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Zinc(II) Perchlorate Hexahydrate Catalyzed Opening of Epoxide Ring by Amines: Applications to Synthesis of (*RS*)/(*R*)-Propranolols and (*RS*)/(*R*)/(*S*)-Naftopidils

Shivani, Brahmam Pujala, and Asit K. Chakraborti*

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar 160 062, Punjab, India

akchakraborti@niper.ac.in

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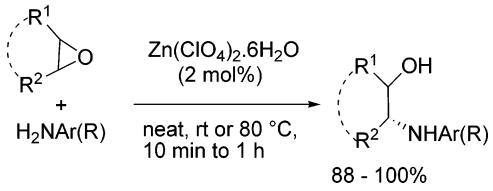

Commercially available zinc(II) perchlorate hexahydrate [$Zn(ClO_4)_2 \cdot 6H_2O$] was found to be a new and highly efficient catalyst for opening of epoxide rings by amines affording 2-amino alcohols in high yields under solvent-free conditions and with excellent chemo-, regio-, and stereoselectivities. For unsymmetrical epoxides, the regioselectivity was influenced by the electronic and steric factors associated with the epoxides and the amines. A complementarity in the regioselectivity was observed during the reaction of styrene oxide with aromatic and aliphatic amines: aromatic amines provided amino alcohols from nucleophilic attack at the benzylic carbon as major products whereas aliphatic amines resulted in formation of the amino alcohols through reaction at the terminal carbon atom of the epoxide ring as the major/sole products. Reaction of aniline with various glycidic ethers gave the amino alcohols by regioselective nucleophilic attack at the terminal carbon atom of the epoxide ring as the only/major product. Zinc(II) perchlorate hexahydrate was found to be the best catalyst compared to other metal perchlorates. The counteranion modulated the catalytic property of the various Zn(II) compounds that followed the order $Zn(ClO_4)_2 \cdot 6H_2O \gg Zn(BF_4)_2 \sim Zn(OTf)_2 \gg ZnI_2 > ZnBr_2 > ZnCl_2 > Zn(OAc)_2 > Zn(CO_3)_2$ in parallelism with the acidic strength of the corresponding protic acids (except for TfOH). The applicability of the methodology was demonstrated by the synthesis of cardiovascular drugs propranolol and naftopidil as racemates and optically active enantiomers.

Introduction

Nucleophilic opening of epoxide rings by amines is an important reaction for synthetic organic/medicinal chemists as the resultant 2-aminoalcohols represent a broad range of β-adrenergic blockers widely used in the management of cardiovascular disorders,[1] including hypertension,[2] anginapectoris, cardiac arrhythmias, and also other disorders[3] related to the sympathetic nervous system. The versatility of this transformation is recognized well as it constitutes the key step for synthesis of β_2-adrenoceptor agonists,[4] novel anti-HIV agents,[5]

* To whom correspondence should be addressed. Fax: 91-(0)-172 2214692. Tel: 91-(0)-172 2214683.

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4-demethoxydaunomycin,[6] protein kinase C inhibitor balanol,[7] glycosidase inhibitor,[8] antimalarial agents,[9] liposidomycin B class of antibiotics,[10] naturally occurring brassinosteroids,[11] taxoid side chain,[12] diverse heterocycles, for example, benzodiazepinones/benzoxazines/benzoxazepinones[13] and indoles,[14] a vast range of biologically active natural and synthetic products,[15] unnatural amino acids,[16] and chiral auxiliaries.[17] The classical approach for the synthesis of 2-amino alcohols from epoxides involves the treatment of an epoxide with an amine under heating.[18] However, this procedure has limitations such as the requirement of excess of amines and elevated temperature, often works less well with poorly nucleophilic and sterically hindered amines, lacks appreciable regioselectivity, and poses problems in dealing with sensitive epoxides because of potential side reactions such as rearrangement or polymerization. Thus, there have been incessant efforts to develop methodologies for opening of epoxide rings by amines as evidenced by recent reports.[19] Still, some of these methods could not overcome the shortcomings such as the use of solvents, requirement of long reaction times (2.5 − 24 h), high pressure, and moisture/air sensitive and costly catalysts. In continuation of our interest for the development of newer methodologies for epoxide ring opening by amines,[20] we thought that a metal salt of a strong protic acid should possess a strong Lewis acid property and activate the epoxide ring more effectively and enable the epoxide ring-opening reaction under milder conditions and in short times. Thus, metal triflates should be ideal catalysts as TfOH is the strongest protic acid ($H_0 = -14.1$)[21] known. However, TfOH is liberated during the triflate-catalyzed reactions[22] and becomes detrimental because of the potential side reactions such as dehydration of the resultant amino alcohols and acid-catalyzed rearrangement of the epoxides. This necessitates the requirement of solvent, excess of reagent, low temperature (−8 to −60 °C), and additives (e.g., molecular sieves, $MgSO_4$, TBAB, SDS, etc.) during the acetylation,[23] α-amino phosphonate formation,[24] and epoxide ring-opening[19j,p,r,25] reactions carried out in the presence of metal triflates. Hence, attention is given to metal triflimides as $HNTf_2$ is a weaker Brønsted acid than TfOH[26] and ligand exchange has not been observed with triflimides.[27] However, triflimides are costly, some are not available commercially and involve a high cost for preparation, and they are not good contenders for industrial applications. Since perchloric acid is the next strongest protic acid, we focused our attention to metal perchlorates as they are efficient electrophilic activation catalysts for acylation,[28] imine formation,[29] thia-Michael addition,[30] acylal

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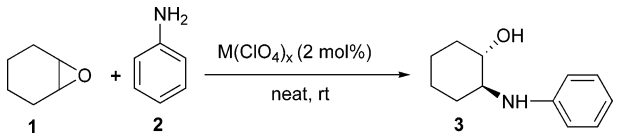
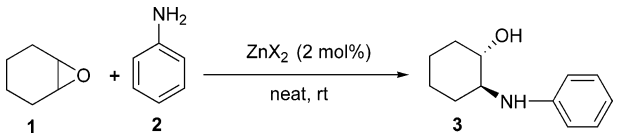
TABLE 1. Epoxide Ring-Opening Reaction of 1 with 2 in the Presence of Various Metal Perchlorates[a]



entry	catalyst	time (min)	yield (%)[b,c]
1	$Zn(ClO_4)_2 \cdot 6H_2O$	15	100[d]
2	$Mg(ClO_4)_2 \cdot xH_2O$	60	48
3	$BiO(ClO_4)_2 \cdot xH_2O$	60	55
4	$LiClO_4 \cdot xH_2O$	60	2
5	$Fe(ClO_4)_2 \cdot 6H_2O$	60	81
6	$Fe(ClO_4)_3 \cdot 6H_2O$	60	82
7	$Co(ClO_4)_2$	60	88
8	$ZrO(ClO_4)_2 \cdot xH_2O$	60	73
9	$Cu(ClO_4)_2 \cdot xH_2O$	60	100

[a] **1** (2.5 mmol) was treated with **2** (2.5 mmol, 1 equiv) in the presence of the metal perchlorate (2 mol %) at rt under solvent-free conditions. [b] **3** was the only product (NMR). [c] GCMS conversion. [d] Isolated yield was 99%.

TABLE 2. Epoxide Ring-Opening Reaction of 1 with 2 in the Presence of Various Zinc Salts[a]



entry	Zn(II) salt	time (min)	yield (%)[b,c]
1	$Zn(ClO_4)_2 \cdot 6H_2O$	15	100[d]
2	$ZnCl_2$	60	25[e,f]
3	$ZnBr_2$	60	52[e,f]
4	ZnI_2	60	65[f,g]
6	$Zn(OAc)_2$	60	20[f]
7	$Zn(OTf)_2$	60	92
8	$Zn(BF_4)_2$	60	94
9	$Zn(CO_3)_2$	60	11[f]

[a] **1** (2.5 mmol) was treated with **2** (2.5 mmol, 1 equiv) in the presence of the zinc salts (2 mol %) at rt under solvent-free conditions. [b] **3** was the only product (NMR). [c] GCMS conversion. [d] Isolated yield was 99%. [e] Trace amount of halohydrine formation was observed. [f] The unreacted epoxide remained intact (GCMS). [g] The iodohydrine was formed in 6% yield.

formation,[31] and α-aminophosphonate formation[32] reactions. We observed that the potentiality of metal perchlorates for the use as catalyst for opening of the epoxide rings by amines is underexplored and only $LiClO_4$ has been used for this purpose. However, the $LiClO_4$-catalyzed aminolysis of epoxides required 2 equiv of the amines, 1−10 equiv of $LiClO_4$, the use of solvent, and long times (1−38 h).[33] Thus, we planned to evaluate the catalytic efficiency of various metal perchlorates for opening of epoxide rings by amines and report that commercially available zinc(II) perchlorate hexahydrate [$Zn(ClO_4)_2 \cdot 6H_2O$] is a new and highly efficient catalyst operative under solvent-free conditions, at room temperature (rt), and in short times.

Results and Discussion

To find the most effective catalyst, cyclohexene oxide **1** was treated with aniline **2** in the presence of catalytic quantities of various metal perchlorates, and the results are summarized in Table 1. The reactions were monitored by tandem gas chromatography mass spectrometry (GCMS). In each case, the *trans*-2-phenylaminocyclohexanol **3** was formed as the sole product.[20]

The reaction was best catalyzed by $Zn(ClO_4)_2 \cdot 6H_2O$ with 100% conversion (GCMS) to **3** after 15 min at rt. The use of $Fe(ClO_4)_2 \cdot xH_2O$, $Fe(ClO_4)_3 \cdot xH_2O$, $Co(ClO_4)_2 \cdot xH_2O$, $ZrO(ClO_4)_2 \cdot xH_2O$, and $Cu(ClO_4)_2 \cdot xH_2O$ provided 81, 82, 88, 73, and 100% conversion, respectively, after 60 min (entries 5−9, Table 1). Moderate yields (GCMS) of **3** were obtained in the presence of $Mg(ClO_4)_2 \cdot xH_2O$ and $BiO(ClO_4)_2 \cdot xH_2O$ (entries 2 and 3, Table 1), but no significant amount of formation of **3** was observed after 60 min in the presence of $LiClO_4 \cdot xH_2O$ (entry 4, Table 1).[34]

As the Lewis acid property of a metal salt depends on the corresponding protic acid, we planned to evaluate the influence of the counteranion on the catalytic efficiency of various zinc compounds for the reaction of **1** with **2** (Table 2). The best result was obtained with $Zn(ClO_4)_2 \cdot 6H_2O$ (entry 1, Table 2). The use of $Zn(OTf)_2$ and $Zn(BF_4)_2 \cdot xH_2O$ (entries 7 and 8) also gave excellent results but required longer times (compare entry 1 with entries 7 and 8, Table 2). Moderate yield (52% after 60 min, GCMS) of **3** was obtained in the presence of $ZnBr_2$ (entry 3, Table 2) but $ZnCl_2$,[19k] $Zn(OAc)_2$,[35] and $ZnCO_3$ (entries 2 and 6, Table 2) gave poor conversion to **3**. The overall catalytic activity of the various zinc compounds were found to be in the order $Zn(ClO_4)_2 \cdot 6H_2O \gg Zn(BF_4)_2 \cdot xH_2O \sim Zn(OTf)_2 > ZnI_2 > ZnBr_2 > ZnCl_2 > Zn(OAc)_2 > ZnCO_3$ that exhibited parallelism with the acidity of the corresponding protic acids (except for TfOH).[36]

The applicability of $Zn(ClO_4)_2 \cdot 6H_2O$ was evaluated for aminolysis of **1** with various aromatic and aliphatic amines (Table 3). Excellent results were obtained in each case affording 90−100% yields of the corresponding *trans*-2-aryl/alkylaminocyclohexanols (NMR). The reactions were, in general, faster (10−60 min, rt) with aromatic amines compared to that for aliphatic amines (60 min, 80 °C). Electron-rich aromatic amines (entries 2−5, Table 3) required longer times (30−60 min) compared to that required for **2** (15 min), but in case of 4-chloroaniline the reaction was faster (10 min).

To establish the benefit of this new method over the standard epoxide opening by amines, the reactions of **1** with morpholine and piperidine were separately carried out under solvent-free conditions at 80 °C for 60 min in the absence of any catalyst. The corresponding amino alcohols were formed in 20% yields. The corresponding amino alcohols were prepared in 100 and 97% yields, respectively, under this new method (entries 7 and 9, Table 3). The standard reported uncatalyzed procedure required heating the mixture of the epoxide and the amine under reflux for 24 h to afford 85−86% yields of the amino alcohols.[18k]

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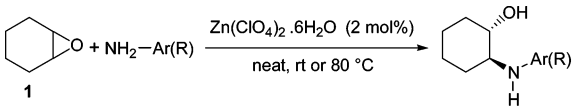
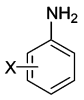
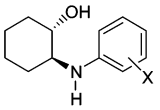
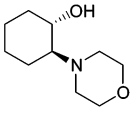
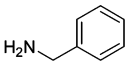
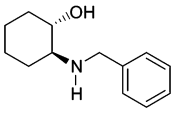
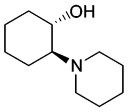
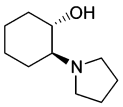
(36) The pK_a values of aqueous $HClO_4$, HI, HBr, HCl, and HOAc are −10, −9, −8, −6.1, and 4.76, respectively. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 1960.

TABLE 3. $Zn(ClO_4)_2 \cdot 6H_2O$-Catalyzed Epoxide Ring-Opening Reaction of 1 with Various Aromatic and Aliphatic Amines[a]



Entry	Amine	Time (min)	Product	Yield (%)[b,c]
				
1	X = H	15	X = H	99
2	X = 4-OMe	60	X = 4-OMe	100
3	X = 4-Me	30	X = 4-Me	98
4	X = 2-Me	30	X = 2-Me	90
5	X = 3-Me	30	X = 3-Me	95
6	X = 4-Cl	10	X = 4-Cl	97
7		60		100[d,e]
8		60		97[d]
9		60		97[d,e]
10		60		100[d]

[a] **1** (2.5 mmol) was treated with the amine (2.5 mmol, 1 equiv) in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol %) at rt (except for entries 7−10) under solvent-free conditions. [b] Isolated yield of the corresponding *trans*-2-aryl/alkylaminocyclohexanol. [c] The products were characterized by IR, NMR, and MS. [d] The reaction was carried out at 80 °C. [e] The desired amino alcohol was formed in 20% yield when the reaction was carried out in the absence of any catalyst at 80 °C for 60 min (to compare with the reported standard procedure under ref 18k).

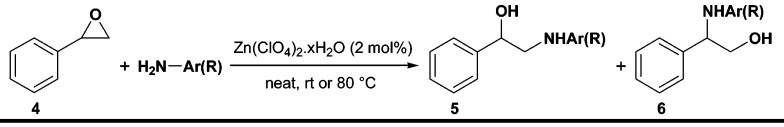
To determine the regioselectivity, styrene oxide **4** was used as a representative unsymmetrical epoxide and was treated with various aromatic and aliphatic amines in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (Table 4).

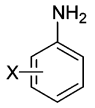
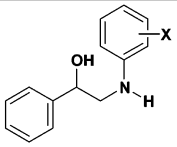
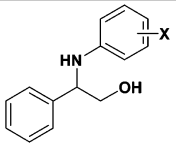
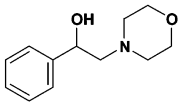
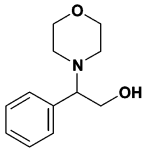
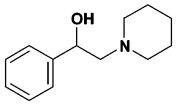
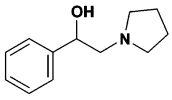
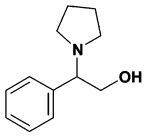
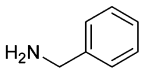
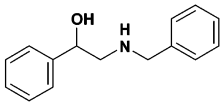
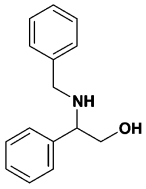
During the reaction with aromatic amines, an exothermic reaction occurred which was completed after 15−30 min (entries 1−5, Table 4) affording 90−99% yields of the amino alcohols. In case of aliphatic amines, the conversion to the amino alcohols took place in 97−100% yields after heating the reaction mixtures at 80 °C for 60 min (entries 6−9, Table 4). A complementarity in the regioselectivity was observed during the reaction with aromatic and aliphatic amines. Reaction with aromatic amines afforded the amino alcohols from nucleophilic attack at the benzylic carbon atom of the epoxide ring as the major products (entries 1−5, Table 4). In case of aliphatic amines, the major/exclusive product was the regioisomeric amino alcohol produced by nucleophilic attack at the less hindered carbon atom of the epoxide ring (entries 6−9, Table 4). The major regioisomeric alcohol formed during the reaction of **4** with aromatic amines was isolated by column chromatography of the crude product isolated from the reaction mixture. However, the regioisomeric amino alcohols formed by the reaction of **4** with aliphatic amines could not be separated by column chromatography. In each case, the regioselectivity was determined by GCMS.[20] The regioisomer formed by the reaction of the amine at the benzylic carbon atom of the epoxide ring showed the characteristic ion peak at m/z [$M^+ - 31$] because of the loss of the CH_2OH in the GCMS. The characteristic ion peak was at m/z [$M^+ - 107$] because of the loss of PhCHOH for the product formed by the reaction at the terminal carbon atom of the epoxide ring.

To establish the generality, various epoxides were treated with **2** in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (Table 5). Excellent yields of the 2-amino alcohols were obtained in each case. Cyclopentene oxide (entry 1, Table 5) afforded the *trans*-2-phenylaminocyclopentanol as the only product. In case of glycidic ethers (entries 2−4, Table 5) and epichlorohydrin (entry 5, Table 5), excellent regioselectivity was observed. The amino alcohols derived from nucleophilic attack at the less substituted carbon atom of the epoxide rings were obtained as the exclusive/major products (GCMS). The reaction with epichlorohydrin provided an example of excellent chemoselectivity and no product from nucleophilic substitution of the chlorine atom was formed (GCMS). Ethyl phenylglycidate (entry 6, Table 5) afforded the amino alcohol from nucleophilic attack at the benzylic carbon atom as the only product (GCMS).[19k] This observation further highlighted the influence of electronic factor of the phenyl ring in controlling the regioselectivity analogous to that observed during the reaction of aromatic amines with **4** (Table 4).

The role of the metal perchlorates in catalyzing the epoxide ring-opening reaction by amines is depicted in Scheme 1. The coordination of the metal cation [M^{+n}] with the epoxide oxygen atom generates the transition-state **I**. The positive charge that is developed on the oxygen atom of the epoxide ring is delocalized through the adjacent carbon atoms constituting the epoxide ring and increases the electrophilicity at these two sites. The nucleophilic attack by the nitrogen atom of the amine at the carbon atom of the epoxide ring forms the transition-state **II**. An intramolecular proton shift takes place via the transition-state **III** as the oxyanionic site forms hydrogen bond with one of the hydrogen atoms of the (R)$ArNH_2^+$ moiety. This leads to the amino alcohol and releases the metal perchlorate to complete the catalytic cycle. Thus, the efficiency of the methodology depends on the (1) oxophilicity of the central metal cation so as to form strong coordinate bond with the oxygen atom of the epoxide ring and (2) the pK_a value of the amine so that the

TABLE 4. $Zn(ClO_4)_2 \cdot 6H_2O$-Catalyzed Opening of Epoxide Ring of 4 by Amines[a]



Entry	Amine	Time (min)	Yield (%)[b]	Regioisomeric Ratio (**5**:**6**)[c]			Major isomer (%)[d]
							
1	X = H	15	99	11	:	89	81
2	X = 4-Me	15	98	10	:	90	84
3	X = 2-Me	30	90	10	:	90	78
4	X = 3-Me	30	95	12	:	88	75
5	X = 4-Cl	15	97	5	:	95	86
6		60	97[e]	 98	:	 2	[f]
7		60	97[e]				[g]
8		60	100[e]	 83	:	 17	[f]
9		60	85[e]	 56	:	 44	[f]

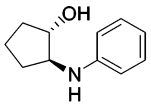
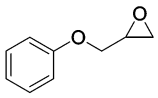
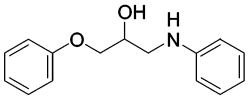
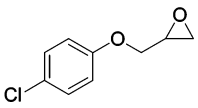
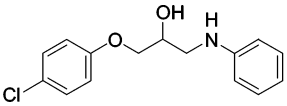
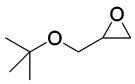
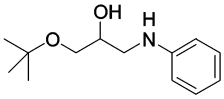
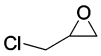
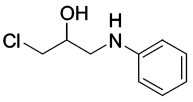
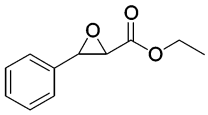
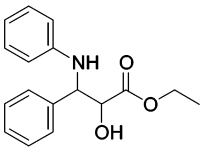
[a] **4** (2.5 mmol) was treated with the amine (2.5 mmol, 1 equiv) in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol %) at rt (except for entries 6−9) under solvent-free conditions. [b] Isolated yield of the corresponding 2-amino alcohols (mixture of regioisomers). [c] Determined by GCMS. [d] The yield of the major regioisomer obtained after column chromatographic purification of the mixture of the regioisomeric amino alcohols. [e] The reaction was carried out at 80 °C. [f] The regioisomeric amino alcohols could not be separated by column chromatography. [g] The regioisomeric amino alcohol from nucleophilic attack at the terminal carbon atom of the epoxide ring of **4** was the only product formed.

intramolecular proton transfer in the transition-states **II**/**III** takes place efficiently.

The results of Tables 1−5 can be rationalized with the help of the mechanism proposed in Scheme 1. The better catalytic activity of $Zn(ClO_4)_2 \cdot 6H_2O$ compared to that of $LiClO_4 \cdot xH_2O$ (Table 1) was due to stronger oxophilicity of Zn^{+2} compared to that of Li^+ because of the higher charge-to-size ratio of the former cation (Zn^{+2} 5.33 and Li^+ 1.35 $e^2\ m^{-10}$).[37] However, the inferior results obtained in the presence of $Mg(ClO_4)_2 \cdot xH_2O$, $BiO(ClO_4)_2 \cdot xH_2O$, $Fe(ClO_4)_2 \cdot xH_2O$, $Fe(ClO_4)_3 \cdot xH_2O$, $Co(ClO_4)_2 \cdot xH_2O$, and $Cu(ClO_4)_2 \cdot xH_2O$ were due to the increasing tendency

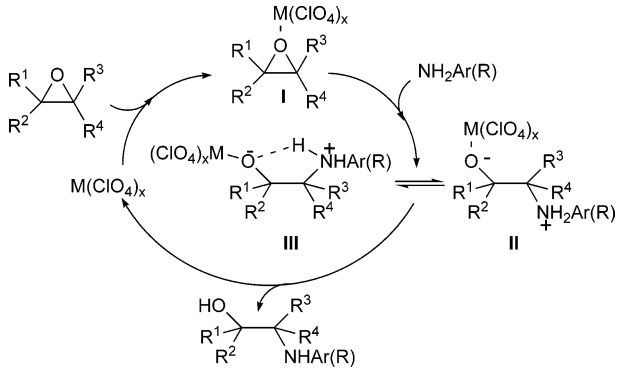
(37) Huheey, J. E. *Inorganic Chemistry: Principle of Structure and Reactivity*, 3rd ed.; Harper & Row: Singapore, 1983.

TABLE 5. $Zn(ClO_4)_2 \cdot 6H_2O$-Catalyzed Ring Opening of Various Epoxides by 2[a]

Entry	Epoxide	Time (min)	Product	Yield (%)[b,c]
1		15		75[d]
2		15		98[e]
3		15		97[e]
4		60		88[f]
5		60		85[g]
6		60		90[h]

[a] The epoxide (2.5 mmol) was treated with **2** (2.5 mmol, 1 equiv) in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol %) at rt under solvent-free conditions. [b] Isolated yield of the corresponding 2-amino alcohols. [c] The products were characterized by IR, NMR, and MS. [d] The trans-2-phenylaminocyclopentanol was formed as the only product. [e] The 2-amino alcohol from nucleophilic attack at the less substituted carbon atom of the epoxide ring was formed as the only product. [f] The 2-amino alcohol from nucleophilic attack at the less substituted carbon atom of the epoxide ring was formed as the major product along with the regioisomeric product in ~2% yield (GCMS and NMR). [g] The 2-amino alcohol from nucleophilic attack at the less substituted carbon atom of the epoxide ring was formed as the major product along with the regioisomeric product in 6% yield (GCMS and NMR). [h] The 2-amino alcohol from nucleophilic attack at the benzylic carbon atom of the epoxide ring was formed as the only product (GCMS and NMR).

SCHEME 1. The Role of Metal Perchlorates in Catalyzing the Epoxide Ring-Opening Reaction by Amines



of the corresponding metal ions to hydrolyze compared to that of Zn^{+2} ion as evidenced by the lower pK_h values of these ions compared to that of Zn^{+2} ion.[38] The water molecules in these metal perchlorate hydrates decrease the oxophilicity of the central metal cation. It has been reported that in case of $Mg(ClO_4)_2$ (anhydrous from) the catalytic efficiency decreases on repeated exposure of the catalyst to air.[27c,e] The ability of the Fe^{+2}, Fe^{+3}, Co^{+2}, and Cu^{+2} ions to form strong coordination complexes with an amine also reduces the catalytic activity of the perchlorate salt of these cations.

The relative catalytic efficiency of various zinc compounds (Table 2) may be explained by taking into consideration the fact that the Lewis acid property (oxygen affinity) of the central metal cation is influenced by the counteranion and a salt of a stronger protic acid should be a better Lewis acid. Thus, the

(38) (a) Yatsimirksii, K. B.; Vasil'ev V. P. *Instability Constants of Complex Compounds*; Pergamon: Elmsford, NY, 1960. (b) *Stability Constants of Metal-Ion Complexes: PartII. Inorganic Ligands*; Bjerrum, J.; Schwarzenbach, G.; Sillen, L. G., Eds.; The Chemical Society: London, 1958.

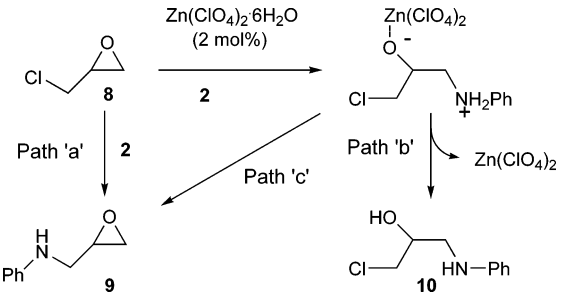
order of the catalytic activity $Zn(ClO_4)_2 \cdot 6H_2O \gg Zn(BF_4)_2 \cdot xH_2O \sim Zn(OTf)_2 \gg ZnI_2 > ZnBr_2 > ZnCl_2 > Zn(OAc)_2 > ZnCO_3$ is in compliance with the acidic strength of the respective protic acids.[36] Surprisingly, $Zn(OTf)_2$ was found to be inferior to $Zn(ClO_4)_2 \cdot 6H_2O$ although triflic acid is a stronger protic acid than perchloric acid.[36] A similar comparative catalytic activity between $Mg(ClO_4)_2$ and $Mg(OTf)_2$ was observed during acylation reaction.[20c] The requirement of 50 mol % of LiOTf for epoxide ring opening by amines further exemplifies the inferior catalytic property of metal triflates.[39]

The longer time (60 min) required for 4-methoxyaniline (entry 2, Table 3) was because of sluggishness of intramolecular proton transfer in the transition-states **II**/**III** because of increased pK_a value. The resonance effect of the 4-OMe group decreases/neutralizes the positive charge on the nitrogen atom of the $4\text{-}MeOC_6H_4NH_2^+$ moiety in the transition-states **II**/**III**. This decreases the hydrogen bond formation ability of the hydrogen atoms attached to the nitrogen atom of the $4\text{-}MeOC_6H_4NH_2^+$ moiety and makes the intramolecular proton transfer sluggish which eventually retards the rate of the reaction. The relatively faster rate of reaction with 4-chloroaniline (entry 6, Table 3) compared to that with the more nucleophilic amines such as aniline and methoxy/methyl substituted anilines (entries 2−5, Table 3) supports the importance of the intramolecular proton transfer in the transition-states **II**/**III**. The reactions with aliphatic amines that are better nucleophiles than the aromatic amines required heating because of the weak acidic property of the amino group that did not permit formation of the transition-state **III** at rt.

The regioselective outcome (Tables 4 and 5) can be explained by the steric and electronic factors associated with the epoxide and the amine. Complex formation between the epoxide oxygen atom of **4** and the Zn^{+2} generated the transition-state **I** (R^1 = Ph; $R^2 = R^3 = R^4$ = H; Scheme 1) in which the positive charge was accumulated on the oxygen atom and was delocalized through the carbon atoms of the epoxide ring. The benzylic carbon atom of the epoxide ring exhibited better carbocationic character and became more electrophilic compared to the less substituted carbon atom. Since aromatic amines were less nucleophilic compared to the aliphatic amines, selective nucleophilic attack took place at the more electrophilic benzylic carbon atom of the epoxide ring. The preference of nucleophilic attack by **2** on the benzylic carbon atom of ethyl phenylglycidate (entry 6, Table 5) further supports the influence of resonance/electronic effect of the phenyl group in controlling regioselectivity. In the absence of such resonance effect in glycedic ethers (entries 2−4, Table 5), and epichlorohydrin (entry 5, Table 5), the regioselectivity is controlled by the steric factor and selective nucleophilic attack took place at the less substituted/terminal carbon atom of the epoxide ring.

The preferential reaction at the non-benzylic position of **4** (Table 4) by aliphatic amines was due to the complex formation between the nitrogen atom and the catalyst (as aliphatic amines were stronger bases compared to the aromatic amines) that made the effective nucleophilic species sterically hindered, and the reaction took place at the less hindered position. This is supported by the result obtained during the reaction of **4** with benzyl amine (entry 9, Table 4) in which case the selectivity of benzylic versus terminal carbon of the epoxide ring in **4** was 44:56. As the steric factor surrounding the nitrogen atom of benzyl amine was less compared to that of the secondary amine

SCHEME 2. Chemoselective Nucleophilic Opening of the Epoxide Ring in Epichlorohydrine by 2



substrates of entries 6−8 (Table 4), the nucleophilic attack at the benzylic and terminal carbon atom of the epoxide ring of **4** by benzyl amine was less discriminatory.

The excellent yield (81%) of the amino alcohol corresponding to nucleophilic attack at the terminal carbon atom of the epoxide ring obtained during the reaction of **2** with epichlorohydrin **8** (entry 5, Table 5) demonstrates the importance of the counteranion of the metal catalyst in controlling the chemoselectivity. The reaction, in principle, may proceed via two distinct pathways: (1) direct displacement of chlorine (path a) leading to the formation of the oxiran **9** or (2) nucleophilic attack on the least substituted carbon atom of the epoxide ring leading to opening of the epoxide ring followed by protonation of the alkoxide anion to form the amino alcohols (path b) or extrusion of the chlorine atom through intramolecular nucleophilic substitution by the adjacent alkoxide anion (path c) to give **9** (Scheme 2).[40] It is anticipated that the perchlorate anions in $Zn(ClO_4)_2 \cdot xH_2O$ make the Zn^{+2} ion sufficiently electrophilic so as to hold the negative charge of the alkoxide anion generated after the nucleophilic attack of the amine on the metal-complexed epoxide. Thus, the free alkoxide anion is not available for subsequent elimination of the chloride anion to make "path c" to be operative, and the amino alcohol **10** is obtained as the sole/major product.

The applicability of this newly developed methodology is demonstrated for the synthesis of cardiovascular drugs such as propranolol and naftopidil as racemates and optically active enantiomers. The common synthetic strategy for these cardiovascular agents involve the nucleophilic opening of the epoxide ring of 1-naphthyl glycidyl ether **11** with isopropyl amine and 1-(2-methoxyphenyl)piperizine **12**, respectively, (Scheme 3).

The key starting material (*RS*)-**11** was prepared in 80% yield by the reaction of 1-naphthol with (*RS*)-**8**, in the presence of K_2CO_3 in MeCN under reflux by modification of the reported procedure.[41] The treatment of (*RS*)-**11** with $^iPrNH_2$ (1 equiv) at rt for 1 h in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ under neat conditions afforded (*RS*)-propranolol in 72% yield. The synthesis of (*RS*)-naftopidil was achieved by the $Zn(ClO_4)_2 \cdot 6H_2O$-catalyzed opening of the epoxide ring of (*RS*)-**11** by **12** (1 equiv), prepared following reported procedure.[42] An initial attempt in carrying out the reaction of (*RS*)-**11** with **12** at rt under solvent-free condition led to incomplete conversion probably because of improper mixing of **12** (floppy solid) with **11** (liquid). However, the use of dichloromethane (DCM) afforded the desired product in 92% yield at rt after 16 h. To

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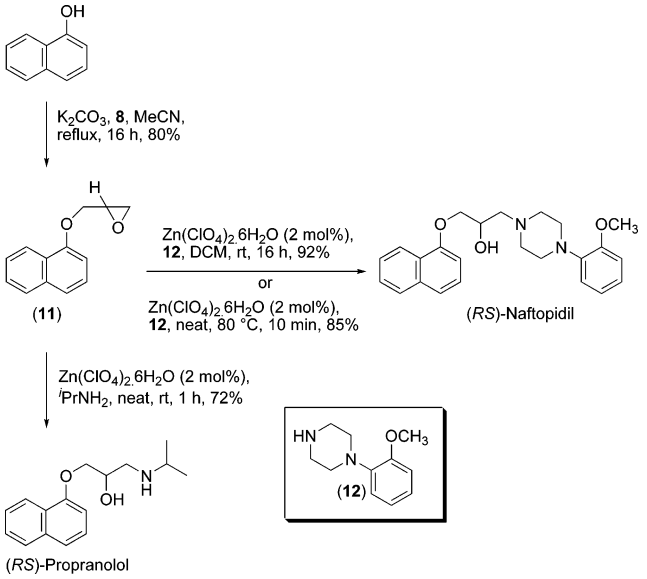
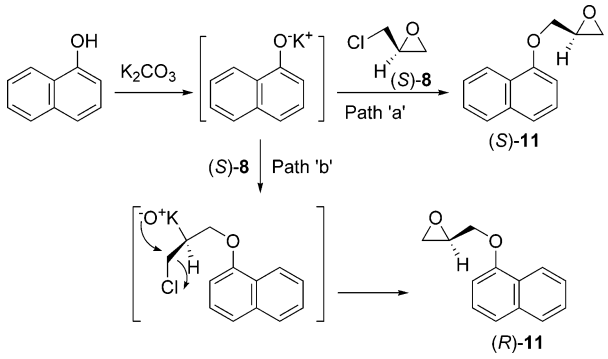
SCHEME 3. The Application of $Zn(ClO_4)_2 \cdot 6H_2O$-Catalyzed Epoxide Ring Opening by Amine for the Synthesis of (*RS*)-Propranolol and (*RS*)-Naftopidil

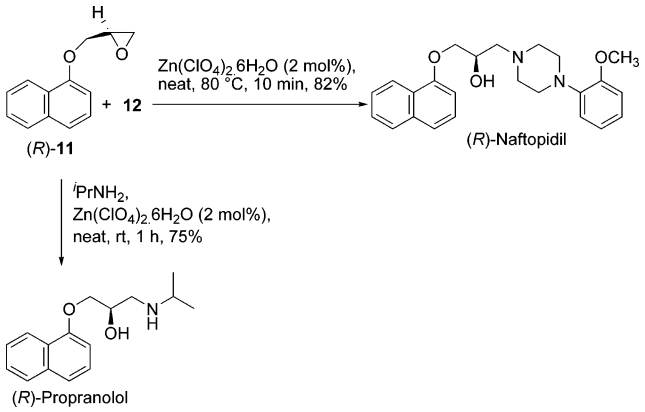


SCHEME 4. Formation of (*R*)-(11) from (*S*)-8



claim a solvent-free synthesis, the reaction of (*RS*)-**11** with **12** was carried out at 80 °C under neat condition, and (*RS*)-naftopidil was obtained in 85% yield after 10 min. Being encouraged by the results of the syntheses of (*RS*)-propranolol and (*RS*)-naftopidil, we planned to extend this methodology for the synthesis of the chiral drugs. Although currently these drugs are therapeutically used as racemates, it is reported that the (*S*)-isomers are more potent than the (*R*)-isomers.[43] Thus, we planned to synthesize (*S*)-propranolol and (*S*)-naftopidil from (*S*)-**11**. The reaction of 1-naphthol with (*S*)-**8** following the modified procedure (Scheme 4) afforded the 1-naphthylglycedic ether in 78% yield with an $[\alpha]_D$ value of − 28.8 ($c = 1$, MeOH) indicating it to be (*R*)-**11** with 85% optical purity on comparison with the reported $[\alpha]_D$ value of − 33.9 ($c = 1.55$, MeOH).[44] In the chiral high-performance liquid chromatography (HPLC), the (*RS*)-**11** exhibited the enantiomers in a ratio of 48:52 eluting after 12 and 14.5 min, respectively. The 1-naphthylglycedic ether obtained from the reaction of 1-naphthol with (*S*)-**8** showed the

SCHEME 5. Synthesis of (*R*)-(−)-Propranolol and (*R*)-(−)-Naftopidil from (*R*)-11



enantiomeric distribution of ∼91:9 [ee = 82%] eluting at 10.9 and 14 min, respectively. The formation of (*R*)-**11** from (*S*)-**8** revealed that **11** is not obtained following a direct alkylation route by nucleophilic substitution of the chlorine atom in (*S*)-**8** by the 1-naphthoxide anion (path a, Scheme 4) but is formed via the opening of the epoxide ring by nucleophilic attack at the unsubstituted carbon atom of the epoxide ring forming the intermediate alkoxide anion followed by 1,2 elimination of the chlorine atom to form (*R*)-**9** (path b, Scheme 4).

Having (*R*)-**11** on hand, we planned to extend the applicability of the $Zn(ClO_4)_2 \cdot 6H_2O$-catalyzed epoxide ring-opening reaction for the synthesis of (*R*)-propranolol and (*R*)-naftopidil (Scheme 5). The treatment of (*R*)-**11** with $^i PrNH_2$ at rt for 1 h under solvent-free condition in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ afforded (*R*)-propranolol in 75% yield. The enantiomeric product mixture was analyzed by HPLC and tandem liquid chromatography mass spectrometry (LCMS) on a chiral column and was compared with the HPLC and LCMS data of (*RS*)-propranolol. These indicated an ee of 82%. However, the optical purity was found to be 87.5% on comparison of the observed value of the optical rotation of the product with the reported value of optical rotation of (*R*)-propranolol (Experimental Section). The reaction of (*R*)-**11** with **12** at 80 °C under neat conditions for 10 min in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ afforded (*R*)-naftopidil in 82% yields. However, the optical rotation was found to be −11.7 [c 1.5, MeOH] as compared to the reported[42] value of −3.94 [c 1.5, MeOH]. To establish the optical and chemical integrity, the product was subjected to HPLC and LCMS studies on chiral column, and the results were compared with those of (*RS*)-naftopidil. The product showed the enantiomeric distribution of 94.5:5.5 (89% ee) with $t_R = 54.6$ min and $t_S = 75.1$ min (hexane:2-propanol:diethylamine = 80:20:0.1) on chiral HPLC. In the case of the LCMS studies using a chiral column, the enatiomers eluted at $t_R = 60.3$ min and $t_S = 85.0$ min (hexane: 2-propanol:diethylamine = 85:15:0.1) with the corresponding *m*/*z* of 437 $[(M - H)^+ + 2Na]$.

Finally, we planned to demonstrate the effectiveness of the $Zn(ClO_4)_2 \cdot 6H_2O$-catatlyzed epoxide ring-opening reaction for the synthesis of (*S*)-naftopidil (Scheme 6). The key starting material (*S*)-**11**, prepared by the reaction of (*R*)-**8** with 1-naphthol following the modified procedure, on treatment with **12** at 80 °C under neat conditions for 10 min in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ afforded (*S*)-naftopidil in 95% yield. However, similar to the case of the (*R*)-enatiomer, the optical rotation was found to be +11.7 [c 1.5, MeOH] instead of the reported[42] value of +3.8 [c 1.5, MeOH]. Thus, HPLC and LCMS studies of the

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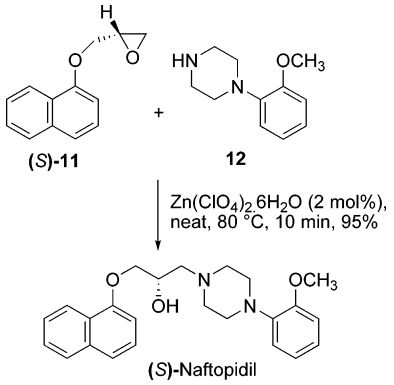
SCHEME 6. Synthesis of (*S*)-(+)-Naftopidil from (*S*)-11



isolated product were carried out on a chiral column and were compared with those of (*RS*)-naftopidils to determine the optical and chemical integrity. In the HPLC using a chiral column, the product was found to be a 9.7:90.3 mixture of the two enantiomers (ee ~80%) eluting (hexane:2-propanol:diethylamine = 80:20:0.1) at t_R = 62.2 min and t_S =75.1 min. In the LCMS on the chiral column, the corresponding values were t_R = 70.54 min and t_S = 86.21 min (hexane:2-propanol:diethylamine = 85:15:0.1) with the *m*/*z* of 437 [(M − H)$^+$+ 2Na].

Conclusions

In summary, we have described herein $Zn(ClO_4)_2 \cdot 6H_2O$ as a new and highly efficient catalyst for opening of epoxide ring by amines affording β-amino alcohols. The advantages include high yields, short reaction times, excellent regio-, chemo-, and stereoselectivities, and the use of a cheap and commercially available catalyst. The extension of this methodology for the synthesis of (*RS*)-propranolol, (*RS*)-naftopidil, (*R*)-propranolol, (*R*)-naftopidil, and (*S*)-naftopidil demonstrated the potentiality of industrial applications for the synthesis of cardiovascular drugs. The use of LCMS with a chiral column along with the chiral HPLC unambiguously established the optical purity of the chiral products.

Experimental Section

Typical Procedure for Epoxide Ring Opening by Amine. *trans*-2-(Phenylamino)cyclohexanol (3). To the mixture of **1** (245 mg, 2.5 mmol) and **2** (233 mg, 2.5 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (18 mg, 2 mol %) was added and the mixture was magnetically stirred at rt under nitrogen. After completion of the reaction (15 min, TLC, GCMS), the reaction mixture was diluted with Et_2O (15 mL), was washed with water (5 mL), was dried (Na_2SO_4), and was concentrated in vacuo to afford **3** (472 mg, 99%), mp 57−59 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03−1.42 (m, 4 H), 1.72−1.78 (m, 2 H), 2.10−2.16 (m, 2 H), 28−3.0(m, 2 H, D_2O exchangeable), 3.13 (ddd, 1 H, J = 3.9, 10.0, 10.1 Hz), 3.33 (ddd, 1 H, J = 4.2, 10.4, 10.5 Hz), 6.7−7.2 (m, 5 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.3, 25.0, 31.6, 33.2, 60.2, 74.5, 114.4, 118.4, 129.3, 147.8. EIMS (*m*/*z*) 191 (M$^+$) identical with an authentic sample.[20] The remaining reactions were carried out following this general procedures. On each occasion, the spectral data (IR, NMR, and MS) of prepared known compounds were found to be identical with those reported in the literature. The unknown compounds (entry 5, Table 3; entries 3 and 4, Table 4) were characterized by spectral (IR, ^{1}H and ^{13}C NMR, and MS) and elemental data.

Typical Procedure for the Preparation of (*RS*)-Naphthylglycidic Ether (11). To a magnetically stirred solution of 1-naphthol (360 mg, 2.5 mmol) and K_2CO_3 (690 mg, 5 mmol) in anhydrous MeCN (10 mL) was added (*RS*)-epichlorohydrin **8** (0.29 mL, 3.75 mmol), and the reaction mixture was heated under reflux for 16 h. The cooled (rt) reaction mixture was filtered, the filtrate was concentrated under vacuum, and the residue was purified by passing through a column chromatography of silica gel (60−120 mesh) and eluting with EtOAc:hexane (1:19) to affored (*RS*)-**11** (400 mg, 80%), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84−2.87 (m, 1 H), 2.95−2.98 (m, 1 H), 3.48−3.49 (m, 1 H), 4.15 (dd, 1 H; J = 5.5, 11.0 Hz), 4.40 (dd, 1 H; J = 3.0, 11.0 Hz), 6.81 (d, 1 H; J = 7.5 Hz), 7.36 (t, 1 H; J = 8.0 Hz), 7.43−7.52 (m, 3 H), 7.78−7.81 (m, 1 H), 8.28−8.31 (m, 1 H) identical with those reported in the literature.[41] The (*RS*)-**11** was subjected to HPLC on CHIRAL OD-H column and was eluted with hexane:2-propanol (85:15) containing diethyl amine (0.1%). The two enantiomers eluted after 11.9 and 14.5 min and were present in a ratio of 48:52.

Typical Procedure for Preparation of (*R*)-Naphthylglycidic Ether (11). The reaction of 1-naphthol (360 mg, 2.5 mmol) with (*S*)-(**8**) (290 mg, 3.75 mmol) followed by the usual workup and purification as stated for the (*RS*)-**11** afforded (*R*)-**11** (390 mg, 78%). The product was subjected to chiral HPLC analysis using chiral OD-H column and the two enantiomers were eluted at t_R = 10.9 min and t_S = 14.0 min (85:15 hexane: 2-propanol containing 0.1% diethylamine) with peak areas of 91 and 9%, respectively, indicating the optical purity of 82%. However, the ee was found to be 85% on the basis of the observed $[\alpha]_D$ value of −28.8 (c = 1, MeOH) [lit.[44] = −33.9 (c = 1.55, MeOH)]. ^{1}H NMR ($CDCl_3$): δ 2.84−2.87 (m, 1 H), 2.95−2.98 (m, 1 H), 3.48−3.49 (m, 1 H), 4.15 (dd, 1 H; J = 5.5, 11.0 Hz), 4.40 (dd, 1 H; J = 3.0, 11.0 Hz,, 6.81 (d, 1 H; J = 7.5 Hz,), 7.36 (t, 1 H; J = 8.0 Hz,), 7.43−7.52 (m, 3 H), 7.78−7.81 (m, 1 H), 8.28−8.31 (m, 1 H). MS (APCI) = 200.9 (MH$^+$).

Typical Procedure for the Preparation of (*RS*)-Propranolol. The mixture of (*RS*)-**11** (200 mg, 1 mmol), isopropyl amine (58 mg, 1 mmol), and $Zn(ClO_4)_2 \cdot 6H_2O$ (7.4 mg, 2 mol %) was stirred magnetically at rt under nitrogen. After completion of the reaction (60 min, TLC, GCMS), the reaction mixture was diluted with Et_2O (15 mL), was washed with water (5 mL), was dried (Na_2SO_4), and was concentrated under vacuum to afford (*RS*)-propranolol (189 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 3 H), 2.60 (bs, 1 H, OH), 2.90−3.02 (m, 3 H), 4.19 (m, 3 H), 6.82 (d, 1 H; J = 6.6 Hz), 7.25−7.46 (m, 5 H), 7.78 (m, 1 H), 8.22 (m, 1 H), identical with an authentic sample.[41] The product on subjection to HPLC analysis uisng CHIRAL OD-H column and elution with 85:15 hexane:2-propanol containing 0.1% diethylamine showed to be a 1:1 mixture (peak areas of 49.45 and 50.55%) of the two enantiomers eluting at 12.2 and 24.3 min. The LCMS under similar condtion exhibited the two enantiomers eluting at 14.89 and 23.09 min with the corresponding *m*/*z* of 260 (MH$^+$).

Typical Procedure for the Preparation of (*RS*)-Naftopidil. The mixture of (*RS*)-**11** (200 mg, 1 mmol), 1-(2-methoxyphenyl)-piperizine **12** (190 mg, 1 mmol), and $Zn(ClO_4)_2 \cdot 6H_2O$ (7.4 mg, 2 mol %) in DCM (2 mL) was stirred magnetically at rt under nitrogen. After completion of the reaction (16 h, TLC, GCMS), the reaction mixture was diluted with Et_2O (15 mL), was washed with water (5 mL), was dried (Na_2SO_4), and was concentrated under vacuum to afford (*RS*)-naftopidil (360 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36−3.71 (m, 8 H), 4.01 (s, 3 H), 4.26−4.36 (m, 5 H), 6.96 (d, 1 H; J = 7.3 Hz), 7.08−7.14 (m, 2 H), 7.29 (t, 1 H; J = 7.5 Hz), 7.41 (t, 1 H; J = 7.6 Hz), 7.52 (t, 1 H; J = 7.6 Hz), 7.58−7.67 (m, 3 H), 7.97 (d, 1 H; J = 8.5 Hz), 8.39 (d, 1 H; J = 8.5 Hz). The treatment of the reaction mixture at 80 °C under neat conditions for 10 min afforded (*RS*)-naftopidil (321 mg, 82%). The product on subjection to HPLC analysis using CHIRAL OD-H column and elution with 80:20 hexane:2-propanol containing 0.1% diethylamine showed to be a 1:1 mixture of the two enantiomers eluting at 57.1 and 71.6 min. The LCMS under similar condition exhibited the two enantiomers eluting at 66.5 and 84.2 min with the corresponding *m*/*z* of 437 [(M − H)$^+$+ 2Na].

Typical Procedure for the Preparation of (*R*)-Propranolol. The reaction of (*R*)-**11** (200 mg, 1 mmol) with isopropyl amine (58 mg, 1 mmol) in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (7.4 mg, 2 mol %) followed by usual workup and purification as described for (*RS*)-propranolol afforded (*R*)-propranolol (200 mg, 75%). ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 6 H), 2.44 (bs, 1 H, OH), 2.89−3.03 (m, 3 H), 4.18−4.45 (m, 3 H), 6.82 (m,1 H), 7.36−7.47 (m, 4 H), 7.80 (m, 1 H), 8.24 (m, 1 H). MS (APCI) = 260 (MH^+). The product on subjection to HPLC analysis uisng CHIRAL OD-H column and elution with 85:15 hexane:2-propanol containing 0.1% diethylamine showed to be a 91:9 mixture of the two enantiomers eluting at 11.6 and 21.4 min, respectively, indicating the optical purity of 82%. However, the ee was calculated to be 87.5% on the basis of the observed $[\alpha]_D$ value of +22.5 (c = 1, EtOH) [lit.[45] = +25.7 (c = 1.23, EtOH)]. The LCMS under similar condition exhibited the two enantiomers eluting at 14.59 and 25.16 min, respectively, with the corresponding m/z of 260 (MH^+).

Typical Procedure for the Preparation of (*R*)-Naftopidil. The reaction of (*R*)-**11** (200 mg, 1 mmol) with 1-(2-methoxyphenyl)-piperizine **12** (190 mg, 1 mmol) in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (7.4 mg, 2 mol %) at 80 °C under neat condition under nitrogen for 10 min followed by usual workup and purifiaction as described for (*RS*)-naftopidil afforded (*R*)-naftopidil (321 mg, 82%). $[\alpha]_D$: −11.7 (c = 1, MeOH) [lit.[42] = −3.94 (c = 1, MeOH)]. The ee of the product was determined to be 89% by chiral HPLC analysis using chiral OD-H column with the enantiomeric distribution of 94.5:5.5 and t_R = 54.6 min and t_S =75.1 min, respectively, (hexane:2-propanol:diethylamine = 80:20:0.1). In the LCMS (chiral OD-H column), the enantiomers eluted at t_R = 60.3 min and t_S = 85.0 min (hexane:2-propanol:diethylamine = 85:15:0.1) with the corresponding m/z of 437 [$(M - H)^+$ + 2Na].

Typical Procedure for the Preparation of (*S*)-Naftopidil. The reaction of (*S*)-**11** (200 mg, 1 mmol) with 1-(2-methoxyphenyl)-piperizine **12** (190 mg, 1 mmol) in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (7.4 mg, 2 mol %) at 80 °C under neat condition under nitrogen for 10 min followed by usual workup and purifiaction as described for (*RS*)-naftopidil afforded (*S*)-naftopidil (372 mg, 95%). $[\alpha]_D$: +11.7 (c = 1.5, MeOH) [lit.[42] = +3.8 (c = 1.5, MeOH)]. The ee of the product was determined to be ∼80% by chiral HPLC analysis using chiral OD-H column with the enantiomeric distribution of 9.7:90.3 eluting (hexane:2-propanol:diethylamine = 80:20:0.1) at t_R = 62.2 min and t_S =75.1 min. In the LCMS (chiral OD-H column), the enantiomers eluted (hexane:2-propanol:diethylamine = 85:15:0.1) at t_R = 70.54 min and t_S = 86.21 min, respectively, with the corresponding m/z of 437 [$(M - H)^+$ + 2Na].

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Supporting Information Available: Experimental details, scanned spectra, and spectral data of all known and unknown compounds. This material is available free of charge via the Internet at http:// pubs.acs.org.

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