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# Ruthenium(III) Chloride–Catalyzed Ring Opening of Epoxides with Aromatic Amines

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**Abstract:** Ruthenium(III) chloride catalyzes the nucleophilic opening of epoxides by anilines, leading to the efficient synthesis of β-amino alcohols. High regioselectivity can be considered as a noteworthy advantage of this method.

**Keywords:** β-Amino alcohols, aromatic amines, epoxides, ruthenium(III) chloride

β-Amino alcohols are versatile intermediates in the synthesis of natural products, synthetic amino acids, and chiral auxiliaries for asymmetric synthesis.[1] Epoxides are an important class of building blocks that have found much use in synthetic organic chemistry.[2] Thus, nucleophilic ring opening of the oxirane ring is often employed for the synthesis of sophisticated bioactive molecules.[3] One of the most straightforward synthetic methods for the preparation of β-amino alcohols involves the ring opening of epoxides with amines;[4] however, these reactions are generally carried out with a large excess of the amines at elevated temperatures. Subsequently, a variety of activators/promoters such as metal triflates,[5] metal halides,[6] metal amides,[7] alkali metal perchlorates,[8] silica under high pressure,[9] ionic liquid,[10] and clay[11] have been introduced. The most important

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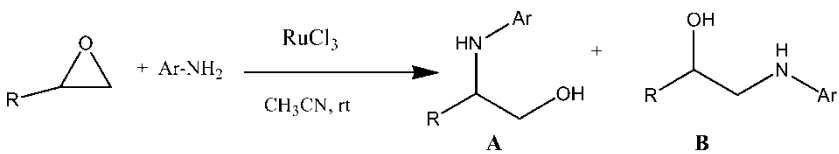
shortcomings of these methods are the long reaction times, high-temperature conditions, poor regioselectivity (especially with metal amides), and the use of stoichiometric amounts of reagents. To overcome these limitations, we report an efficient method for the ring opening of epoxide with aromatic amine catalyzed by ruthenium(III) chloride at room temperature.

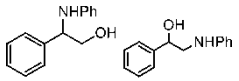
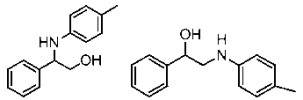
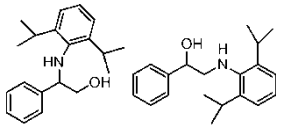
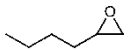
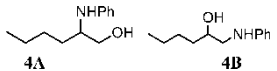
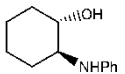
We have been interested in ruthenium-based organic transformations. Recently, we have reported that ruthenium(III) chloride is a mild Lewis acid for the acetalization of alcohols,[12] acetalization of aldehydes,[13] and conversion of ketoximes to amides.[14] In this communications, we propose that ruthenium(III) chloride, which acts as a mild Lewis acid, might be a useful catalyst for the preparation of $\beta$-amino alcohols by regioselective ring opening of epoxides. Aryl oxiranes underwent cleavage by a variety of aromatic amines in a regioselective fashion with preferential attachment at the benzylic position in the presence of a catalytic amount of $RuCl_3$ at room temperature in acetontrile (Scheme 1). Interestingly, the sterically bulky 2,6-diisopropylaniline underwent the ring opening reaction of epoxide to afford the corresponding $\beta$-amino alcohols in good yield (Table 1, entry 3). Aliphatic amines did not give any satisfactory yields under the reaction conditions. Similar observations were reported with other reagents.[5–11] Aliphatic oxirane gave the major product with the opposite regiochemistry (entry 4). Therefore, we suggest that attack of the nucleophile is governed by the nature of oxirane and the stability of carbonium ion. In aryl oxirane, the positive charge on oxygen appears to be localized on the more highly substituted benzylic carbon leading to the major product (Scheme 2). Aliphatic oxirane gave the opposite regiochemistry; possibly steric factors predominate over electronic factors. In the case of cyclohexene oxide (entry 5), the stereochemistry of the ring-opened product was found to be trans from the coupling constants of ring hydrogens with characteristic $^1$H NMR peaks appearing at $\delta$ 3.14 (ddd, $J = 4.1$, 10.1, 10.2 Hz, 1 H) for CHNH and at 3.36 (ddd, $J = 4.2$, 10.2, 10.4 Hz, 1 H) for CHOH. The scope and generality of this method is illustrated with respect to various epoxides and aryl amines and the results are presented in Table 1.

In conclusion, a very simple and convenient method for the synthesis of $\beta$-amino alcohols has been developed using a catalytic amount of ruthenium(III) chloride. The experimental simplicity, mild reaction conditions, inexpensive catalyst, and high yields of products makes it a useful and important addition to the existing methodologies.

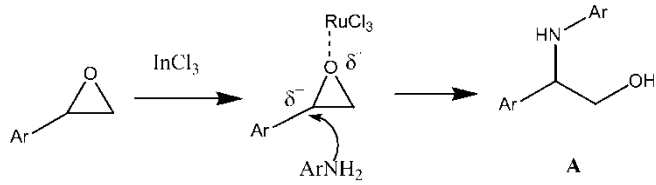



*Scheme 1.*

***Table 1.*** $RuCl_3$-catalyzed ring opening of oxiranes with anilines

| Entry | Oxirane | Aniline | Time (h) | Products | A:B[a] | Yield[b](%) |
|---|---|---|---|---|---|---|
| 1 |  |  | 8 |  **1A** **1B** | 92 : 8 | 82 |
| 2 |  |  | 10 |  **2A** **2B** | 91 : 9 | 85 |
| 3 |  |  | 12 |  **3A** **3B** | 90 : 10 | 78 |
| 4 |  |  | 10 |  **4A** **4B** | 8 : 92 | 81 |
| 5 |  |  | 8 |  **5** | —[c] | 88 |

[a]Regioisomers were calculated using $^1H$ NMR.
[b]Isolated yields.
[c]One isomer formed.




*Scheme 2.*

## EXPERIMENTAL

All products are known compounds and were identified by comparison of their spectral data and physical properties with those of authentic samples. The progress of reaction was monitored by thin-layer chromatography (TLC) on silica gel. All yields refer to isolated products.

### Typical Procedure

Anhydrous $RuCl_3$ (1 mmol) was added to a mixture of cyclohexene oxide (5 mmol) and aniline (5 mmol) in acetontrile (10 mL) at room temperature. After completion of the reaction (TLC), the solvent was removed under reduced pressure; the reaction mixture was diluted with water (40 mL) followed by extraction with ethyl acetate (60 mL). The organic layer was washed with aqueous $NaHCO_3$ (20 mL), water (30 mL), and brine (40 mL) respectively, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (30% ethyl acetate in hexane) to give a pure trans-2-(phenylamino)cyclohehanol.

### Product Characterization Data

**2-Anilino-2-phenyl-1-ethanol (1A)**[6]: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.73 (dd, $J = 10$, 7 Hz, 1H), 3.94 (dd, $J = 10$, 4 Hz, 1H), 4.53 (dd, $J = 10.8$, 6.8 Hz, 1H), 6.52 (d, $J = 7.2$ Hz, 2H), 6.72 (t, $J = 7.2$ Hz, 1H), 7.11 (t, $J = 7.2$ Hz, 2H), 7.31–7.45 (m, 5H); EIMS $m/z$ 213 ($M^+$), 195, 107, 77, 57. Anal. calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found C, 78.86; H, 7.08; N, 6.55.

**2-(4-Methylphenyl)amino-2-phenyl-1-ethanol (2A)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (2.16 (s, 3H), 3.69 (dd, $J = 7.4$, 11.2 Hz, 1H), 3.87 (dd, $J = 4.2$, 11.2 Hz, 1H), 4.45 (dd, $J = 4.2$, 7.4 Hz, 1H), 6.48 (d, $J = 8$ Hz, 2H), 6.92 (d, $J = 8$ Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (20.5, 60.3, 66.9, 114.2, 119.6, 126.6, 127.3, 128.5, 129.6, 140.2, 144.8; EIMS $m/z$ 227 ($M^+$), 196, 77. Anal. calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found C, 79.25; H, 7.57; N, 6.13.

**2-(2,6-Diisopropylphenyl)amino-2-phenyl-1-ethanol (3A)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.18–1.27 (m, 12H), 3.04–3.27 (m, 4H), 4.95 (dd, $J = 7.9$, 3.6 Hz, 1H), 7.02–7.46 (m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$) 24.4, 27.6, 58.5, 73.4, 123.6, 124.2, 125.9, 127.8, 128.7, 142.2, 142.3, 142.8; EIMS $m/z$ 297 ($M^+$), 190, 175, 160, 107. Anal. calcd. for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found C, 80.79; H, 9.16; N, 4.73.

**1-(4-Methylphenylamino)hexan-2-ol (4B)**: liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (t, $J = 6.9$ Hz, 3H), 1.24–1.63 (m, 6H), 2.21 (s, 3H), 2.94 (dd, $J = 12.4$, 8.2 Hz, 1H), 3.26 (dd, $J = 12.4$, 3.4 Hz, 1H), 3.82 (m, 1H), 6.62 (d, $J = 8$ Hz, 2H), 6.89 (d, $J = 8$ Hz, 2H); EIMS $m/z$ 207 ($M^+$), 190, 178, 135, 121, 107, 84, 57. Anal. calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.19; N, 7.25. Found C, 74.56; H, 9.18; N, 7.21.

***trans*-2-(Phenylamino)cyclohexanol (5)**: mp 61–63°C; lit.[6] 60–61°C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.02–1.43 (m, 4 H), 1.71–1.82 (m, 2H), 2.11–2.23 (m, 2H), 2.82 (brs, 1 H, NH), 3.14 (ddd, $J = 4.1$, 10.1, 10.2 Hz, 1H), 3.36 (ddd, $J = 4.2$, 10.2, 10.4 Hz, 1H), 6.71–7.23 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.3, 25.4, 31.7, 33.2, 60.3, 74.5, 114.5, 118.5, 129.4, 147.9; EIMS $m/z$ 191 ($M^+$), 174, 99, 82, 77, 41. Anal. calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found C, 75.34; H, 8.98; N, 7.30.

## REFERENCES


1. (a) Corey, E. J.; Zhang, F. Re-and si-face-selective nitroaldol reactions catalyzed by a rigid chiral quarternary ammonium salt. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1931; (b) Chang, H. T.; Sharpless, K. B. Catalytic asymmetric aminohydroxylation of olefins. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451; (c) Ager, D. J.; Prakash, I.; Shaad, D. R. 1,2-Amino alcohols and their heterocyclic derivatives as chiral auxiliaries in asymmetric synthesis. *Chem. Rev.* **1996**, *96*, 835.
2. (a) Rogers, G. A.; Parson, S. M.; Anderson, D. C.; Nilson, L. M.; Bahr, B. A.; Kornreich, W. D.; Kaufman, R.; Jacobs, R. S.; Kirtman, B. Synthesis, in vitro acetylcholine-storage-blocking activities, and biological properties of derivatives and analogs of trans-2-(4-phenylpiperidino)cyclohexanol (vesamicol). *J. Med. Chem.* **1989**, *32*, 1217; (b) Cheng, B. L.; Ganesan, A. A solution-phase synthesis of a $\beta$-amino alcohol combinatorial library. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1511; (c) Ghosh, A. K.; Wang, Y. Total synthesis of (+)-polyoxin J. *J. Org. Chem.* **1999**, *64*, 2789.
3. Yamaguchi, T.; Harada, N.; Ozaki, K.; Hashiyama, T. Synthesis of taxoids 3. A novel and efficient method for preparation of taxoids by employing *cis*-glycidic acid. *Tetrahedron Lett.* **1998**, *39*, 5575.
4. (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. Enantioselective desymmetrisation of achiral epoxides. *Tetrahedron* **1996**, *52*, 14361; (b) Hanson, R. M. The synthetic methodology of nonracemic glycidol and related 2,3-epoxy alcohols. *Chem. Rev.* **1991**, *91*, 437; (c) Chini, M.; Croti, M.; Machia, F. *J. Org. Chem.* **1991**, *66*, 5939.
5. (a) Fujiwara, M.; Imada, M.; Baba, A.; Matsuda, H. Tetraphenyl stibonium as a regio- and chemoselective catalyst in the reaction of oxiranes with amines. *Tetrahedron Lett.* **1989**, *30*, 739; (b) Sekar, G.; Singh, V. K. An efficient method for cleavage of epoxides with aromatic amines. *J. Org. Chem.* **1999**, *64*, 287.

6. (a) Chadrasekhar, S.; Ramchandar, T.; Prakash, J. S. $TaCl_5$-catalyzed cleavage of epoxides with aromatic amines. *Synthesis* **2000**, *22*, 1818; (b) Chakraborti, A. K. Kondaskar, A. $ZrCl_4$ as a new and efficient catalyst for the opening of epoxide rings by amines. *Tetrahedron Lett.* **2003**, *44*, 8315; (c) Swamy, N. R.; Goud, T. V.; Reddy, S. M.; Krishnaiah, P.; Vekateswarlu, Y. Zirconium(IV) chloride–catalyzed ring opening of epoxides with aromatic amines. *Synth. Commun.* **2004**, *34*, 727.
7. (a) Kissel, C. L.; Rickborn, B. Base-induced rearrangement of epoxides. IV. Reaction of cyclohexene oxide with various lithium alkylamides. *J. Org. Chem.* **1972**, *37*, 2060; (b) Overman, L. E.; Flippin, L. A. Facile aminolysis of epoxides with diethylaluminium amides. *Tetrahedron Lett.* **1981**, *22*, 195.
8. Chini, M.; Crotti, P.; Machia, F. Metal salts as new catalysts for mild and efficient aminolysis of oxiranes. *Tetrahedron Lett.* **1990**, *31*, 4661.
9. Kotsuki, H.; Hayashida, K.; Shimanouchi, T.; Nishizawa, H. High-pressure organic chemistry. 19. High-pressure-promoted, silica gel-catalyzed reaction of epoxides with nitrogen heterocycles. *J. Org. Chem.* **1996**, *61*, 984.
10. Yadav, J. S.; Reddy, B. V.; Basak, A. K.; Narsaiah, A. V. [Bmin]$BF_4$ ionic liquid: A novel reaction medium for the synthesis of $\beta$-amino alcohols. *Tetrahedron Lett.* **2003**, *44*, 1047.
11. Mojtahedi, M. M.; Saidi, M. R.; Bolortchian, M. *J. Chem. Res.* **1999**, 128.
12. De, S. K. Ruthenium(III) chloride–catalyzed acylation of alcohols, phenols, thiols, and amines. *Tetrahedron Lett.* **2004**, *45*, 2919.
13. De, S. K.; Gibbs, R. A. Ruthenium(III) chloride–catalyzed chemoselective synthesis of acetal from aldehydes. *Tetrahedron Lett.* **2004**, *45*, 8141.
14. De, S. K. $RuCl_3$-catalyzed facile conversion of arylalkyl ketoximes to amides. *Synth. Comm.* **2004**, *34*, 3431.