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Synthesis of β-amino alcohols by regioselective ring opening of arylepoxides with anilines catalyzed by cobaltous chloride

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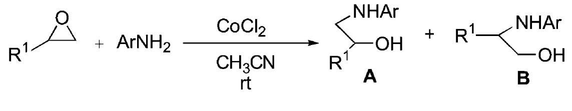
Abstract—$CoCl_2$ has been used as a mild and effective catalyst for regioselective ring opening of oxiranes with anilines to synthesize β-amino alcohols in good yields.

β-Amino alcohols are key intermediates to many organic compounds, mainly in biologically active natural and synthetic products[1] and are chiral auxiliaries for asymmetric synthesis.[2] The classical synthetic approach towards β-amino alcohols involves aminolysis of epoxides in protic solvents.[3] There are many limitations to this classical approach such as the requirement for elevated reaction temperatures for less nucleophilic amines and lower reactivity for sterically crowded amines/epoxides. In addition, as a rule, these reactions are accompanied by poor regioselectivity of ring opening. Several activators/promoters have been used in order to overcome these problems. These include the use of metal salts[4] (lithium, sodium, magnesium and calcium), metal amides (lithium,[5a] magnesium,[5b] lead,[5c] tin,[5d] and amide cuprate[5e]), metal alkoxides (DIPAT,[6a] Ti(O^{i}Pr)$_4$[6b]), metal triflates (lithium,[7a] lanthanides(III),[7b,c] Ph_4SbOTf[7d]), alumina,[8a,b] microwave assisted solvent-free montmorillonite clay,[9] transition metal halides ($TaCl_5$,[10a] $ZrCl_4$,[10b,c] VCl_3,[10d] $ZnCl_2$[10e]), rare earth metal halides ($SmI_2(THF)_2$,[11a] $CeCl_3 \cdot 7H_2O$[11b]), transition metal salts under solvent-free conditions,[12] ionic liquids,[13] and $Bi(OTf)_3$ and $Bi(TFA)_3$ under microwave irradiation.[14] Some of these methods suffer one or more limitations such as the use of costly chemicals, refluxing temperatures, inert atmosphere conditions, less regioselectivity, side reactions, etc. Hence there is a demand for cost effective regioselective synthetic routes to β-amino alcohols at ambient temperature.

Herein, we discuss $CoCl_2$-catalyzed regioselective synthesis of various β-amino alcohols. First, we tried to ring-open styrene oxide with the sterically bulky 2,6-diisopropylaniline in the presence of $CoCl_2$ catalyst at room temperature in acetonitrile. Upon work-up, two regioisomers **1A** and **1B** were produced in moderate yields with selectivity favouring the latter (Table 1, entry 1).[16,17]



The structure of the regioisomer **1B** was established unequivocally by single crystal X-ray analysis and the solved structure is given in Figure 1.[18] The observed regioselectivity in this reaction is contrary to that reported earlier.[15] In order to generalize the observed regioselectivity, we investigated the reactions of several epoxides with various amines. We realized that $CoCl_2$ catalyzes the ring opening of oxiranes with anilines both regioselectively as well as chemoselectively. In these $CoCl_2$ catalyzed reactions, styrene oxide undergoes regioselective addition of the anilines to the most substituted carbon (benzylic carbon) yielding amino alcohols **B** predominantly. The regioselective formation of amino alcohols **B** ranges from 88 to 98.5% (entries 1–5). In general we found that there was very little change in the

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Keywords: β-Amino alcohols; Epoxides; Anilines; Ring opening; Regioselectivity.

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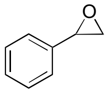
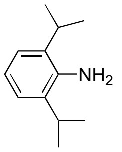
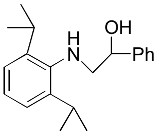
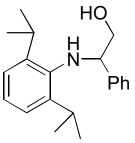
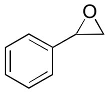
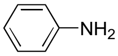
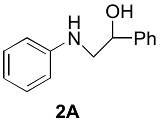
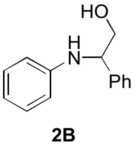
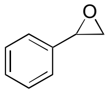
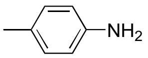
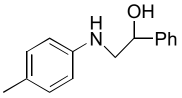
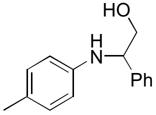
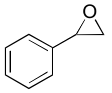
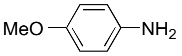
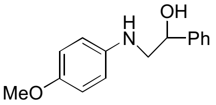
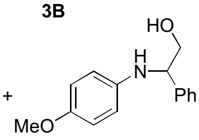
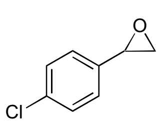
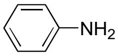
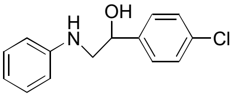
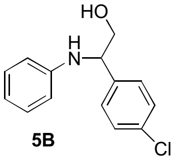
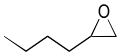
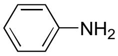
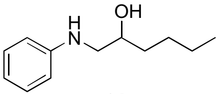
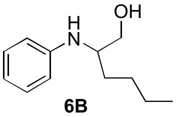
Table 1. $CoCl_2$ catalyzed ring opening of oxiranes with anilines

Entry	Oxirane	Aniline	Time (h)	Products		Yield (%)[a]	**A**:**B**[b]
1			24	 **1A**	+  **1B**	76	12:88
2			3	 **2A**	+  **2B**	98	5:95 (24:76)[c]
3			7	 **3A**	+  **3B**	74	1.5:98.5
4			24	 **4A**	+  **4B**	76	3.5:96.5 (26:74)[c]
5			7	 **5A**	+  **5B**	60	19:81
6			4	 **6A**	 **6B**	96	95:5

[a] Isolated yields.

[b] % of regioisomers were calculated using ^1H NMR.

[c] Corresponding ratio of regioisomers obtained via the classical synthesis (aminolysis of styrene oxide in ethanol at room temperature).

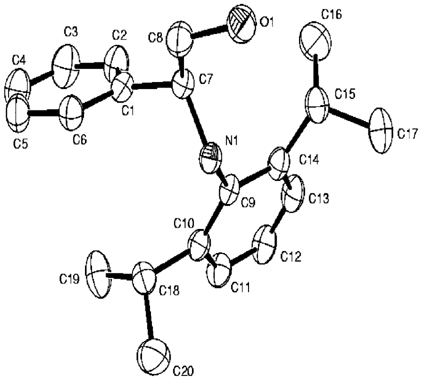
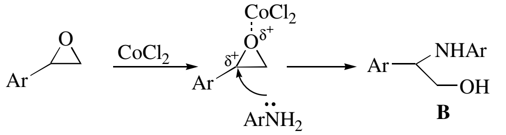


Figure 1. ORTEP diagram of amino alcohol **1B**.

regioselectivity of the products when anilines containing different substituents were used. With electron-withdrawing groups such as Cl, in the aromatic ring of the oxirane there was a slight decrease in reactivity (entry 5) as well as in regioselectivity. In strict contrast, the aliphatic oxirane gave the major product with the opposite regiochemistry (entry 6). Benzylamine and other aliphatic amines failed to ring open the oxirane even after long reaction periods with only trace amounts of the expected product amino alcohols being observed. Shortly after the addition of benzylamine to the $CoCl_2$ solution, a white precipitate formed. We suspect that this may be due to prior complexation of the highly basic benzylamine and other aliphatic amines with the catalyst system. Similar behaviour has been reported with $TaCl_5$,[10a] $CeCl_3$[11b] and metal triflates systems.[7] The ^1H NMR spectrum of this crude reaction product was too complex to offer any meaningful clues to the course of the reaction.

We also discovered that anilines act as superior ring-opening reagents even when the reactions were performed with $CoCl_2{\cdot}6H_2O$ or under aerobic conditions thereby ruling out the possibility of the mediation by free radicals. Therefore we speculate that an ionic process occurs, which explains the regioselectivity of the reaction (Scheme 1).

Thus we suggest that $CoCl_2$ coordinates with the oxirane oxygen to promote nucleophilic attack of the anilines leading to two regioisomers **A** and/or **B**. Attack of the nucleophile is governed by the nature of the oxirane and the stability of the incipient carbonium ion. In



Scheme 1. The ionic intermediate in the ring-opening reaction mediated by $CoCl_2$.

the case of metal coordinated styrene oxide, the positive charge on oxygen appears to be localized on the more highly substituted benzylic carbon. Thus the nucleophile attacks the benzylic carbon of the styrene oxide leading to amino alcohol **B**.[10a,b,11b] This suggestion is supported by the lower reactivity of *p*-chlorostyrene oxide towards ring opening under these conditions. To explain the reversal of stereochemistry in the ring opening of 1-hexene oxide, where the rate of formation of the less stable carbonium ion would be sluggish, we infer that steric factors predominate over electronic factors.

General procedure: To a solution of anhydrous $CoCl_2$ (1 mmol) in acetonitrile (10 mL), styrene oxide (10 mmol) and aniline (10 mmol) were added. The reaction mixture was stirred at room temperature for the required time (Table 1). After completion of the reaction, the solvent was removed under reduced pressure; the reaction mixture was diluted with water and extracted with diethyl ether (3 × 20 mL). The organic extracts were washed with aqueous $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to provide the crude product, which was purified by column chromatography (60–120 mesh silica gel) to give a mixture of **A** and **B**. Preparative HPLC of the mixture yielded pure components. $CoCl_2{\cdot}6H_2O$ also promotes the reaction in similar manner.

In summary, $CoCl_2$ has been used as a mild and effective catalyst for regioselective ring opening of oxiranes with anilines to synthesize β-amino alcohols in good yields. Here, styrene oxides undergo regioselective addition of anilines at the highly substituted carbon to yield regioisomers **B**, predominantly.

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16. Regioisomers **B** gives a base peak at *m/z* ($M^+{-}31$) after losing CH_2OH. In the ^1H NMR spectrum the benzylic protons of the regioisomer **B** resonate upfield compared to **A**. The benzylic protons of **A** resonate at around 4.9 ppm and those of **B** resonate at around 4.5 ppm. See Refs. 4a and 10b.
17. Spectral data for new compounds, entry 1, **1A**: viscous liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.06 (m, 8H, ArH), 4.95 (dd, 1H, $J = 7.9$, 3.7 Hz), 3.24–3.05 (m, 4H), 1.25–1.19 (AB quartet, 6H each, $J = 5.9$, 6.4 Hz, $4CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 142.2, 142.1, 128.5, 127.8, 125.8, 124.1, 123.6, 73.4, 58.8, 27.5, 24.2. IR (neat)/cm^{-1}: 3392, 2960, 1590. MS (*m/z*): 297, 190 (base peak), 175, 160, 107. HRMS calculated for (M+H) = 298.2171, found = 298.2195. Compound **1B**: white solid, mp = 54–55 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.03 (m, 8H, ArH), 4.10–3.85 (m, 3H), 3.13 (septet, 2H, $J = 0.17$ Hz), 1.19 and 1.00 (2d, 6H each, $J = 0.17$ Hz, $4CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 141.1, 140.5, 128.6, 127.6, 127.0, 123.5, 65.9, 65.3, 27.5, 24.0. IR (neat)/cm^{-1}: 3392, 2960, 1587. MS (*m/z*): 297, 266 (base peak), 190, 175, 160, 91. HRMS calculated for (M+H) = 298.2171, found = 298.2149.

18. Crystallographic data for the structure of **1B** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 248686. Crystal data for **1B**: intensity data were collected on an Enraf Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71069$ Å) using the $\omega - 2\theta$ technique to a maximum 2θ of 49.94°. $C_{21.5}H_{30.5}NO$, $M = 318.97$, triclinic, $a = 11.370(8)$ Å, $b = 13.812(7)$ Å, $c = 14.395(7)$ Å, $\alpha = 107.49(9)°$, $\beta = 99.57(9)°$, $\gamma = 106.39(9)°$, $V = 1989(2)$ Å^3, space group $P\bar{1}$, $Z = 4$, $d_{calcd} = 1.065$ g/cm^3, 6978 reflections measured, 4443 reflections [$I > 2\sigma(I)$] were used in all calculations, $R1 = 0.0620$, $wR2 = 0.1412$, R indices (all data) $R1 = 0.1059$, $wR2 = 0.1619$.