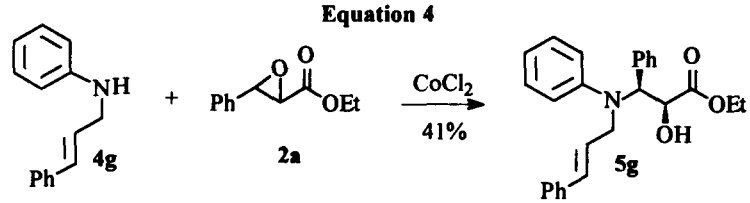
Scheme 2



4a) X = H, Y = H, Z = H	2a) G = OEt	5a) 45%
4b) X= Cl, Y= Br, Z = H	2a) G = OEt	5b) 33%
4c) X= OCH_3, Y= CH_3, Z = Cl	2a) G = OEt	5c) 46%
4d) X= OCH_3, Y= Cl, Z = Cl	2a) G = OEt	5d) 36%
4e) X= CH_3, Y= Br, Z = H	2b) G = $NHCH_2Ph$	5e) 41%

The N-allylated aniline **4g**, having no substituent in the *para* position of the aromatic ring attached to nitrogen atom, was also found to be highly *syn* selective and afforded the corresponding amino alcohol **5g** on cobalt catalysed opening of the epoxy cinnamoyl ester **2a** (**Equation 4**). *The moderate yields in these cases is again due to the incomplete reaction of the amines with cinnamoyl epoxides.*

Equation 4



The unambigous assignment[3] of the *syn* and *anti* stereochemistry to these amino alcohols were assigned based on the proton NMR chemical shift of the methine proton (N-CHCH-O) attached to nitrogen atom. Interestingly the chemical shift of this proton for *anti* diastereomer was below 5 *ppm* , whereas in case of the *syn* amino alcohols it always appeared above 5 *ppm*. The observation in the proton NMR was also supported by the single crystal X-ray data (**Fig. 1**) of the amino alcohols **3c** and **5b** obtained by opening of **2a** with aniline derivatives containing the *anti* selective (methoxy) **1c** and *syn* selective (bromo) **4b** *para* substituents respectively.

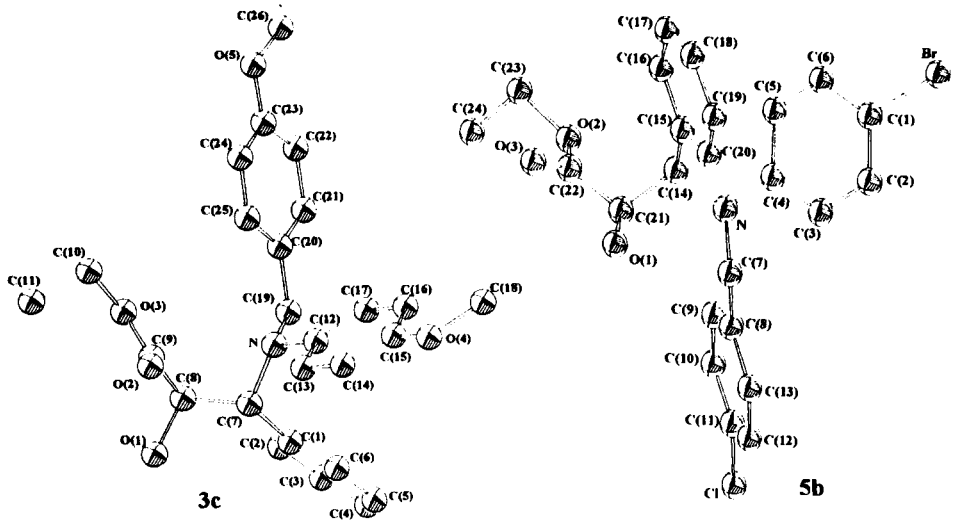


Fig. 1 ORTEP Plot for Amino Alcohol (a) **3c** and (b) **5b**

In conclusion, the cobalt(II) chloride catalysed opening of *anti* cinnamoyl epoxides with N-substituted anilines is highly diastereoselective and this selectivity is controlled by the *para* substituent present in the aromatic ring directly attached to the nitrogen atom.

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References and Notes

1. (a) Bhatia, B.; Jain, S.; De, A.; Bagchi, I.; Iqbal, J. *Tetrahedron Lett.* **1996**, *37*, 7311. (b) Punniyamurthy, T.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 4466. (c) Das, B.C.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 2903.
2. *Experimental Procedure*: The epoxide (5 mmol) (prepared according to reference 1a) was dissolved in acetonitrile (20 ml) and dry cobalt(II) chloride (5 mol%) was added to this solution. The resulting mixture was stirred under nitrogen atmosphere for 5 to 6 hrs at ambient temperature. Removal of solvent gave a residue which was taken in ethyl acetate (50 ml) and washed with saturated solution of sodium bicarbonate and water. Drying (magnesium sulphate) and removal of the solvent gave a residue which was chromatographed over silica gel (hexane-ethyl acetate) to afford the amino alcohols.
3. ^{1}H NMR: **3d:** (400 MHz, $CDCl_3$): 7.35-7.16 (m,5H), 6.95 (d, J=6.5Hz, 4H), 6.82 (d, J=10Hz, 2H), 6.5 (d, J=10Hz, 2H), 4.95 (d, J=6.7Hz. 1H), 4.65 (dd, J1=J2=6.7Hz, 1H), 4.4 (d, J=16.65Hz. 1H), 4.10 (m, 3H), 3.64 (s, 3H), 2.7 (d, J=6.7Hz, 1H), 2.18 (s, 3H), 1.14 (t, J=8.9Hz, 3H). **5a**: 7.44-7.07 (m, 12H), 6.90-6.69 (m, 3H), 5.45 (d, J=6.7Hz, 1H), 4.9 (d, J=16.6Hz, 1H), 4.83 (dd, J1=J2=6.7Hz, 1H), 4.59 (d, J=16.6Hz, 1H), 4.14 (q, J=7Hz, 2H), 2.83 (d, J=6.7Hz, 1H), 1.16 (t, J=8.9Hz, 3H). FAB mass (m/e, relative intensity): **3d**: 420 [(m+1), 30%], 316 [(m-103), 100%] and 105 [(m-314), 70%]. **5a:** 376 [(m+1), 80%], 272 [(m-103), 100%], 182 [(m-193), 70%] and 91 [(m-284),100%].

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