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Zinc Tetrafluoroborate Hydrate as a Mild Catalyst for Epoxide Ring Opening with Amines: Scope and Limitations of Metal Tetrafluoroborates and Applications in the Synthesis of Antihypertensive Drugs (*RS*)/(*R*)/(*S*)-Metoprolols

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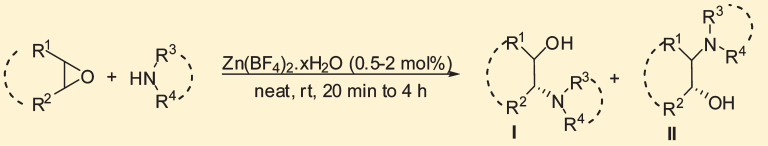
Supporting Information

ABSTRACT:



$R^1 = R^2$ = Cycloalkyl, Phenyl; R^3 = H, R^4 = Aryl, Phenylmethyl; $R^3 = R^4$ = Cycloalkyl: 86 - 97% (**I** = **II**)
R^1 = H; R^2 = Ph; R^3 = H, R^4 = Aryl: 89 - 95% (**I**:**II** 89:11 - 99:1)
R^1 = H; R^2 = Ph; R^3 = H, R^4 = Arylmethyl; $R^3 = R^4$ = Alkyl, Cycloalkyl; R^3 = Me, R^4 = Ph: 86 - 100% (**I**:**II** = 27:73 - 9:91)
R^1 = H; R^2 = Alkyl, Chloromethyl, *t*-Butoxymethyl, Aryloxy/heteroaryloxymethyl; R^3 = H, R^4 = Ph, ^{i}Pr: 71 - 92% (only **II**)
R^1 = Carboethoxy, R^2 = Ph; R^3 = H, R^4 = Ph: 91% (only **I**)

The scope and limitations of metal tetrafluoroborates have been studied for epoxide ring-opening reaction with amines, and $Zn(BF_4)_2 \cdot xH_2O$ has been found to be a mild and efficient catalyst affording high yields under solvent-free conditions at rt with excellent chemo-, regio-, and stereoselectivities. The catalytic efficiency followed the order $Zn(BF_4)_2 \cdot xH_2O \gg Cu(BF_4)_2 \cdot xH_2O > Co(BF_4)_2 \cdot 6H_2O \gg Fe(BF_4)_2 \cdot 6H_2O > LiBF_4$ for reactions with cyclohexene oxide and $Zn(BF_4)_2 \cdot xH_2O \gg Co(BF_4)_2 \cdot 6H_2O \gg Fe(BF_4)_2 \cdot 6H_2O > Cu(BF_4)_2 \cdot xH_2O$ for stilbene oxide, but $AgBF_4$ was ineffective. For reaction of styrene oxide with aniline, the metal tetrafluoroborates exhibited comparable regioselectivity (1:99−7:93) with preferential reaction at the benzylic carbon of the epoxide ring. A reversal of regioselectivity (91:1−69:31) in favor of the reaction at the terminal carbon of the epoxide ring was observed for reaction with morpholine. The regioselectivity was dependent on the electronic and steric factors of the epoxide and the pK_a of the amine and independent of amine nucleophilicity. The role of the metal tetrafluoroborates is envisaged as "electrophile nucleophile dual activation" through cooperativity of coordination, charge−charge interaction, and hydrogen-bond formation that rationalizes the catalytic efficiency, substrate reactivity, and regioselectivity. The methodology was used for synthesis of cardiovascular drug metoprolol as racemic and enriched enantiomeric forms.

INTRODUCTION

The epoxide ring opening by amines is the key step for synthesis of novel therapeutic agents, biologically active compounds of natural and synthetic origin,[1] unnatural amino acids,[2] and chiral auxiliaries.[3] The manifold limitations such as the requirement of an excess of amines and elevated temperature, failure with less/poor nucleophilic and sterically hindered amines, lack of appreciable regioselectivity, undesired side reactions such as rearrangement or polymerization with sensitive epoxides, etc. associated with the classical approach of heating the mixture of epoxide and amine led to the development of various catalytic procedures.[4] Still, a better methodology is in demand for this industrially important reaction as some of these methods are associated with shortcomings such as the use of solvents that are not preferred in the context of the solvent selection guide of the pharmaceutical industry[5] and the requirement of long reaction times (2.5−30 h), high pressure, and the use of moisture-/air-sensitive and costly catalysts. In continuation of our efforts for the synthesis of 2-amino alcohols by ring opening of epoxides with amines,[6] we planned to develop newer/better catalytic processes. As the Lewis acid character of a metal salt is strongly influenced by the associated counteranion, the metal salts derived from stronger protic acids are better Lewis acids and would be more effective in inducing electrophilic activation of the epoxide ring. Hence, metal triflates become good contenders as Lewis acid catalysts, as triflic acid is the strongest protic acid ($H_0 = -14.1$),[7] and have been used for the desired reaction.[8] However, TfOH is liberated during the use of metal triflates in organic reactions,[9] which raises concern about the detrimental effect of the *in situ* formed/liberated TfOH on acid-sensitive substrates apart from the query on the nature of the actual catalytic species/agent involved in promoting the reaction

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in such cases. Therefore, metal triflate catalyzed reactions are often carried out in the presence of solvent, an excess of reagent, and additives (e.g., molecular sieves, $MgSO_4$, etc.) or at low temperature (−8 to −60 °C) to minimize/avoid the undesired side reactions.[8f−j,10] The weaker Brønsted acidity of $HNTf_2$ compared to that of triflic acid[11] makes metal triflimidates the next choice,[12] particularly as ligand exchange is not common with triflimidates.[13] The highly delocalized nature and steric hindrance of the triflimidate anion enhances the electrophilic (Lewis acid) character of the central metal ion.[14] However, metal triflimidates are costly, only a few triflimidates are commercially available, and their preparation require additional efforts and costly reagents. These drew our attention toward metal perchlorates[15] to develop $Zn(ClO_4)_2 \cdot xH_2O$-catalyzed opening of the epoxide ring by amines.[6e] However, the reactions with aliphatic amines required heating.[6e] We attributed this to the strong Lewis acid property of $Zn(ClO_4)_2 \cdot xH_2O$ (and metal perchlorates in general) as a result of which a strong complex formation takes place between the $Zn(ClO_4)_2 \cdot xH_2O$ and more basic/nucleophilic aliphatic amines leading to less effective electrophilic activation of the epoxide ring. Hence for a milder Lewis acid catalyst we shifted our attention to metal tetrafluoroborates as HBF_4 is a weaker Brønsted acid and $Cu(BF_4)_2 \cdot xH_2O$ has been found to efficiently catalyze various organic reactions.[16] The present study relates to the scope and limitations of metal tetrafluoroborates as electrophilic activation catalysts for the opening of an epoxide ring by amines,[17] and herein we report that $Zn(BF_4)_2 \cdot xH_2O$ is a mild and efficient catalyst under solvent-free conditions at rt and finds application in the synthesis of the antihypertensive drugs (*RS*)/(*R*)/(*S*)-metoprolols.

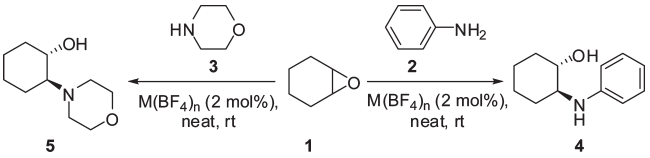
RESULTS AND DISCUSSION

In search for an effective catalyst, cyclohexene oxide **1** was used as symmetrically substituted epoxide and treated with aniline **2** and morpholine **3** as representative aryl and alkyl amines, respectively, in the presence of catalytic quantities of various metal tetrafluoroborates (Table 1). The reactions were monitored by GC−MS. In each case, the reaction of **1** separately with **2** and **3** afforded the *trans*-2-phenylaminocyclohexanol **4** and the *trans*-2-(1-morpholino)cyclohexanol **5**, respectively, as the sole products (NMR).[6]

The best catalytic effect was observed with $Zn(BF_4)_2 \cdot xH_2O$ exhibiting 94% and 97% conversion (GC−MS) and affording 89% and 92% yields (after isolation and purification) of **4** and **5** after 30 and 120 min, respectively, at rt. The use of $Cu(BF_4)_2 \cdot xH_2O$ provided lower (64% and 47%) conversions. The catalytic efficiency of the metal tetrafluoroborates followed the order $Zn(BF_4)_2 \cdot xH_2O \gg Cu(BF_4)_2 \cdot xH_2O > Co(BF_4)_2 \cdot 6H_2O \gg Fe(BF_4)_2 \cdot 6H_2O > LiBF_4$, but no significant amount of product formation was observed with $AgBF_4$. The reaction rate appeared to be influenced by the nature of the amine, which however does not correspond to the amine nucleophilicity as the reactions performed using **2** (an aromatic amine) took less time than those with **3** (secondary aliphatic amine and more nucleophilic than **2**).

To further assess whether the catalytic activity of the metal tertrafluoroborates is specific to a symmetrically disubstituted cyclic epoxide and is influenced by the strain of the cyclic epoxide ring, *trans*-stilbene oxide **6** was considered as a model acyclic symmetrically *trans*-disubstituted epoxide and treated with **2** and **3** in the presence of various metal tetrafluoroborates (Table 2).

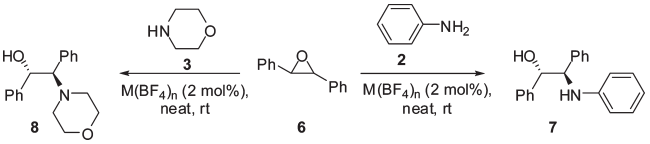
Table 1. Reaction of 1 with 2 and 3 in the Presence of Various Metal Tetrafluoroborates[a]



Entry	Catalyst	Yield (%)[b] 4	5
1	$Zn(BF_4)_2 \cdot xH_2O$	94 (89)	97 (92)
2	$Cu(BF_4)_2 \cdot xH_2O$	64	47
3	$Co(BF_4)_2 \cdot 6H_2O$	55	38
4	$Fe(BF_4)_2 \cdot 6H_2O$	32	37
5	$LiBF_4$	25	49
6	$AgBF_4$	nil	nil

[a] **1** (1 mmol) was treated separately with 1 mmol (1 equiv) of **2** and **3** in the presence of the metal tetrafluoroborate (2 mol %) at rt under solvent-free conditions for 30 and 120 min, respectively. [b] GC−MS conversion. The unreacted starting materials remained unchanged wherever poor conversion to product was observed. The figure in the parentheses is the isolated yield.

Table 2. Reaction of 6 with 2 and 3 in the Presence of Various Metal Tetrafluoroborates[a]



Entry	Catalyst	Yield (%)[b] 7	8
1	$Zn(BF_4)_2 \cdot xH_2O$	92 (86)	56
2	$Co(BF_4)_2 \cdot 6H_2O$	56	31
3	$Fe(BF_4)_2 \cdot 6H_2O$	32	trace
4	$Cu(BF_4)_2 \cdot xH_2O$	12	22

[a] **6** (1 mmol) was treated separately with 1 mmol (1 equiv) of **2** and **3** in the presence of the metal tetrafluoroborate (2 mol %) at rt under solvent-free conditions for 4 and 12 h, respectively. [b] GC−MS conversion. The unreacted starting materials remained unchanged wherever poor conversion to product was observed. The figure in the parentheses is the isolated yield after chromatographic purification.

The epoxide ring-opening reactions of **6** took longer time due to the steric effect of the phenyl rings. Herein also the reaction of **6** with the more nucleophilic amine **3** was sluggish compared to that with **2**. The $Zn(BF_4)_2 \cdot xH_2O$ was found to be the most effective catalyst. The least catalytic efficiency of $Cu(BF_4)_2 \cdot xH_2O$ reflects the stronger coordination ability of the Cu^{2+} ion with the amine resulting in a decrease of the electrophilic character of the metal cation.

To find out the most effective/suitable reaction parameters such as catalyst loading and time, a detailed study was performed on the epoxide ring-opening reaction of **1** separately with **2** and **3** using a varied amount of $Zn(BF_4)_2 \cdot xH_2O$ for varied reaction period (5−120 min). The minimum loading of $Zn(BF_4)_2 \cdot xH_2O$

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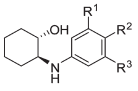
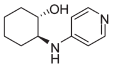
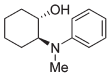
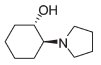
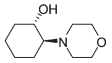
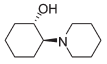
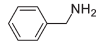
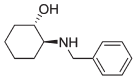
was found to be 0.5 mol % for the reaction of **1** with the aromatic amine **2** affording 92% yield of **4** in 40 min (GC−MS conversion 96%), and significant decrease in reaction time was observed when larger amounts of the catalyst were used (95% and 86% conversion after 2 and 5 min with 10 and 5 mol % of the catalyst, respectively). However, 52% yield of **4** was obtained in performing the reaction using $Cu(BF_4)_2 \cdot xH_2O$ (0.5 mol %) for 40 min, reflecting an inferior catalytic potency of $Cu(BF_4)_2 \cdot xH_2O$. The reaction of **1** with the aliphatic amine **3** required a minimum amount of 2 mol % of $Zn(BF_4)_2 \cdot xH_2O$ to afford 97% conversion (GC−MS) to **5** in 120 min, and the use of a lesser amount of the catalyst (1 mol %) resulted in decreased yield (81% conversion). However, **5** was obtained in 22% yield in performing the reaction in the presence of 2 mol % of $Cu(BF_4)_2 \cdot xH_2O$ for 120 min, which further proved that it is less effective compared to $Zn(BF_4)_2 \cdot xH_2O$. Increase in the loading of $Zn(BF_4)_2 \cdot xH_2O$ to 5 mol % afforded 98% conversion (GC−MS) to **5** in a shorter time period (30 min). Hence for further reactions 2 mol % of the catalyst was used.

To evaluate the general catalytic use of $Zn(BF_4)_2 \cdot xH_2O$ with respect to amines, **1** was treated with various aromatic and aliphatic amines (Table 3). The reactions with aromatic amines required shorter time (10−45 min) compared to that for aliphatic amines (2−12 h). The substituent/functional group present in the aromatic amine was found to have significant influence on the reaction. In general, electron-rich aromatic amines (entries 2 and 3, Table 3) required longer time (40−45 min) compared to that with **2** (entry 1, Table 3). However, the reaction with 4-hydroxyaniline afforded inferior result (entry 11, Table 3), and no significant product formation was observed after 1 h in using 3,4,5-trimethoxy substituted aniline (entry 12, Table 3). Reactions with aromatic amines bearing electron withdrawing substituent/functionality such as 4-fluoro, 4-chloro, 4-trifluoromethyl, and 4-carboethoxy (entries 4−7, Table 3) required shorter times (10−20 min). However, inferior/poor results were obtained with 4-acetyl, 4-cyano, and 4-nitroanilines (entries 8−10, Table 3). During the reaction with 4-nitroaniline a solid mass was formed immediately after mixing the two reactants that inhibited effective stirring of the reaction mixture. Anticipating that the lack of proper mixing of the reactants could be the reason for poor yield, we planned to perform the reaction under homogeneous condition, and DCM was chosen as the solvent as it would not interact/coordinate with the catalyst. However, the use of solvent was found to have a retarding effect on the reaction. The reaction of **1** with **2** afforded **4** in 89% yield after 4 h in DCM as compared to 90% yield obtained after 30 min under solvent-free condition and highlighted the implication/importance of performing the reaction under solvent-free reaction condition. However, 20% yield was obtained after 4 h during the reaction of **1** with 4-nitroaniline in DCM. This indicated that the poor results obtained with 4-nitroaniline are not associated with the lack of proper stirring of the reaction mixture. The reaction with 4-aminopyridine also did not produce any significant amount of the amino alcohol (entry 13, Table 3). The reaction with *N*-methyl aniline (entry 14, Table 3) required longer time compared to that of **2** and further indicated that the outcome of the epoxide ring opening is not solely governed by the amine nucleophilicity. Through a few selected examples (footnotes f, i, l, and o, Table 3) the superiority of $Zn(BF_4)_2 \cdot xH_2O$ over $Cu(BF_4)_2 \cdot xH_2O$ was demonstrated. The distinct advantage/need of the catalytic assistance of $Zn(BF_4)_2 \cdot xH_2O$ was established through the representative examples during the reaction of **1** separately with morpholine

Table 3. $Zn(BF_4)_2 \cdot xH_2O$-Catalyzed Epoxide Ring Opening of 1 with Various Amines[a]

Entry	Amine	Time (min)	Product	Yield (%)[b,c]
				
1	$R^1 = R^2 = R^3 = H$	30	$R^1 = R^2 = R^3 = H$	90[d]
2	$R^1 = R^3 = H$; $R^2 = Me$	45	$R^1 = R^3 = H$; $R^2 = Me$	86
3	$R^1 = R^3 = H$; $R^2 = OMe$	45	$R^1 = R^3 = H$; $R^2 = OMe$	82
4	$R^1 = R^3 = H$; $R^2 = F$	10	$R^1 = R^3 = H$; $R^2 = F$	84
5	$R^1 = R^3 = H$; $R^2 = Cl$	20	$R^1 = R^3 = H$; $R^2 = Cl$	92
6	$R^1 = R^3 = H$; $R^2 = CF_3$	15	$R^1 = R^3 = H$; $R^2 = CF_3$	91
7	$R^1 = R^3 = H$; $R^2 = CO_2Et$	20	$R^1 = R^3 = H$; $R^2 = CO_2Et$	82
8	$R^1 = R^3 = H$; $R^2 = COMe$	20	$R^1 = R^3 = H$; $R^2 = COMe$	42[e,f]
9	$R^1 = R^3 = H$; $R^2 = CN$	20	$R^1 = R^3 = H$; $R^2 = CN$	10[g,h,i]
10	$R^1 = R^3 = H$; $R^2 = NO_2$	20	$R^1 = R^3 = H$; $R^2 = NO_2$	15[g,j]
11	$R^1 = R^3 = H$; $R^2 = OH$	20	$R^1 = R^3 = H$; $R^2 = OH$	52[k]
12	$R^1 = R^2 = R^3 = OMe$	60	$R^1 = R^2 = R^3 = OMe$	trace[g]
13		60		trace[g]
14		120		89
15		120		89[l]
16		120		97[m]
17		120		95[n]
18		12 h		85[o]

[a] **1** (2.5 mmol) was treated with the amine (2.5 mmol, 1 equiv) in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (2 mol %) at rt under solvent-free conditions. [b] Isolated yield of the corresponding *trans*-2-aryl/alkylaminocyclohexanol after usual workup (and chromatographic purification in case of the former). [c] The products were characterized by IR, NMR, and MS. [d] The product was obtained in 89% yield after 4 h in performing the reaction in DCM. [e] The product was formed in 70% yield after 1 h. [f] The use of $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %) as the catalyst afforded 30% yield after 1 h. [g] The unreacted starting material remained unchanged. [h] The product was formed in 45% after 2 h. [i] The use of $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %) as the catalyst afforded 10% yield after 2 h. [j] The product was formed in 20% after 4 h in performing the reaction in DCM. [k] The product was obtained in 84% after 1 h. [l] The product was formed in 48% yield when the reaction was carried out in the presence of $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %) for 2 h. [m] The amino alcohol was formed in 20% yield in carrying out the reaction in the absence of any catalyst at 80 °C. [n] The amino alcohol was formed in 22% yield in carrying out the reaction in the absence of any catalyst at 80 °C. [o] The amino alcohol was formed in 24% yield when the reaction was carried out in the presence of $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %) for 12 h.

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and piperidine performed under solvent-free conditions at 80 °C for 1 h in the absence of any catalyst that led to poor yields (20 and 22%, respectively) of the respective products (footnotes m and n, Table 3). In case of the reaction with aliphatic amines the products isolated after the usual workup were obtained in pure form (NMR) except for the product obtained during the reaction with benzyl amine (entry 18, Table 3) wherein the pure product was obtained after isolation followed by chromatographic purification. However, for the reactions with aromatic amines the pure product was obtained after column chromatographic purification of the material isolated after usual workup except for the reaction using 4-fluoroaniline (entry 4, Table 3) in which case the product was obtained in pure (NMR) form after usual workup.

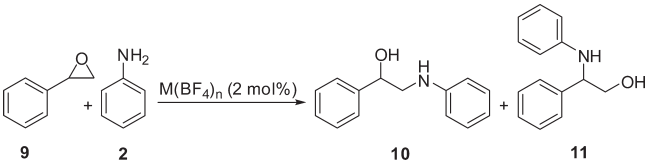
To evaluate the regioselectivity, styrene oxide **9** was considered as a representative unsymmetrical epoxide and treated separately with **2** and **3** in the presence of various metal tetrafluoroborates (Tables 4 and 5). The conversion and selectivity were determined by GC−MS.[6] A reversal of the regioselectivity was observed for the reactions performed with aryl and alkyl amines.

The reaction of **9** with the aromatic amine **2** was best catalyzed by $Zn(BF_4)_2 \cdot xH_2O$ to afford 96% conversion to the amino alcohols with preferential nucleophilic attack at the benzylic carbon of the epoxide ring affording the regioisomer **11** as the major product with 1:99 regioselectivity. Comparable regioselectivities (7:93, 6:94, 7:93, and 2:98, respectively) with preference toward the formation of **11** was observed with $Co(BF_4)_2.6H_2O$, $Cu(BF_4)_2 \cdot xH_2O$, $Fe(BF_4)_2 \cdot 6H_2O$, and $LiBF_4$, which however gave lower conversion to the amino alcohols (86%, 78%, 55%, and 15%, respectively; Table 4). No significant reaction took place in the presence of $AgBF_4$.

To observe any influence of the amount of the catalyst used on the time period and more specifically on the regioselective outcome, **9** was treated with the aromatic amine **2** in the presence of different amounts of $Zn(BF_4)_2 \cdot xH_2O$ for different time period at rt. The use of larger amounts (10 and 5 mol %) of the catalyst afforded 93−92% conversion to the products in shorter reaction times (2 and 15 min) without much effect on the regioselectivity (1:99). A lesser amount (1 mol %) of the catalyst afforded 93% conversion after 60 min with 1:99 regioselectivity and 87% yield of the major regioisomer after isolation and chromatographic purification. However, it was observed that when larger amount (>1 mol %) of the catalyst is used, the initiation of the reaction takes place at much earlier but after that the progress of the reaction becomes sluggish due to solidification of the reaction mixture. When 0.5 mol % of $Zn(BF_4)_2 \cdot xH_2O$ was used the reaction was completed in 40 min with 95% conversion (GC−MS) and the major regioisomer was obtained in 91% yield after purification. However, the use of $Cu(BF_4)_2 \cdot xH_2O$ (0.5 mol %) under similar conditions gave poor (32%) conversion and 3.5:96.5 regioselectivity.

During the reaction of **9** with the aliphatic amine **3**, superior catalytic activity both in terms of conversion to the amino alcohol(s) and regioselectivity was exhibited by $Zn(BF_4)_2 \cdot xH_2O$ with 100% conversion (GC−MS) and 91:9 selectivity for preference of nucleophilic attack at the terminal (less hindered) carbon of the epoxide ring forming the amino alcohol **12** as the major product (table 5). Other metal tetrafluoroborates such as $Cu(BF_4)_2 \cdot xH_2O$, $Co(BF_4)_2 \cdot 6H_2O$, and $Fe(BF_4)_2 \cdot 6H_2O$ were less effective (66%, 63%, and 48% conversion with 76:24, 74:26, and 69:31 selectivities, respectively). No catalytic activity was exhibited by $AgBF_4$. The $Cu(BF_4)_2 \cdot xH_2O$-catalyzed reaction was associated with 34% conversion to phenyl acetaldehyde,

Table 4. Regioselectivity of Opening of the Epoxide Ring of 9 by 2 Catalyzed by Various Metal Tetrafluoroborates[a]

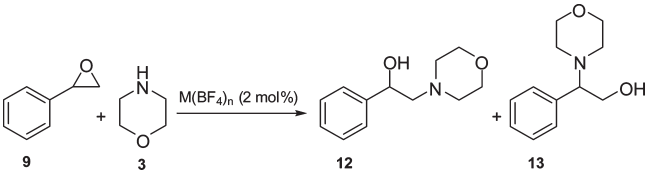


9 2 10 11

Entry	Catalyst	Yield (%)[b]	Ratio (**10**:**11**)[c,d]
1	$Zn(BF_4)_2 \cdot xH_2O$	96	1:99 (92)
2	$Co(BF_4)_2 \cdot 6H_2O$	86	7:93
3	$Cu(BF_4)_2 \cdot xH_2O$	78	6:94
4	$Fe(BF_4)_2 \cdot 6H_2O$	55[e]	7:93
5	$LiBF_4$	15[e]	2:98
5	$AgBF_4$	nil[e]	

[a] **9** (2.5 mmol) was treated with **2** (2.5 mmol, 1 equiv) in the presence of the metal tetraflouroborate (2 mol %) at rt under solvent-free conditions for 60 min. [b] GC−MS conversion. [c] The regioisomeric ratio was determined by GC−MS. [d] The figure in the parentheses is the isolated yield of the pure major regioisomer after chromatographic separation. [e] The unreacted starting materials remained unchanged.

Table 5. Regioselectivity of Opening of the Epoxide Ring of 9 by 3 Catalyzed by Various Metal Tetrafluoroborates[a]



9 3 12 13

Entry	Catalyst	Yield (%)[b]	Ratio (**12**:**13**)[c]
1	$Zn(BF_4)_2 \cdot xH_2O$	100	91:9
2	$Cu(BF_4)_2 \cdot xH_2O$	66[d,e]	76:24
3	$Co(BF_4)_2 \cdot 6H_2O$	63[e]	74:26
4	$Fe(BF_4)_2 \cdot 6H_2O$	48[e]	69:31
5	$AgBF_4$	nil[e]	

[a] **9** (2.5 mmol) was treated with **3** (1 equiv) in the presence of the metal tetraflouroborate (2 mol %) at rt under solvent-free conditions for 60 min. [b] GC−MS conversion. [c] The regioisomeric ratio was determined by GC−MS. [d] The isolated product was found to be a 66:34 mixture of the amino alcohols and phenyl acetaldehyde. [e] The unreacted starting materials remained unchanged.

indicating that the Meinwald's rearrangement[18] is a potential side reaction with the use of $Cu(BF_4)_2 \cdot xH_2O$ as the catalyst.

To further show the applicability of $Zn(BF_4)_2 \cdot xH_2O$ for regioselective ring opening of unsymmetrical epoxide, **9** was treated with various aromatic and aliphatic amines (Table 6). In each case the products were isolated by usual workup and the regioselectivity was determined by GC−MS without further purification. 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 $[M^+ - 31]$ due to the loss of the CH_2OH in the GC−MS.[11] The characteristic ion peak was at m/z $[M^+ - 107]$ due to the loss of PhCHOH for the product formed by the reaction at the terminal carbon of the epoxide ring. The major regioisomeric amino alcohol was isolated in pure form

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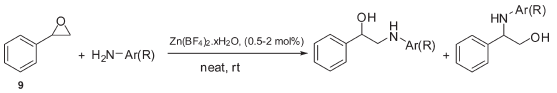
Table 6. $Zn(BF_4)_2 \cdot xH_2O$-Catalyzed Opening of the Epoxide Ring of 9 by Various Aryl and Alkyl Amines[a]



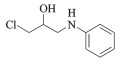
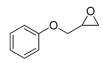
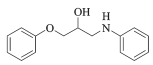
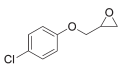
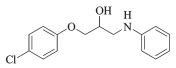
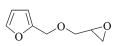
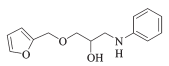
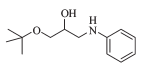
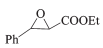
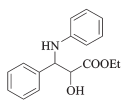
9

Entry	Amine	Time (min)	Yield (%)[b]	Regioisomeric Ratio[c]	Major Isomer Yield (%)[d]
1	R = H	40	95	1 : 99	91
2	R = 4-Me	60	89	11 : 89	80
3	R = 4-Cl	30	92	13 : 87	79
4	R = 4-OMe	60	96	2 : 98	86
5	R = 2-OMe	60	96	4 : 96	85
6	R = 2-F	10	96	10 : 90	74
7	R = 2,6-di-Me	60	89	3 : 97	83
8	R = 2,6-di-Pr[i]	120	94	4 : 96	72
9		4 h	92	9 : 91	79
10		60	90	99 : 1	
11		60	100	91 : 9	
12		60	100	89 : 11	
13		4 h	86[e]	73 : 27	
14		2 h	95	92 : 8	
15		4 h	86	75 : 25	

[a] The epoxide **9** (2.5 mmol) was treated with the amine (2.5 mmol, 1 equiv) in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (0.5 mol % for aromatic amines and 2 mol % for aliphatic amines) at rt under solvent-free conditions. [b] Isolated yield of the corresponding 2-aminoalcohols. [c] Determined by GC−MS and NMR. [d] Yield of the major regioisomer obtained after flash column chromatographic purification. [e] A 52% yield was obtained when the reaction was carried out in the presence of $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %) for 4 h with 63:37 selectivity.

(72−91% yields) through flash column chromatographic separation of the product mixtures isolated from the reaction of **9** with

Table 7. $Zn(BF_4)_2 \cdot xH_2O$-Catalyzed Ring Opening of Various Epoxides by 2[a]

Entry	Epoxide	Time (min)	Product	Yield (%)[b,c]
1		20		97[d,e,f,g]
2		30		88[h]
3		45		83[h]
4		60		89[h]
5		30		87[h]
6		30		92[h]
7		60		91[i]

[a] The epoxide (2.5 mmol) was treated with **2** (2.5 mmol, 1 equiv) in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (0.5− 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 product was found to be a 73:27 mixture of the amino alcohols formed as 1:1 [regioisomeric ratio 85:15 in favor of the regioisomer from nucleophilic attack at the less substituted carbon atom of the epoxide ring] and 2:1 adducts of the epoxide and the amine, respectively. [e] A 56% yield was obtained as 89:11 mixture of the amino alcohols formed as 1:1 (with 74:26 regioselectivity) and 2:1 adducts of the epoxide and the amine when the reaction was carried out in the presence of $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %) for 20 min. [f] A 97% yield was obtained as 59:41 mixture of the amino alcohols formed as 1:1 (86:14 regioselectivity) and 2:1 adducts of the epoxide and the amine when the reaction was carried out in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol %) for 20 min. [g] The 1:1 regioisomeric 2-amino alcohol adducts were formed exclusively (GC−MS) with 85:15 regioselectivity in favor of the nucleophilic attack at the terminal carbon of the epoxide ring in performing the reaction using 0.5 mol % of $Zn(BF_4)_2 \cdot xH_2O$ for 20 min at rt. [h] The 2-amino alcohol from nucleophilic attack at the less substituted carbon atom of the epoxide ring was formed as the only product (GC−MS). [i] The 2-amino alcohol from nucleophilic attack at the benzylic carbon atom of the epoxide ring was formed as the only product (GC−MS and NMR).

aromatic amines (entries 1−9, Table 6). However, the regioisomeric amino alcohols obtained as a mixture from the reaction of **9** with aliphatic amines could not be separated using various chromatographic (gravity/flash column) techniques.

A complementarity in the regioselectivity was observed during the reaction with aromatic and aliphatic amines. The aromatic amines underwent nucleophilic attack selectively at the benzylic carbon atom of the epoxide ring of **9** (entries 1−9, Table 6), but alkyl amines showed a preference toward nucleophilic attack at the terminal carbon (less hindered site) of the epoxide ring (entries 10−15, Table 6).

To establish the generality, various epoxides were treated with **2** in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (Table 7). Excellent regioselectivity was observed during the reaction of propylene oxide (entry 1, Table 7), epichlorohydrin (entry 2, Table 7), and

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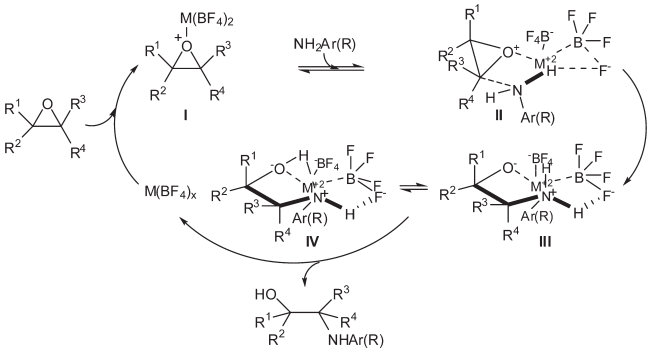
glycidic ethers (entries 3−6, Table 7), affording the amino alcohols from nucleophilic attack at the less substituted carbon atom of the epoxide ring as the exclusive/major products (GC−MS). The reaction works well in case of acid-sensitive epoxide (entry 5, Table 7). The reaction with epichlorohydrin provided an example of excellent chemoselectivity as no product from nucleophilic substitution of the chlorine atom by the amine was formed (GC−MS). Ethyl phenylglycidate (entry 7, Table 7) afforded the amino alcohol from nucleophilic attack at the benzylic carbon atom as the only product (GC−MS).[11e] 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 **9** (Table 6).

A careful analysis (GC−MS and NMR) of the product obtained from the reaction of propylene oxide with **2** revealed it to be a 73:27 mixture of the amino alcohols formed as 1:1 and 2:1 adducts of the epoxide and the amine, respectively. For the 2-amino alcohols formed as the 1:1 adduct, the regioisomer *N*-(2-hydroxypropyl)aniline formed by nucleophilic attack at the less substituted carbon atom of the epoxide ring was the major product (85:15) (NMR). The 1:2 adduct *N*,*N*-bis(2-hydroxypropyl) aniline is formed by further nucleophilic attack at the epoxide ring of propylene oxide by the 1:1 adduct *N*-(2-hydroxypropyl)-aniline. The $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %)-catalyzed reaction afforded a 89:11 mixture of the corresponding 1:1 and 2:1 adducts in 56% yield with 74:26 regioisomeric selectivity (NMR) of the 1:1 adduct. When the reaction was performed in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol %), 97% yield of the 1:1 and 1:2 adducts were obtained as a 59:41 mixture with 86:14 selectivity (NMR) of the regioisomers of the 1:1 adduct. The formation of *N*,*N*-bis(2-hydroxypropyl) aniline as the side product was avoided in performing the reaction of propylene oxide with 1 molar equiv of **2** in the presence of 0.5 mol % of $Zn(BF_4)_2 \cdot xH_2O$ at rt for 20 min, which resulted in the exclusive formation of the regioisomeric 1:1 adducts in a ratio of 85:15 with *N*-(2-hydroxypropyl)-aniline being the major isomeric amino alcohol. Compared to this, the $Cu(BF_4)_2 \cdot xH_2O$ (0.5 mol %)-catalyzed reaction resulted in the formation of the regioisomeric 1:1 adducts in 48% yield with 74:26 selectivity in favor of *N*-(2-hydroxypropyl)aniline. However, although the use of lesser amounts of $Zn(ClO_4)_2 \cdot 6H_2O$ (0.5 mol %) gave near quantitative conversion (98%) to the amino alcohol, the formation of the side product *N*,*N*-bis(2-hydroxypropyl) aniline could not be suppressed as the isolated product was found to be a 61:39 mixture of the 1:1 (regioselectivity 86:14) and the 1:2 adducts.

The catalytic role of the metal tetrafluoroborate is envisaged as an initial electrophilic activation of the epoxide ring through coordination with the central metal cation $[M^{+n}]$ to form **I** (Scheme 1). The resulted oxonium species (**I**) is stabilized by delocalization through the adjacent C−C σ bond of the epoxide ring (due to partial π-character).[19] This induces polarization of the epoxide C−C bond and increases the electrophilicity at these two carbon atoms/sites. The fluorine atom of one of the BF_4^- anions forms hydrogen bond (H−B) with the amine and induces nucleophilic activation.[20] This holds/locks the amine in close proximity to the electrophilic carbon of the epoxide moiety via the supramolecular assembly **II** to facilitate nucleophilic attack to form **III**. This is followed by intramolecular proton shift via **IV**, in which the oxyanionic site forms H−B (in the form of hydrogen bridge) with other hydrogen atom of the positively charged nitrogen, forming the amino alcohol and releasing the metal tetrafluoroborate to complete and restart the catalytic cycle.

Scheme 1. Role of the Metal Tetrafluoroborates in Catalyzing the Epoxide Ring-Opening Reaction by Amines



Thus, the overall role of the metal tetrafluoroborates can be designated as electrophile−nucleophile dual activation[21] involving a network of coordinative, charge−charge, and H−B interactions.[22] Supramolecular assemblies akin to **II**−**IV** that are devoid of any metal ion participation are involved during "electrophile nucleophile dual activation catalysis" by ionic liquids.[21i−m] The mechanistic model implies that the catalytic efficiency would depend on (i) the oxophilicity/electron deficiency of the central metal cation, (ii) the H−B donor ability of the amine for effective construction of **II** and **III**, and (iii) intramolecular proton transfer through the hydrogen-bonded/bridged **IV** in the final stage of the catalytic process.

The mechanistic model (Scheme 1) adequately rationalizes the various results of the epoxide ring opening (Tables 1−7). The inferior catalytic activity of the transition metal tetrafluoroborates, e.g., $Cu(BF_4)_2 \cdot xH_2O$, $Co(BF_4)_2 \cdot 6H_2O$, and $Fe(BF_4)_2 \cdot 6H_2O$, compared to that of $Zn(BF_4)_2 \cdot xH_2O$ is due to the strong coordination of these transition metal cations (due to the vacant d orbitals) with the amine that decreases the electrophilicity of the central metal ion and its propensity to form the intermediates **I**−**IV**. This is more pronounced in case of aliphatic amines (entries 2−5, Table 1; entries 2−4, Table 2) as they are more nucleophilic (better ligands) than the aromatic amines, and hence a competitive complex formation between the aliphatic amines and the epoxide with the transition metal cation occurs. The inferior catalytic activity of $Cu(BF_4)_2 \cdot xH_2O$ based catalyst system is also evidenced through a recent example that affords 62% yield of the amino alcohol during the reaction of **1** with **2** (used in excess amounts) at rt for 4 h.[23] The better catalytic activity of $Zn(BF_4)_2 \cdot xH_2O$ compared to that of $LiBF_4$ (Tables 1 and 2) is because of the stronger oxophilicity of Zn^{2+} compared to that of Li^+ due to the higher charge to size ratio of the former cation (Zn^{2+} 5.33 and Li^+ 1.35 $e^2\ m^{-10}$).[24] The inferior results obtained in the presence of the transition metal tetrafluoroborates $Fe(BF_4)_2 \cdot 6H_2O$, $Co(BF_4)_2 \cdot 6H_2O$, and $Cu(BF_4)_2 \cdot xH_2O$ could also be due to the increasing tendency of the corresponding metal ions to hydrolyze (in addition to their ability to form coordination complex with the amine) compared to that of Zn^{2+} ion due to lower pK_h values of these ions.[25] The water molecules in these metal tetrafluoroborate hydrates decrease the oxophilicity of the central metal cation.

The involvement of the intermediates **II**− **IV** during the progress of the reaction provides rational for the observed reactivity and selectivity during the reaction of different amines with a common substrate. The longer time required for the reactions of aliphatic amines compared to that of aromatic

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amines is due to the inferior hydrogen bond donor ability[26] of the aliphatic amines compared to that of aromatic amines (pK_a values of aromatic and aliphatic amines: aniline 4.58, 4-methyl aniline 5.07, 4-methoxy aniline 5.29, 4-chloroaniline 3.81, 4-fluoro aniline 4.52, 4-trifluoro aniline 2.57, 4-carboethoxy aniline 2.38, *N*-methyl aniline 4.85, pyrolidine 11.27, morpholine 8.36, piperidine 11.22, benzylamine 9.34).[27] Thus, in the case of aromatic amines the hydrogen-bonded structures **II**− **IV** are formed more readily. Hence the reactions with aromatic amines take place in shorter times than those of aliphatic amines, although aliphatic amines, in general, are better nucleophilic than the aromatic amines. The longer time (45 min) required for 4-methylaniline and 4-methoxyaniline (entries 2 and 3, Table 4) compared to aniline, although the amino group in 4-methylaniline and 4-methoxyaniline is more nucleophilic, is due to their inferior H−B donor ability compared to that of aniline as the pK_a are in the order 5.07, 5.29, and 4.58, respectively.[27] The more effective H−B donor ability of the amino group in 4-chloroaniline, 4-fluoroaniline, 4-trifluoromethylaniline, and 4-carboethoxyaniline (entries 4−7, Table 4), due to lower pK_a value (3.81, 4.52, 2.57, and 2.38, respectively), drives the epoxide ring-opening reaction with these amines to take place in shorter times than with aniline. The importance of the hydrogen-bonded/bridged structure **IV** to facilitate the intramolecular proton transfer from the ammonium moiety to the oxyanionic site formed by nucleophilic attack of the amino group on the epoxide ring is further revealed by the requirement of longer reaction time with *N*-methylaniline, a better nucleophilie than aniline. Due to the higher pK_a (4.85)[27] of *N*-methylaniline, the hydrogen-bonded intermediate **II** (Scheme 1) is less readily formed. Moreover, the transition state **IV** is not feasible with *N*-methylaniline as it is devoid of the hydrogen that forms the hydrogen bridge in **IV** during intramolecular proton transfer in the final stage of the reaction. Hence, the final proton transfer occurs in intermolecular fashion. The longer reaction time required with *N*-methylaniline does not appear to be due to the steric effect (although the steric factor may have some contribution in retarding the nucleophilic attack) as the reaction of *N*-methyl aniline with **9** takes place at the more substituted (sterically hindered) benzylic carbon (vide infra).

The inferior results obtained with substrates bearing the COMe, CN, and NO_2 functionalities (entries 8−10, Table 3) could be due to the competitive coordination of these groups with the central metal cation of the catalyst that inhibits the electrophilic activation of the epoxide. Due to the strong donor/coordinating ability of the pyridine nitrogen atom, in 4-aminopyridine (entry 13, Table 3) the catalyst is engaged in coordination with the pyridine nitrogen and loses its ability to activate the epoxide ring. In the case of 4-aminophenol (entry 11, Table 3) exchange of the OH proton with the central metal cation reduces the catalytic efficiency and might be the reason for the inferior yields obtained in comparison to that of 4-methoxyaniline (entry 3, Table 3), although its pK_a (5.50)[27] is comparable to that of 4-methoxyaniline. On the other hand, the lack of formation of the product during the reaction with 3,4,5-trimethoxyaniline (entry 12, Table 3) is due to the chelation of the catalyst with the 1,2-di-OMe moiety in the substrate. The sluggishness of 4-acetyl aniline (entry 8, Table 3) compared to 4-carboethoxyaniline (entry 7, Table 3) in participating in the epoxide ring-opening reaction, although its NH_2 hydrogens have lower pK_a (2.19) value,[28] is due to the higher enolate character of ketone carbonyl[29] as a result of which the catalyst undergoes competitive coordination with the acetyl group of 4-acetyl aniline. The strong coordination ability of the CN group toward the catalyst reduces the catalytic efficiency for epoxide ring activation and accounts for the poor yields obtained with 4-cyanoaniline (entry 9, Table 3) despite of its lower pK_a (1.74)[30] compared to that of aniline.

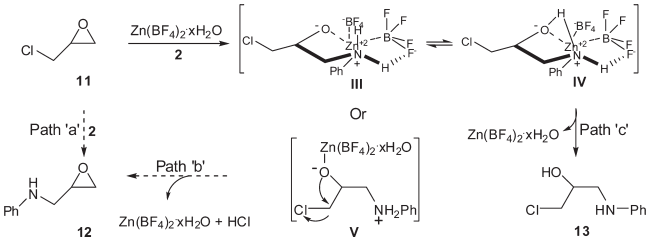
The regioselective outcome (Tables 5−7) can be explained in terms of the electronic and steric factors associated with the substrates as well as the effectiveness of activation of the epoxide. Complex formation between the epoxide oxygen atom of **9** and Zn^{2+} forms **I** (R^1 = Ph; $R^2 = R^3 = R^4$ = H; Scheme 1) in which the positive charge generated on the oxygen atom is delocalized on carbon atoms of the epoxide ring. The better carbocationic character of the benzylic carbon atom, due to the resonance stabilization by the phenyl ring, makes it more electrophilic compared to the less substituted carbon atom of the epoxide ring. Hence the less nucleophilic aromatic amines react preferably at the more electrophilicly activated benzylic carbon of the epoxide ring. On similar ground the electronic/resonance effect of the phenyl ring in ethyl phenylglycidate (entry 7, Table 7) induces the electrophilic activation at the benzylic carbon of the epoxide ring resulting in the observed regioselectivity. Therefore, the regioselective outcome during the reaction of unsymmetrical substituted epoxide with aromatic amines is primarily controlled by the electronic environment surrounding the epoxide ring (differential polarization at the epoxide ring carbons) and the aromatic amine (propensity to act as H−B donor and decreased ligation ability). The importance of the electronic effect over the steric effect in controlling the regioselectivity is further reflected by the preferential reaction of sterically hindered aromatic amines 2,6-dimethylaniline and 2,6-diisopropylaniline (entries 7 and 8, Table 6) at the sterically hindered benzylic carbon in **9**. In the absence of such overriding influence of the electronic factor (resonance effect of the phenyl ring), in propylene oxide (entry 1, Table 7), epichlorohydrin (entry 2, Table 7), and the glycedic ethers (entries 3−6, Table 7), the regioselectivity is controlled by the steric factor as **2** reacts selectively at the less substitute/terminal carbon atom of the epoxide ring. The regioselectivity of the reaction of **9** with aliphatic amines is governed by the steric factor. Complex formation takes place between the aliphatic amine nitrogen and the catalyst as aliphatic amines are stronger bases (better ligation ability) compared to the aromatic amines. This makes the effective nucleophilic species sterically hindered, and preferential nucleophilic attack takes place at the less hindered nonbenzylic (terminal) carbon atom of the epoxide ring.

However, apart from the selective electrophilic activation of the benzylic carbon of the epoxide ring of **9** in directing regioselective nucleophilic attack at this center with aromatic amines, the BF_4^- counteranion also plays a crucial/major role in controlling the regioselectivity through the hydrogen-bonded assembly **II**. The engagement of the amine hydrogen in H−B formation with the fluorine of the BF_4^- anion appears to be the determining factor to control the regioselectivity by locking/fixing the aromatic amine nitrogen in close proximity to the benzylic carbon of **9** to establish the electrostatic attraction between the electron deficient benzylic carbon and the nitrogen lone pair and facilitate the concomitant nucleophilic attack. Hence, although different metal tetrafluoroborates having varying electrophilic activation ability form the product in different amounts/yields, they exhibit comparable regioselectivity (Table 4). As aliphatic amines have poor H−B donor ability, the hydrogen-bonded assemblies akin to **II** are unlikely to be formed during the reaction of **9** with aliphatic amines. The aliphatic amines, on the other hand, may

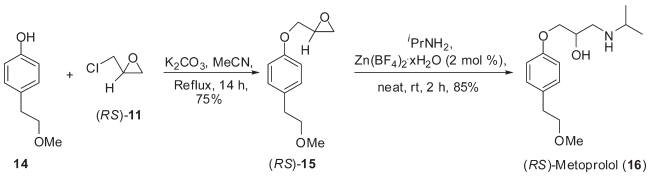
undergo complex formation with the metal cation through the nitrogen lone pair that would generate a bulky species and would undergo nucleophilic attack at the less substituted/hindered carbon center of the epoxide ring of **9**, perhaps in intermolecular fashion.

The reaction of **2** with epichlorohydrin (**11**) (entry 2, Table 7) represents an excellent example of chemoselectivity as there is no competitive formation of the oxiran **12** (Scheme 2) through a direct nucleophilic displacement of the chlorine by the amino group (path a) or extrusion of the chlorine atom through intramolecular nucleophilic substitution by the adjacent alkoxide anion (path b), formed by opening of the epoxide ring through nucleophilic attack on the least substituted carbon atom of the epoxide ring.[31] The chemoselective formation of the desired product is controlled by activation of the epoxide ring by $Zn(BF_4)_2 \cdot xH_2O$ leading to the opening of the epoxide ring by nucleophilic attack on the least substituted carbon atom of the epoxide ring followed by protonation of the alkoxide anion to form the amino alcohol(s) (path c). In the relevant intermediates **III**/**IV** ($R^1 = CH_2Cl$, $R^2 = R^3 = R^4 = H$; Scheme 1) the negative charge of the alkoxide anion is engaged in coordination with the Zn^{2+} ion and H−B formation with one of the ammonium hydrogen through the hydrogen bridge in **IV** (Scheme 2). Thus, the free alkoxide anion (structure **V** in Scheme 2) is not available for subsequent elimination of the chloride anion via path b and the amino alcohol **13** is formed as the sole (major) product via intramolecular proton transfer through **III**/**IV** (path c).

Scheme 2. $Zn(BF_4)_2 \cdot xH_2O$-Catalyzed Epoxide Ring Opening of 11 by 2



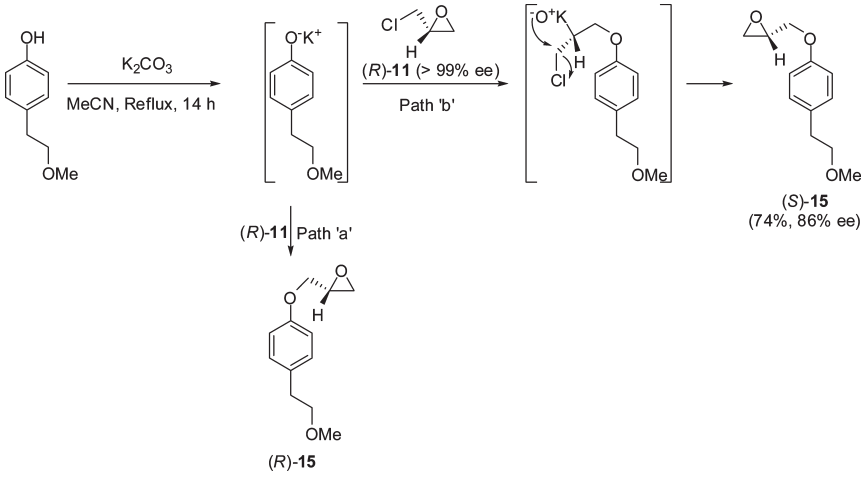
Scheme 3. Application of $Zn(BF_4)_2 \cdot xH_2O$-Catalyzed Epoxide Ring Opening by Amine for the Synthesis of (*RS*)-Metoprolol (16)



The applicability of this methodology is demonstrated for the synthesis of cardiovascular drug metoprolol (**16**), widely used in the treatment of angina and hypertension, as racemates as well as the optically active enantiomer. The common synthetic strategy for these cardiovascular agents involves nucleophilic opening of the epoxide ring of 2-[4-(2-methoxy-ethyl)-phenoxymethyl]-oxirane **15** with an isopropyl amine (Scheme 3).

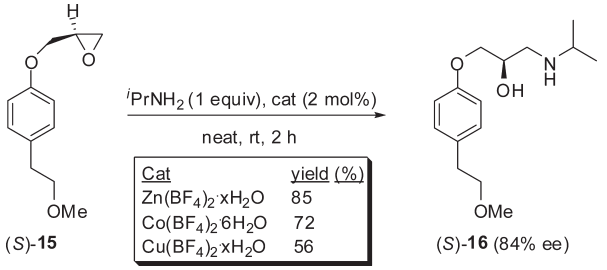
The key starting material (*RS*)-**15** was prepared in 75% yield by the reaction of 4-(2-methoxyethyl)-phenol (**14**) with (*RS*)-**11**, in the presence of K_2CO_3 in MeCN under reflux.[11] The treatment of (*RS*)-**15** with $^iPrNH_2$ (1 equiv) at rt for 2 h in the presence of $Zn(BF_4)_2 \cdot xH_2O$ under neat conditions afforded (*RS*)-**16** in 85% yield. Although metoprolol has a stereogenic carbon center, its current therapeutic administration is in the racemic form. However, the therapeutic efficacy of a racemic drug often resides on the single enantiomer.[32] It is reported that the (*S*)-isomer of **16** is more potent[33] and that the (*R*)-isomer is responsible for the side effects.[34] Therefore, we planned to synthesize the enantiomeric forms (*S*)-**16** and (*R*)-**16**. To prepare the key intermediate **15** in enatiomeric forms, the phenolate anion of **14** was subjected to alkylation separately with (*R*)-**11** and (*S*)-**11**. In each case, the optical purity was determined by comparison of the optical rotation with reported values and by chiral HPLC (selected examples). It was observed that the alkylation using (*R*)-**11** resulted in (*S*)-**15** in 74% yield [ee = 86% based on comparison of the optical rotation of (*R*)-**15**)].[35,36] The (*R*)-**15** was obtained in 75% yield (ee = 84% based on optical rotation)[36] from (*S*)-**11**. The formation of (*S*)-**15** from (*R*)-**11** revealed that a direct alkylation of the phenolate anion of **14** through nucleophilic displacement of the chlorine atom in (*R*)-**11** (path a, Scheme 4) does not occur. Rather, **15** is formed via the nucleophilic opening of the epoxide ring of (*R*)-**11** (path b, Scheme 4) through the reaction at the unsubstituted carbon followed by 1,2 elimination of the chlorine atom in the intermediate alkoxide anion leading to (*S*)-**15**. Thus, the overall reaction involves inversion at the stereogenic carbon center of (*R*)- and (*S*)-**11**.

Scheme 4. Formation of (*S*)-(15) from (*R*)-11

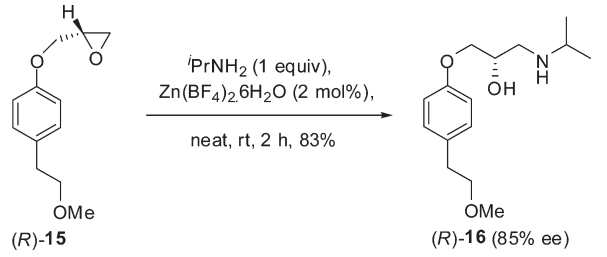


dx.doi.org/10.1021/jo201473f |*J. Org. Chem.* 2011, 76, 8768–8780

Scheme 5. Synthesis of (*S*)-(−)-Metorpolol from (*S*)-15



Scheme 6. Synthesis of (*R*)-(+)-Metoprolol from (*R*)-15



The applicability of $Zn(BF_4)_2 \cdot xH_2O$ was extended for the synthesis of (*S*)-**16** during the reaction of (*S*)-**15** with $^iPrNH_2$ (Scheme 5). The treatment of (*S*)-**15** with $^iPrNH_2$ at rt for 2 h under solvent-free condition in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (2 mol %) afforded (*S*)-**16** in 85% yield (ee =84% based on optical rotation[35]). The reaction of (*S*)-**15** with $^iPrNH_2$ under similar conditions in the presence of $Co(BF_4)_2 \cdot 6H_2O$ (2 mol %) and $Cu(BF_4)_2 \cdot xH_2O$ (2 mol %) afforded (*S*)-**16** in 72% and 56% yields, resepectively, without any significant difference in the optical purity.

Subsequently, we planned to demonstrate the effectiveness of $Zn(BF_4)_2 \cdot xH_2O$ for the synthesis of (*R*)-**16** (Scheme 6). The epoxide (*R*)-**15** was treated with $^iPrNH_2$ in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (2 mol %) at rt for 2 h under solvent-free condition to afford (*R*)-**16** in 83% yields (ee = 84% based on comparison of the optical rotation value reported for the (*S*)-enantiomer[35]). In the HPLC (chiral OD-H column), the product exhibited enantiomeric distribution of 92.44:7.56 (85% ee) with the enantiomers eluting at t_R = 18.66 min, t_S = 32.50 min, respectivey (hexane/2-propanol/diethylamine = 95:05:0.1).

CONCLUSIONS

The catalytic potential of metal tetrafluoroborates for epoxide ring opening by amines to form β-amino alcohols has been assessed, and $Zn(BF_4)_2 \cdot xH_2O$ has been found to be a new and highly efficient catalyst. The advantages include high yields; short reaction times; excellent regio-, chemo-, and stereoselectivities; and use of cheap and commercially available catalyst. Other transition metal tetrafluoroborates such as $Cu(BF_4)_2 \cdot xH_2O$, $Co(BF_4)_2 \cdot 6H_2O$, and $Fe(BF_4)_2 \cdot 6H_2O$ were less effective in affording lesser chemical yields and inferior regioselectivity. The catalytic role of $Zn(BF_4)_2 \cdot xH_2O$ has been envisaged as "electrophile nucleophile dual activation" through catalytic species formed by cooperativity of coordination, charge−charge interaction, and hydrogen bond formation involving the epoxide, catalyst, and the amine. The mechanistic model adequately rationalizes the observed reactivity and selectivity. A complementarity in the regioselectivity has been observed for the reaction of an unsymmetrical epoxide bearing an aromatic/phenyl moiety at one of the epoxide ring carbon. Preferential nucleophilic attack occurs at the benzylic carbon of the epoxide ring for reactions with aromatic amines, whereas for aliphatic amines the epoxide ring opening takes place through the reaction at the less hindered carbon atom of the epoxide ring. The extension of this methodology for the synthesis of (*RS*)-metoprolol, (*R*)-metoprolol, and (*S*)-metoprolol demonstrated the potentiality of industrial applications for the synthesis of cardiovascular drugs.

EXPERIMENTAL SECTION

Typical Procedure for Epoxide Ring Opening by Amine: *trans*-2-(Phenylamino)cyclohexanol 4 (entry 1, Table 3). To a mixture of **1** (245 mg, 2.5 mmol) and **2** (233 mg, 2.5 mmol) was added $Zn(BF_4)_2 \cdot xH_2O$ (18 mg, 2 mol %), and the mixture was magnetically stirred at rt under nitrogen. After completion of the reaction (30 min, TLC, GC−MS) the reaction mixture was diluted with EtOAc (15 mL), washed with water (5 mL), dried (Na_2SO_4), and concentrated in vacuum. The crude isolate was purified by flash chromatography using silica gel (230−400 mesh) and eluted with EtOAc/hexane (1:9) to afford **4** (420 mg, 90%). Mp 57−59 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02−1.06 (m, 1 H), 1.26−1.37 (m, 3 H), 1.70−1.77 (m, 2 H), 2.09−2.16 (m, 2 H), 2.93 (s, 2 H, D_2O exchangeable), 3.15 (ddd, 1 H, J = 3.9, 10.0, 10.1 Hz), 3.34 (ddd, 1 H, J = 4.2, 10.4, 10.5 Hz), 6.69−6.76 (m, 3 H), 7.15−7.25 (m, 2 H). EIMS (m/z) 191 (M^+).[8i] The remaining reactions were carried out following this general procedure. On each occasion, the product was characterized by IR, NMR, and MS. The spectral data of known compounds were found to be identical with those reported in the literature.

Typical Procedure for the Preparation of (*RS*)-2-[4-(2-Methoxyethyl)phenoxymethyl]oxirane (15). To a magnetically stirred solution of **14** (380 mg, 2.5 mmol) and K_2CO_3 (690 mg, 5 mmol) in anhydrous MeCN (10 mL) was added (*RS*)-**11** (0.29 mL, 3.75 mmol), and reaction mixture was heated under reflux for 14 h. The cooled (rt) reaction mixture was filtered, the filtrate was concentrated under vacuum, and the residue was purified by passing through a column of silica gel (60−120 mesh) and eluting with EtOAc/hexane (1:9) to afford (*RS*)-**15** (390 mg, 75%). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72−2.90 (m, 4 H), 3.34 (m, 4 H), 3.56 (t, 2 H, J = 7.1 Hz), 3.91−3.96 (dd, 1 H, J = 5.5, 11.0 Hz), 4.15−4.20 (dd, 1 H, J = 3.2, 11.0 Hz), 6.85 (d, 2 H, J = 8.4 Hz), 7.13 (d, 2 H, J = 8.4 Hz). EIMS (m/z) 208 (M^+).[35]

Typical Procedure for Preparation of (*R*)-2-[4-(2-Methoxyethyl)phenoxymethyl]oxirane (15). The reaction of **14** (380 mg, 2.5 mmol) with (*S*)-**11** (290 mg, 3.75 mmol) followed by the usual workup and purification afforded (*R*)-**15** (390 mg, 75%), identical [NMR (^1H and ^{13}C) and EIMS] with an authentic sample of (*RS*)-15.[35] $[\alpha]_D$ = −10.0 (*c* 1, MeOH) (84% ee) [lit.[36] $[\alpha]_D$ = −11.3 (*c* 1, MeOH) for 94.7% ee].

Typical Procedure for the Preparation of (*S*)-2-[4-(2-Methoxyethyl)phenoxymethyl]oxirane (15). The treatment of **14** (380 mg, 2.5 mmol) with (*R*)-**11** (290 mg, 3.75 mmol) followed by the usual workup and purification afforded (*S*)-**15** (380 mg, 73%), identical [NMR (^1H and ^{13}C) and EIMS] with an authentic sample of (*RS*)-15.[35] $[\alpha]_D$ = +10.4 (*c* 1, MeOH) (86% ee in comparison to the optical rotation reported for (*R*)-**15**[36]). The product was subjected to chiral HPLC analysis using CHIRAL OD-H column and the two enantiomers eluted at t_R = 15.35 min, t_S = 16.80 min (95:5 hexane/^{i}PrOH) indicating the optical purity of 89% ee.

Typical Procedure for the Preparation of (*RS*)-Metoprolol (16). The mixture of (*RS*)-**15** (208 mg, 1 mmol), $^iPrNH_2$ (0.086 mL,

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1 mmol), and $Zn(BF_4)_2 \cdot xH_2O$ (7 mg, 2 mol %) was stirred magnetically at rt under nitrogen. After completion of the reaction (120 min, TLC, GC−MS) the reaction mixture was diluted with EtOAc (15 mL), washed with water (5 mL), dried (Na_2SO_4), and concentrated under vacuum. The crude mixture was purified by passing through a column of silica gel (60− 120 mesh) and eluting with DCM/MeOH (98:2) to afford (*RS*)-**16** (225 mg, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (d, 6 H, J = 6.3 Hz), 2.6 (bs, 1 H, D_2O exchangeable), 2.70−2.75 (dd, 1 H, J = 7.8, 12.1 Hz), 2.81−2.90 (m, 4 H), 3.35 (s, 3 H), 3.56 (t, 2 H, J = 7.1 Hz), 3.93−4.04 (m, 3 H), 6.85 (d, 2 H, J = 8.6 Hz), 7.14 (d, 2 H, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 23.2, 35.2, 48.9, 49.3, 58.6, 68.4, 70.6, 73.8, 114.5, 129.7, 131.4, 157.1. EIMS (m/z) 267 (M^+).[35]

Typical Procedure for the Preparation of (*S*)-Metoprolol (16). The reaction of (*S*)-**15** (208 mg, 1 mmol) with ^{i}PrNH$_2$ (58 mg, 1 mmol, 0.086 mL) in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (7 mg, 2 mol %) followed by usual workup and purification as described for (*RS*)-**16** afforded (*S*)-**16** (225 mg, 85%) identical [NMR (^{1}H and ^{13}C NMR) and EIMS] with an authentic sample.[35] $[\alpha]_D = -7.5$ (c 10, $CHCl_3$) (84% ee) [lit.[35] = −8.7 (c 10, $CHCl_3$) for 97.2% ee].

Typical Procedure for the Preparation of (*R*)-Metoprolol (16). The reaction of (*R*)-**15** (208 mg, 1 mmol) with ^{i}PrNH$_2$ (58 mg, 1 mmol, 0.086 mL) in the presence of $Zn(BF_4)_2 \cdot xH_2O$ (7.4 mg, 2 mol %) followed by usual workup and purification as described for (*RS*)-**16** afforded (*R*)-**16** (220 mg, 83%), identical [NMR (^{1}H and ^{13}C) and EIMS] with (*S*)-**16**. $[\alpha]_D = +7.5$ (c 10, $CHCl_3$) (ee = 84% in comparison with the corresponding value as reported for (*S*)-**16**[35]). The product on subjection to HPLC analysis using CHIRAL OD-H column and elution with 95:5 hexane/^{i}PrOH containing 0.1% Et_2NH was shown to be a 92.44:7.56 (85% ee) mixture of the two enantiomers eluting at 18.66 and 32.5 min, respectively.

The spectral data of the compounds are provided below.

***erythro*-1,2-Diphenyl-2-(phenylamino)ethanol 7 (entry 1, Table 2).** Light yellow solid, mp 119−121 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (d, 1 H, J = 5.3 Hz, D_2O exchangeable), 4.47 (bs, 1 H, D_2O exchangeable), 4.68 (d, 1 H, J = 4.3 Hz), 5.08 (t, 1 H, J = 5.1 Hz), 6.53 (d, 2 H, J = 7.7 Hz), 6.66 (t, 1 H, J = 7.3 Hz), 7.06−7.18 (m, 6 H), 7.24−7.29 (m, 6 H). After D_2O exchange ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.66 (d, 1 H, J = 4.8 Hz), 5.05 (d, 1 H, J = 4.8 Hz), 6.51 (dd, 2 H, J = 1, 8.6 Hz), 6.66 (t, 1 H, J = 9.8 Hz), 7.03−7.15 (m, 6 H), 7.21−7.26 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 63.6, 77.1, 113.9, 117.9, 126.5, 127.6, 127.8, 128.0, 128.24, 128.29, 129.1, 138.4, 139.9, 146.7. EIMS (m/z) 289 (M^+).[37]

***erythro*-1,2-Diphenyl-(2-morpholino)ethanol 8 (entry 1, Table 2).** White solid, mp 117−120 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.54 (m, 2 H), 2.67 (bs, 1 H), 3.3 (s, 1 H), 3.35 (d, 1 H, J = 4.1 Hz), 3.72−3.73 (m, 4 H), 5.33 (d, 1 H, J = 4.0 Hz), 6.93−6.97 (m, 4 H), 7.09−7.14 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.0, 67.1, 71.2, 76.4, 126.1, 126.9, 127.4, 127.60, 127.63, 129.5, 135.5, 140.8.[38]

***trans*-2-(4-Methylphenylamino)cyclohexanol (entry 2, Table 3).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02−1.03 (m, 1 H), 1.25−1.36 (m, 3 H), 1.69−1.75 (m, 2 H), 2.08−2.16 (m, 2 H), 2.23 (s, 3 H), 2.94 (bs, 2 H, D_2O exchangeable), 3.06 (ddd, 1 H, J = 4.0, 9.6, 10.3 Hz), 3.34 (ddd, 1 H, J = 4.2, 9.8, 10.4 Hz), 6.62−6.65 (d, 2 H, J = 7.8 Hz), 6.97−7.0 (d, 2 H, J = 7.9 Hz). EIMS (m/z) 205 (M^+).[4a]

***trans*-2-(4-Methoxyphenylamino)cyclohexanol (entry 3, Table 3).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98−1.07 (m, 1 H), 1.25−1.40 (m, 4 H), 1.70−1.78 (m, 2 H), 2.07−2.13 (m, 2 H), 2.23 (s, 3 H), 2.96−3.04 (ddd, 1 H, J = 3.9, 9.3, 9.8 Hz), 3.28−3.36 (ddd, 1 H, J = 4.1, 9.4, 9.9 Hz), 6.68 (d, 2 H, J = 8.9 Hz), 6.78 (d, 2 H, J = 8.9 Hz). EIMS (m/z) 221 (M^+).[8i]

***trans*-2-(4-Fluorophenylamino)cyclohexanol (entry 4, Table 3).** White solid, mp 89−91 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01−1.10 (m, 1 H), 1.25−1.40 (m, 3 H), 1.69−1.79 (m, 2 H), 2.06−2.13 (m, 1 H), 2.99−3.07 (m, 1 H), 3.30 −3.35 (ddd, 1 H, J = 4.5, 9.7, 10.4 Hz), 6.62−6.68 (m, 2 H), 6.85−6.91 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 24.9, 31.4, 33.2, 61.2, 74.3115.6, 115.71, 115.78, 115.8, 143.8, 155.2, 157.5 (d, J = 293.7 Hz). EIMS (m/z) 209 (M^+).[39]

***trans*-2-(4-Chlorophenylamino)cyclohexanol (entry 5, Table 3).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01−1.41 (m, 4 H), 1.70−1.78 (m, 2 H), 2.07−2.16 (m, 2 H), 2.92 (bs, 1 H, D_2O exchangeable), 3.03−3.11 (m, 1 H), 3.30−3.38 (ddd, 1 H, J = 4.5, 9.8, 10.3 Hz), 6.62 (d, 2 H, J = 8.7 Hz), 7.11 (d, 2 H, J = 8.7 Hz). EIMS (m/z) 225 (M^+).[8j]

***trans*-2-(4-Trifluoromethylphenylamino)cyclohexanol (entry 6, Table 3).** White solid, mp 100−102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07−1.47 (m, 4 H), 1.74−1.81 (m, 2 H), 2.05−2.14 (m, 2 H), 2.42 (bs, 1 H, D_2O exchangeable), 3.21−3.28 (m, 1 H), 3.40−3.48 (m, 1 H), 3.79 (bs, 1 H, D_2O exchangeable), 6.72 (d, 2 H, J = 7.9 Hz), 7.41 (d, 2 H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 24.8, 31.5, 33.3, 59.4, 74.6, 113.0, 119.0, 119.3, 119.6, 120.0, 123.4, 126.1, 126.60, 126.64, 126.68, 126.7, 150.5.[4a]

***trans*-Ethyl-4-(2-hydroxycyclohexylamino)benzoate (entry 7, Table 3).** White solid, mp 121−123 °C. IR (KBr) (ν_{max}/cm^{-1}): 3417, 3299, 2932, 2860, 1672, 1602, 1582, 1542, 1369, 1356, 1281, 1168, 1123, 1066, 835, 772. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08−1.45 (m, 7 H), 1.71−1.78 (m, 2 H), 2.08−2.11 (m, 2 H), 2.63 (bs, 1 H, D_2O exchangeable), 3.17−3.25 (m, 1 H), 3.36−3.41 (ddd, 1 H, J = 3.9, 9.4, 9.3 Hz), 4.03 (bs, 1 H, D_2O exchangeable), 4.31 (q, 2 H, J = 7.1 Hz), 6.63 (d, 2 H, J = 8.4 Hz), 7.85 (d, 2 H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 24.2, 24.7, 31.5, 33.4, 59.1, 60.2, 74.5, 112.4, 119.2, 131.5, 151.5, 166.8. EIMS (m/z) 263 (M^+). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.48; H, 7.99; N, 5.29.

***trans*-1-[4-(2-Hydroxycyclohexylamino)phenyl]ethanone (entry 8, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05−1.09 (m, 1 H), 1.23−1.44 (m, 3 H), 1.71−1.79 (m, 2 H), 2.08−2.16 (m, 2 H), 2.47 (s, 3 H), 2.77 (bs, 1 H), 3.21−3.27 (m, 1 H), 3.39−3.45 (ddd, J = 4.1, 9.5, 9.8 Hz, 1 H), 4.28 (bs, 1 H), 6.62 (d, J = 8.7 Hz, 2 H), 7.77 (d, J = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 24.7, 26.0, 31.5, 33.5, 59.0, 74.4, 112.3, 126.9, 130.8, 152.2, 196.6. EIMS (m/z) 233 (M^+).[40]

***trans*-4-(2-Hydroxycyclohexylamino)benzonitrile (entry 9, Table 3).** Low melting solid. IR ($CHCl_3$) (ν_{max}/cm^{-1}) 3359, 2211, 1606, 1525, 1339, 1172, 1065, 913, 824, 743. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18−1.46 (m, 4 H), 1.73−1.80 (m, 2 H), 2.08−2.12 (m, 2 H), 2.32 (bs, 1 H), 3.19−3.23 (m, 1 H), 3.39−3.45 (ddd, J = 4.1, 9.5, 9.8 Hz, 1 H), 4.14 (bs, 1 H), 6.65 (d, J = 8.7 Hz, 2 H), 7.39 (d, J = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 24.7, 31.4, 33.7, 58.9, 74.5, 99.0, 113.0, 120.3, 133.7, 151.3. MALDI (MS) (m/z) 216 (M^+). EIMS (m/z) 207 (M^+). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.24; H, 7.53; N, 12.97.

***trans*-2-(4-Nitrophenylamino)cyclohexanol (entry 10, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19−1.48 (m, 4 H), 1.67−1.82 (m, 2 H), 2.09−2.13 (m, 2 H), 2.38 (bs, 1 H), 3.14−3.32 (m, 1 H), 3.38−3.51 (ddd, J = 4.1, 9.4, 10.1 Hz, 1 H), 4.14 (d, J = 8 Hz,1 H), 6.61 (d, J = 9.2 Hz, 2 H), 8.04 (d, J = 9.2 Hz, 2 H). EIMS (m/z) 236 (M^+).[8a]

***trans*-4-(2-Hydroxycyclohexylamino)phenol (entry 11, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96−1.05 (m, 1 H), 1.21−1.42 (m, 3 H), 1.68−1.77 (m, 2 H), 2.06−2.13 (m, 2 H), 2.94−3.0 (m, 1 H), 3.30−3.36 (ddd, J = 4.0, 9.7, 9.8 Hz, 1 H), 6.62 (d, J = 8.7 Hz, 2 H), 6.69 (d, J = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 25.1, 31.5, 33.0, 61.8, 74.5, 116.2, 116.7, 141.3, 148.9.[8a]

***trans*-2-(*N*-Methylphenylamino)cyclohexanol (entry 14, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27−1.45 (m, 4 H), 1.70−1.80 (m, 3 H), 2.20−2.24 (m, 1 H), 2.78 (s, 3 H), 2.80 (bs, 1 H), 3.42−3.46 (m, 1 H), 3.65−3.71 (ddd, 1 H, J = 10.2, 9.9, 4.3 Hz),

6.83 (t, 1 H, J = 8.1 Hz), 6.97 (d, 2 H, J = 8.6 Hz), 7.25− 7.30 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 25.5, 26.0, 31.1, 33.3, 67.0, 70.0, 115.6, 118.5, 129.0, 151.4. EIMS (m/z) 205 (M^+).[8i]

***trans*-2-(Pyrrolidin-1-yl)cyclohexanol (entry 15, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20−1.24 (m, 4 H), 1.71−1.77 (m, 6 H), 2.07−2.10 (m, 1 H), 2.45−2.68 (m, 5 H), 3.31−3.35 (m, 1 H). EIMS (m/z) 169 (M^+).[6e]

***trans*-2-Morpholinocyclohexanol (entry 16, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18−1.27 (m, 4 H), 1.71−1.83 (m, 3 H), 2.12−2.21 (m, 2 H), 2.40−2.45 (m, 2 H), 2.70−2.74 (m, 2 H), 3.34−3.39 (m, 1 H), 3.67−3.76 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 24.0, 25.4, 33.1, 48.7, 67.5, 68.4, 70.5. EIMS (m/z) 185 (M^+).[6e]

***trans*-2-(Piperidin-1-yl)cyclohexanol (entry 17, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18−1.25 (m, 4 H), 1.43−1.59 (m, 6 H), 1.76−1.78 (m, 3 H), 2.10−2.13 (m, 2 H), 2.28−2.33 (m, 2 H), 2.65−2.67 (m, 2 H), 3.35−3.37 (m, 1 H). EIMS (m/z) 183 (M^+).[6e]

***trans*-2-(Phenylmethylamino)cyclohexanol (entry 18, Table 3).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95−1.05 (m, 1 H), 1.18−1.31 (m, 3 H), 1.71−1.74 (m, 2 H), 2.01−2.06 (m, 1 H), 2.15−2.18 (m, 1 H), 2.28−2.34 (m, 2 H), 3.18−3.24 (ddd, 1 H, J = 4.6, 9.9, 10.4 Hz), 3.70 (d, 1 H, J = 12.9 Hz), 3.97 (d, 1 H, J = 12.9 Hz), 7.24−7.35 (m, 5 H). EIMS (m/z) 205 (M^+).[6e]

2-Phenylamino-2-phenylethanol (entry 1, Table 6). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (dd, 1 H, J = 11.0, 7.0 Hz), 3.94 (dd, 1 H, J = 10.9, 4.0 Hz), 4.51 (dd, 1H, J = 6.9, 4.1 Hz,), 6.57 (d, 2 H, J = 8.0 Hz), 6.67 (t, 1 H, J = 7.3 Hz), 7.10 (t, 2 H, J = 7.4 Hz), 7.25−7.36 (m, 5 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.8, 67.3, 113.8, 117.9, 126.7, 127.6, 128.8, 129.1, 140.1, 147.2. EIMS (m/z) 213 (M^+).[6e]

2-(4-Methylphenyl)amino-2-phenylethanol (entry 2, Table 6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (s, 3 H), 3.71 (dd, 1 H, J = 11.0, 7.2 Hz), 3.91 (dd, 1 H, J = 10.8, 4.0 Hz), 4.46 (dd, 1 H, J = 7.4, 4.4 Hz), 6.49 (d, 2 H, J = 8.4 Hz), 6.90 (d, 2 H, J = 8.4 Hz), 7.22−7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 60.1, 67.3, 114.0, 126.7, 127.1, 127.5, 128, 130, 140.3, 144.9. EIMS (m/z) 227 (M^+).[6e]

2-(4-Chlorophenyl)amino-2-phenylethanol (entry 3, Table 6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (bs, 1 H, D_2O exchangeable), 3.71 (dd, 1 H, J = 10.7, 7.2 Hz), 3.92 (dd, 1 H, J = 11.4, 3.6 Hz), 4.42 (dd, 1 H, J = 6.6, 3.3 Hz), 6.45 (d, 2 H, J = 8.2 Hz), 7.02 (d, 2 H, J = 8.2 Hz), 7.22−7.33 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.9, 67.2, 11.4, 122.4126, 127.7, 128.4, 128.9, 139.6, 145.7. EIMS (m/z) 247 (M^+).[6e]

2-(4-Methoxyphenylamino)-2-phenylethanol (entry 4, Table 6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3 H), 3.70 (dd, 1 H, J = 11.4, 18.7 Hz), 3.89 (dd, 1 H, J = 4.2, 11.1 Hz), 4.41 (dd, 1 H, J = 4.2, 7.4 Hz), 6.52 (d, 2 H, J = 8.9 Hz), 6.79 (d, 2 H, J = 8.9 Hz), 7.23−7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.7, 60.8, 67.3, 114.7, 115.3, 126.7, 127.5, 128.8, 140.3, 141.3, 152.3. EIMS (m/z) 243 (M^+).[8e]

2-(2-Methoxyphenylamino)-2-phenylethanol (entry 5, Table 6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (bs, 1 H, D_2O exchangeable), 3.76 (dd, 1 H, J = 10.8, 7.3 Hz), 3.87 (s, 3 H), 3.89−3.93 (m, 1 H), 4.50 (dd, 1 H, J = 7.9, 4.7 Hz), 5.0 (bs, 1 H, D_2O exchangeable), 6.45 (dd, 1 H, J = 8.1, 1.48 Hz), 6.61−6.78 (m, 3 H), 7.22−7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.4, 59.8, 67.4, 109.4, 111.5, 117.1, 121.1, 126.7, 127.5, 128.7, 137.0, 140.2, 147.1. EIMS (m/z) 243 (M^+).[6a]

2-(2-Fluorophenylamino)-2-phenylethanol (entry 6, Table 6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (bs, 1 H, D_2O exchangeable), 3.75 (dd, 1 H, J = 7.0, 11.1 Hz), 3.91 (dd, 1 H, J = 4.1, 11.1 Hz), 4.49 (dd, 1 H, J = 4.4, 6.7 Hz), 4.74 (bs, 1 H, D_2O exchangeable), 6.45 (t, 1 H, J = 8.6 Hz), 6.56−6.61 (m, 1 H), 6.83 (t, 1 H, J = 7.6 Hz), 6.93−6.98 (m, 1 H), 7.22−7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.6, 67.2, 113.62, 113.62, 114.3, 114.5, 117.2, 117.3, 124.44, 124.48, 126.6, 127.7, 128.9, 135.6, 135.7, 139.7, 150.6, 153.0. EIMS (m/z) 231 (M^+).[37]

2-(2,6-Dimethylphenylamino)-2-phenylethanol (entry 7, Table 6). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 6 H), 3.88−3.95 (m, 2 H), 4.28 (t, 1 H, J = 5.3 Hz), 6.78 (d, 1 H, J = 7.4 Hz), 6.93 (d, 2 H, J = 7.4 Hz), 7.22−7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.5, 63.5, 66.4, 122.4, 126.4, 127.5, 128.1, 129.1, 129.5, 141.5, 144.9. EIMS (m/z) 241 (M^+).[4c]

2-(2,6-Diisopropylphenylamino)-2-phenylethanol (entry 8, Table 6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, 6 H, J = 6.8 Hz), 1.91 (d, 6 H, J = 6.8 Hz), 2.33 (bs, 1 H, D_2O exchangeable), 3.08−3.16 (m, 2 H), 3.88 (d, 2 H, J = 10.9, 4.9 Hz), 3.98 (d, 2 H, J = 10.9, 6.3 Hz), 4.06 (t, 1 H, J = 5.6 Hz), 7.01−7.05 (m, 3 H), 7.21−7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 24.1, 27.5, 65.3, 65.9, 123.6, 125.8, 127.1, 127.6, 128.6, 140.6, 141.2, 142.1. EIMS (m/z) 243 (M^+).[8e]

2-(*N*-Methylphenylamino)-2-phenylethanol (entry 9, Table 6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (bs, 1H, D_2O exchangeable), 4.16 (m, 2 H), 5.11 (dd, 1 H, J = 8.72, 6 Hz), 6.57 (d, 2 H, J = 8.0 Hz), 6.84 (t, 1 H, J = 7.2 Hz), 6.96 (d, 2 H, J = 7.9 Hz), 7.14−7.16 (m, 2 H), 7.26−7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.0, 61.6, 64.5, 114.8, 118.3, 127.1, 127.6, 128.5, 129.2, 137.4, 151.1. EIMS (m/z) 227 (M^+).[8b]

1-Chloro-3-phenylaminopropan-2-ol (entry 2, Table 7). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.62 (bs, 2 H), 3.21−3.27 (dd, 1 H, J = 7.6, 13.8 Hz), 3.363.41 (dd, 1 H, J = 4.4, 13.8 Hz), 3.58−3.70 (m, 2 H), 4.05−4.07 (m, 1 H), 6.66 (d, 2 H, J = 8.1 Hz), 6.76 (t, 1 H, J = 7.5 Hz), 7.20 (t, 2 H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.3, 47.6, 69.7, 113.5, 118.5, 129.4, 147.4.[6e]

1-(Phenylamino)-3-phenoxy-2-propanol (entry 3, Table 7). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.29−3.34 (dd, 1 H, J = 7.2, 12.2 Hz), 3.43−3.48 (dd, 1 H, J = 4.4, 12.1 Hz), 4.04−4.11 (m, 2 H), 4.25−4.29 (m, 1 H), 6.71 (d, 1 H, J = 7.6), 6.70−6.75 (m, 1 H), 6.95−7.04 (m. Three H), 7.21−7.34 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.6, 68.8, 70.0, 113.3, 114.5, 118.0, 121.3, 129.3, 129.6, 148.1, 158.4.[6e]

1-(4-Chlorophenylamino)-3-phenoxy-2-propanol (entry 4, Table 7). White solid, mp 83−85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (bs, 1 H), 3.28−3.33 (dd, 1 H, J = 6.8, 12.8 Hz), 3.42−3.47 (dd, 1 H, J = 4.4, 12.8 Hz), 3.00−4.07 (m, 3 H), 4.24−4.29 (m, 1 H), 6.68−6.88 (m, 5 H), 7.18−7.28 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.5, 68.7, 70.4, 113.3, 115.8, 118.1, 3126.2, 129.3, 129.4, 147.9, 157.0.[6e]

1-(Furan-2-ylmethoxy)-3-phenylaminopropan-2-ol (entry 5, Table 7). Oil. IR (DCM) (ν_{max}/cm^{-1}): 3447, 2919, 1636, 1260, 749. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.12−3.17 (dd, 1 H, J = 7.1, 12.8 Hz), 3.27−3.31 (dd, 1 H, J = 4.4, 12.8 Hz), 3.51−3.55 (dd, 1 H, J = 6.4, 9.6 Hz), 3.59−3.62 (dd, 1 H, J = 3.8, 9.6 Hz), 4.00−4.06 (m, 1 H), 4.52 (s, 2 H), 6.35−6.38 (m, 2 H), 6.64 (d, 2 H, J = 7.7 Hz), 6.72−6.75 (t, 1 H, J = 7.3 Hz), 7.17−7.21 (t, 2 H, J = 7.7 Hz), 7.44 (t, 1 H, J = 0.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.5, 65.2, 69.0, 72.2, 109.7, 110.3, 113.2, 117.7, 129.2, 143.0, 148.2, 151.3. EIMS (m/z) 247 (M^+). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 6.96; N, 5.70.

1-*tert*-Butoxy-3-phenylaminopropan-2-ol (entry 6, Table 7). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (s, 9H), 3.09−3.16 (dd, 1 H, J = 6.8, 12.4 Hz), 3.27 (dd, 1 H, J = 4.2, 12.5 Hz), 3.36−3.50 (m, 3 H), 3.93− 3.96 (m, 1 H), 6.64 (d, 2 H, J = 8.0 Hz), 6.70 (t, 1 H, J = 7.2 Hz), 7.16 (t, 2 H, J = 7.5 Hz).[6e]

Ethyl 3-phenylaminopropionate (entry 7, Table 7). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 3 H, J = 7.2 Hz), 4.11−4.19 (m, 2 H), 4.63−4.64 (d, 1 H, J = 3.6 Hz), 4.84−4.85 (d, 1 H, J = 3.6 Hz), 6.58−6.67 (m, 3 H), 7.05−7.11 (m, 2 H), 7.20−7.33 (m, 5 H).[6e]

■ ASSOCIATED CONTENT

Supporting Information. 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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