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Thiourea catalyzed aminolysis of epoxides under solvent free conditions. Electronic control of regioselective ring opening

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ABSTRACT

A reactant economizing process for the regioselective aminolysis of epoxides using equimolar quantities of reactants catalyzed by the double hydrogen bond donor *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea is reported. Regioselectivity of the reaction is controlled by the electronic nature of the substituent on the styrene oxide, which has been substantiated on the basis of ^{13}C NMR data and DFT calculations.

1. Introduction

Metal based catalysis has been the mainstay of the traditional strategies for the activation of the electrophilic species toward nucleophilic attack. Recently, general acid catalysis with double hydrogen bond donors has emerged as a convenient alternative for electrophile activation in organic synthesis.[1] Hydrogen bond donors use a mode of activation, that is, common in enzyme catalysis; for example, in the action of epoxide hydrolase, tyrosine residues are involved in epoxides activation through hydrogen bonding.[2] Urea and thiourea derivatives can activate oxygen containing functional groups, as has been demonstrated in the seminal work of Curran[3,1e] and subsequent studies by Jacobson[3c] and Schreiner.[3d,1e] As recently reported, epoxide ring opening in water suffers from poor regioselectivity[4a] as well as long reaction time;[4a,b] at the same time regioselective alcoholysis of styrene epoxide has been obtained using twelve times the stoichiometric excess of the nucleophile.[4c] A study by Saidi and Azizi[5] concerning the addition of amines to epoxides in water reveal that aromatic amines react sluggishly to provide adducts in low yields. Connon and co-workers have demonstrated the application of *N*-tosyl urea catalyst in a limited study of the aminolysis of styrene oxide with aromatic amines.[6] In order to systematically evaluate the catalysis by thiourea derivatives we planned to study the ring opening of different epoxides with variety of aromatic amines. Further, due to our interest in developing environmentally benign processes we planned to use solvent free conditions and low molar equivalent of the reactants. Herein, we report, a solvent less process for the regioselective epoxide ring opening reaction using equimolar amount of amine and the epoxide catalyzed by *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea yielding β-amino alcohols in quantitative yields. To gain further insights and account for the observed regioselectivities, DFT based quantum chemical calculations at B3LPY/6-31+G(d) level have been performed.

The significance of the present study stems from the importance of β-amino alcohols, which are important intermediates in the synthesis of a large number of biologically active natural and synthetic products: for example, in the synthesis of β_2-adrenoreceptor agonists,[7a] *anti* HBV-agents,[7b] *anti*-malarial agents,[7c] taxol side chains,[7d] liposidomycin B class of antibiotics,[7e] glycosidase inhibitors,[7f] naturally occurring brassinosteroids,[7g] unnatural amino acids,[7h,i] and chiral auxiliaries.[7j]

2. Results and discussion

Initially the aminolysis of styrene oxide **1a** (1 mmol) with aniline **2a** (1 mmol) was chosen as a model reaction and the effect of different urea and thiourea catalysts under solvent free conditions was investigated at 60 °C (Table 1). We preferred to screen different diarylurea and diarylthiourea derivatives to observe their catalytic abilities under solvent free condition, in the hope of identifying other urea and thiourea derivatives with comparable catalytic effects under these conditions as *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea. The experimental results in Table 1 show that thiourea derivatives are better catalysts than urea derivatives, giving almost complete conversion to products. This difference in their catalytic ability stems from the inherent ability of sulfur to stabilize the negative charge, which increases the hydrogen bond donor ability of thiourea derivatives relative to urea derivatives. The difference is also reflected in their acidities, for example, diphenylthiourea (pK_a=13.5) is more acidic than diphenylurea (pK_a=19.5).[8] In addition, self association of thiourea molecules is less favorable due to the lower electronegativity

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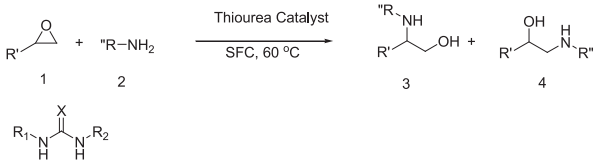
Table 1
Screening of various urea and thiourea catalysts for aminolysis of styrene epoxide (**1a**)

Entry	Catalyst	Time (h)	**3**:**4**[c]	Conversion[c] (%)
1[a]	**5**	3.00	65:30	20
2[a]	**6**	3.00	73:27	68
3[a]	**7**	20 min	81:19	>99
4[a]	**8**	20 min	85:15	>99
5[a]	**9**	3.00	78:22	43
6[b]	**10**	5.00	79:21	70
7[b]	**11**	3.50	83:17	90
8[a]	**12**	5 min	90:10	100
9[b]	**12**	2.75	85:15	100

[a] Amount of catalyst −30 mol %.
[b] Amount of catalyst −5 mol %.
[c] Determined by ^{1}H NMR spectroscopy.

of sulfur. The low conversion in the case of thiourea **10** is probably due to its inability to homogenize with the reaction mixture. Our results reveal that as the electron withdrawing nature of aromatic ring substituents of both urea and thiourea derivatives increases, so does the rate of the reaction. *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea emerged as the best catalyst for this transformation (Table 1, entry 8). It catalyzes the reaction in 5 min when used in 30 mol %, we therefore planned further studies with this catalyst.



(**5**) R_1 = Ph, R_2 = Ph, X = O
(**6**) R_1 = Ph, R_2 = Ph, X = S
(**7**) R_1= *p*-$NO_2C_6H_4$ -, R_2 = Ph, X = S
(**8**) R_1= 3,5- $(CF_3)_2C_6H_3$ -, R_2 = Ph, X = S
(**9**) R_1 = R_2 = *p*-$NO_2C_6H_4$ -, X = O
(**10**) R_1 = R_2 = *p*-$NO_2C_6H_4$ -, X = S
(**11**) R_1 = 3,5-$(CF_3)_2C_6H_3$ -,R_2 = *p*-$NO_2C_6H_4$ -, X = S
(**12**) R_1 = R_2 = 3,5-$(CF_3)_2C_6H_3$ -, X = S

Optimizing the amount of catalyst shows that on decreasing the amount of catalyst from 30 to 5 mol %, there is slight change in regioselectivity, but at 1 mol % regioselectivity decreases (**3**:**4**; 71:29) significantly. The decrease in regioselectivity is probably due to the contribution from the un-catalyzed reaction. Thus for all subsequent reactions 5 mol % catalyst was used.

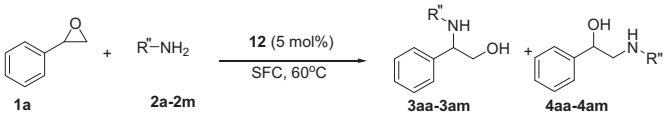
Optimizing the reaction temperature (Table 2) shows that as the temperature increases the rate of our model reaction also increases without affecting the regioselectivity; at 60 °C the reaction completes in 2.75 h. But we were troubled by the general belief that hydrogen bonding interactions are weak at higher temperatures. So, in order to know the role of catalyst **12** we performed the reaction using equimolar amounts of styrene oxide and aniline in the absence of catalyst at 60 °C. We found that in the absence of catalyst it takes 18 h for the reaction to complete to 98%. This does suggest that the catalyst **12** activates the epoxide under solvent free conditions at a higher temperature. In addition to the differences in reaction time, the catalyzed and un-catalyzed reactions also show differences in regioselectivities (Table 3, entry 1 and 2, Table 4, entry 1 and 2, entry 6 and 7). The catalyzed reaction shows higher regioselectivity in

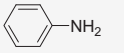
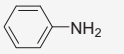
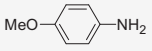
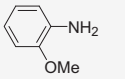
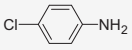
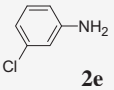
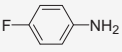
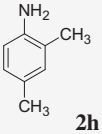
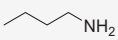
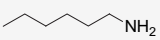
Table 2
Effect of temperature on the aminolysis of styrene oxide catalyzed by **12**

Entry	Temperature (°C)	Time (h)	**3**:**4**[a]	Conversion[a] (%)
1	70	2.50	75:25	100
2	60	2.75	85:15	100
3	50	3.50	85:15	100
4	40	12.00	85:15	84
5	27	18.00	85:15	100

[a] Determined by ^{1}H NMR spectroscopy.

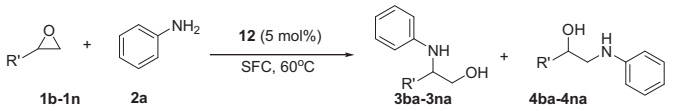
Table 3
Aminolysis of styrene oxide by alkyl- and aryl amine catalyzed by **12** under solvent free conditions at 60 °C



Entry	Amine	Time (h)	**3**:**4**[a]	Yield[b](%)	TON/TOF[10]
1	 **2a**	2.75	85:15	96	19.2/6.98
2[c]	 **2a**	18.00	70:30	85	—
3	 **2b**	1.00	80:20	97	19.4/19.4
4	 **2c**	1.75	80:20	96	19.2/10.9
5	 **2d**	3.00	87:13	87	17.4/5.8
6	 **2e**	7.00	83:17	93	18.6/2.65
7	 **2f**	4.00	85:15	90	18.0/4.5
8	 **2g**	7.00	84:16	78	15.6/2.23
9	 **2h**	7.00	84:16	75	15.0/2.14
10	 **2i**	5.00	82:18	95	19.0/3.8
11	 **2j**	1.00	30:70	92	18.4/18.4
12	 **2k**	1.00	30:70	94	18.8/18.8
13	 **2l**	1.75	17:83	94	18.8/10.7
14	 **2m**	2.00	19:81	95	19.0/9.5

[a] Determined by ^{1}H NMR spectroscopy.
[b] Isolated yield after chromatography.
[c] Reaction performed in the absence of catalyst.

Table 4
Ring opening of epoxides by aniline catalyzed by **12** under solvent free conditions at 60 °C



1b-1n 2a 3ba-3na 4ba-4na

Entry	R′	Time (h)	**3:4**[a]	Yield[b] (%)	TON/TOF[10]
1	*p*-OMeC$_6$H$_4$– (**1b**)	0.2	>99:<1	95	19/95
2[c]	*p*-OMeC$_6$H$_4$– (**1b**)	1.5	97:3	93	—
3	*p*-MeC$_6$H$_4$– (**1c**)	0.5	87:13	94	18.8/37.6
4	*p*-FC$_6$H$_4$– (**1d**)	4.0	86:14	94	18.8/4.7
5	*p*-ClC$_6$H$_4$– (**1e**)	4.0	86:14	93	18.6/4.65
6	*p*-NO$_2$C$_6$H$_4$– (**1f**)	6.5	30:70	83	16.6/2.5
7[c]	*p*-NO$_2$C$_6$H$_4$– (**1f**)	24.0	18:82	84	—
8	*m*-NO$_2$C$_6$H$_4$– (**1g**)	6.5	30:70	84	16.8/2.58
9	C$_6$H$_5$OCH$_2$– (**1h**)	3.5	0:100	80	16/4.57
10	*o*-MeC$_6$H$_4$OCH$_2$– (**1i**)	3.5	0:100	81	16/4.62
11	*m*-Me C$_6$H$_4$OCH$_2$– (**1j**)	3.5	0:100	80	16/4.57
12	*p*-MeC$_6$H$_4$OCH$_2$– (**1k**)	3.5	0:100	80	16/4.57
13	*p*-Cl C$_6$H$_4$OCH$_2$– (**1l**)	3.5	0:100	80	16/4.57
14	CH$_2$=CHCH$_2$OCH$_2$– (**1m**)	6.0	0:100	72	14.4/2.4
15	CH$_3$(CH$_2$)$_8$CH$_2$– (**1n**)	45.0	0:100	90	18.6/0.41

[a] Determined by ^{1}H NMR spectroscopy.
[b] Isolated yield after chromatography.
[c] Reaction performed in the absence of catalyst.

favor of **3**, which is formed as a result of the attack of amine nitrogen on C$_\alpha$ of epoxide.[9] This indicates the role of thiourea in enhancing the regioselectivity of the reaction. To obtain further evidence, we envisaged the use of additives, which form strong hydrogen bonds with hydrogen bonding donor motifs, and thus can inhibit the reaction. The model reaction was therefore performed in the presence of 5 mol % DMSO, which was equimolar to the amount of catalyst **12**. In 2.75 h only 69% of reaction occurred, while after 6 h the completion was 90%. In another similar experiment, the addition of 100 mol % of DMSO resulted in the formation of trace amounts of adduct after 2.75 h, while after 24 h the conversion was only 30%. These experiments clearly show that the catalyst **12** activates the epoxide ring and facilitates the adduct formation with aniline at 60 °C.

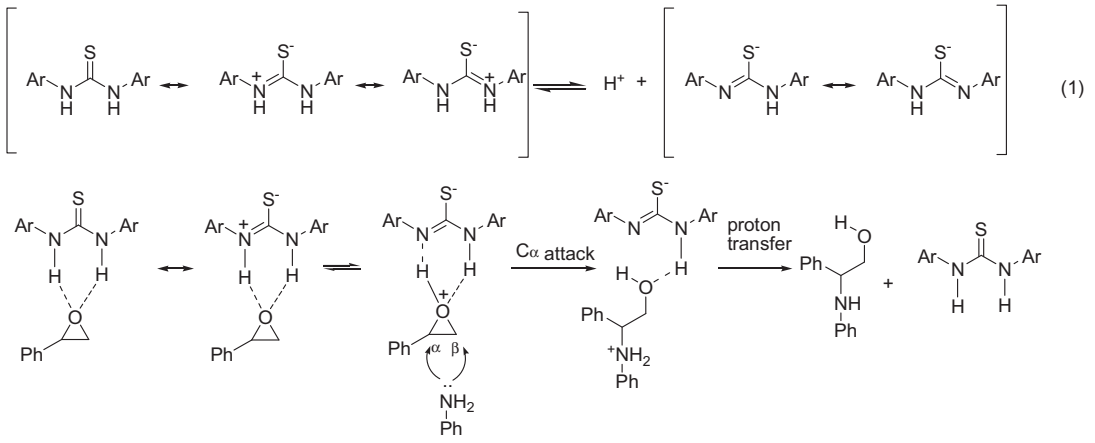
The epoxide ring activation by the thiourea catalyst toward the nucleophilic attack is due to electronic features of the thiourea catalyst. The electron withdrawing group containing phenyl substituents on the nitrogen atom of thiourea and the inherent ability of sulfur to stabilize the negative charge (eq. 1) increases the acidity of N–H bond.[8] Thus the mode of activation of the epoxide ring may be rationalized on the basis of the highly polarized N–H bond, which may undergo dissociation to provide a proton at higher temperatures as shown in Scheme 1.

Further optimization of the reaction conditions by increasing the amount of amine had negligible effect on the rate of the reaction. At the same time it resulted in decreased regioselectivity. This clearly indicates that the catalyst controls the rate as well as the regioselectivity of the reaction. Thus, stirring a mixture of epoxide, amine, and catalytic amount of **12** at 60 °C provides optimal conditions for this transformation.

Under the optimized conditions, the aminolysis of styrene oxide with various amines shows that the aromatic amines preferably attack at the benzylic position (C$_\alpha$) of epoxide, whereas the aliphatic amines attack at the less hindered methylene carbon (C$_\beta$) of the epoxide (Table 3). Anilines with electron donating as well as electron withdrawing groups, such as Me, OMe, Cl, F, were well tolerated and gave the corresponding β-amino alcohols in quantitative yields. Even sterically hindered amines, such as *o*-methyl-aniline, *o*-methoxyaniline, 2,4-dimethylaniline, and α-napthylamine also react smoothly. However, the rate of the reaction depends strongly on the nucleophilicity of the amine so that as the nucleophilicity of the amine decreases, the rate also decreases.

This protocol was extended to the aminolysis of other styrene oxide derivatives and alkyl-1,2-epoxides (Table 4). The aminolysis of styrene oxide derivatives shows that substituents exert a significant effect on the direction as well as the rate of ring opening. The electron donating substituents on the styrene oxide ring increase the rate of reaction (Table 4, entry 1 and 3), while the electron withdrawing substituents decrease the rate (Table 4, entry 4–6 and 8). 4-Methoxy-, 4-methyl-, 4-fluoro-, and 4-chloro-styrene oxides gave products with regioselectivity in line with styrene oxide (Table 4, entries 1, 3–5). Surprisingly, 3-nitro- and 4-nitro-styrene oxide gave products with reversal of regioselectivity[11] (Table 4, entries 6 and 8). This reversal of regioselectivity can be attributed to electronic factors. In case of alkyl-1,2-epoxides, excellent yields of desired β-amino alcohols were obtained (Table 4, entries 9–15). In aliphatic epoxides both steric and electronic factors facilitate the attack of amine at the less hindered β-carbon of the epoxide ring. Further, in the case of glycidyl ethers (**4h**–**4m**) the hydrogen bonding between the ethereal oxygen and amine provides the favorable positioning of amine for attack at β-carbon via six-membered cyclic intermediate.[12]

The substituent dependent reversal of regioselectivity of nucleophilic addition to styrene oxide derivative originates from the activation of the epoxide ring by a thiourea catalyst. The hydrogen bond donor activation of the epoxide ring results in the activation of both C$_\alpha$–O and C$_\beta$–O bonds. The incipient positive charge on α-carbon is stabilized due to conjugation with the phenyl ring, which leads to the activation and elongation of C$_\alpha$–O, with respect to the C$_\beta$–O bond. Thus the nucleophile preferentially attacks at the α-carbon.[11] However, under the powerful electron-withdrawing



Scheme 1.

effect of the nitro group, the conjugative stabilization of the positive charge on C_α is inhibited, which deactivates the C_α toward nucleophilic attack, consequently the nucleophile then preferably reacts at C_β, although at a slow rate.

Further, ^{13}C NMR spectroscopy provides a useful measure of electron density on the carbon atom. The upfield chemical shift of carbon resonance corresponds to higher electron density and hence greater shielding of the carbon nuclei. The comparison of the ^{13}C NMR resonance of C_α and C_β of the substituted styrene oxides (Table 5) shows that C_α-carbon resonates downfield than C_β-carbon except in the case of nitrostyrene oxide. Thus the lower electron density at C_β in nitrostyrene oxide makes it the preferred site for nucleophilic attack. The difference in chemical shift of C_α and C_β, $\Delta\delta_{(C\alpha-C\beta)}$ can be correlated with regioselectivity of the nucleophilic epoxide ring opening reaction. In case of nitro derivatives the $\Delta\delta$ is the reverse of that obtained with substituted styrene oxides that have positive $\Delta\delta$ values (Table 5).

Table 5
^{13}C NMR resonance of C_α and C_β carbons of styrene oxide and its derivatives

Epoxide	$\delta_{(C\alpha)}$	$\delta_{(C\beta)}$	$\Delta\delta_{(C\alpha-C\beta)}$
1a	52.11	50.97	1.14
1b	51.96	50.70	1.26
1c	52.28	51.02	1.26
1d	51.79	51.11	0.68
1e	51.53	50.96	0.43
1f	51.39	51.63	−0.24

In order to obtain atomic level details of the model reaction and to estimate the thermodynamic versus kinetic control on the reaction, quantum chemical calculations have been performed. The epoxides **1a**, **1b**, and **1f** have been chosen as representative epoxides; reaction with aniline (**2a**) in the presence of the unsubstituted thiourea (**13**) was studied using B3LYP/6-31+G(d) method.

Since, under the studied experimental conditions it is evident that the activation of epoxide by thiourea takes place prior to the nucleophilic attack by aniline, it is necessary to study the complexation of thiourea with various epoxides to understand the potential energy surface of the nucleophilic epoxide ring opening. The stabilization energy due to complexation of thiourea (**13**) with **1a**, **1b**, and **1f**, respectively, are 6.31, 6.76, and 4.40 kcal/mol. This can be traced to the electron density (charge) on the bridging oxygen atom of the epoxides: −0.554 (**1a**), −0.557 (**1b**), and −0.546 **(1f)**. The greater the charge on the O-atom of the epoxide, the greater is the complexation energy. The complexation energy in *p*-nitrostyrene oxide is much less than styrene oxide and *p*-methoxystyrene oxide, co-relatable to the relatively low rate of reaction. Also, the complexation energy in *p*-methoxystyrene oxide is largest among the three and again co-relatable to the highest rate of the reaction observed in the experimental conditions.

Complexation with H^+ has been shown to increase the C–O bond length in epoxides like 2-methyl-1,2-epoxypropane,[13] however only a marginal lengthening of C–O bond lengths (~0.01 Å) has been observed for the epoxide–thiourea complexes. Notable changes have been observed in the atomic charges at α (positive) and β (negative) carbons of the epoxide upon complexation with thiourea. The electron density at both the carbons marginally decreased due to complexation with thiourea, however the difference between the atomic charges at α and β carbons are deterministically modulated. The positive charge at both the carbons marginally increases due to complexation. NBO charge analysis shows that the charge difference between α and β carbons in styrene oxide–thiourea complex is 0.168, which decreases to 0.154 in *p*-nitrostyrene oxide–thiourea complex but increases marginally to 0.171 in *p*-methoxystyrene oxide–thiourea complex (Table 6). This analysis indicates that the charge balance at α and β carbons in styrene oxide–thiourea complex is differentially modulated by nitro and methoxy groups at the *para*-position of phenyl ring in styrene oxide–thiourea complex. Though these values are very small, they seem to contribute to the delicate balance between α and β preference for nucleophilic attack and the trends are in line with experimental observations.

Table 6
NBO Charge analysis of the epoxide, epoxide–thiourea complexes and the transition states at B3LYP/6-31+G(d)

Mol.	α-C	β-C	O	S
Epoxide				
1a	0.038	−0.130	−0.554	
1b	0.040	−0.133	−0.557	
1f	0.030	−0.124	−0.546	
Epoxide–thiourea complexes				
C1a	0.044	−0.124	−0.590	−0.290
C1b	0.045	−0.126	−0.595	−0.293
C1f	0.034	−0.120	−0.577	−0.266

Compounds **1a**, **1b**, and **1f** correspond to styrene, *p*-methoxystyrene, and *p*-nitrostyrene oxide, respectively; **C1a**, **C1b**, **C1f** epoxide–thiourea complexes.

Further, following trends have been observed during the analysis of the potential energy surface of the epoxide ring opening reaction (Fig.1, Table 7).

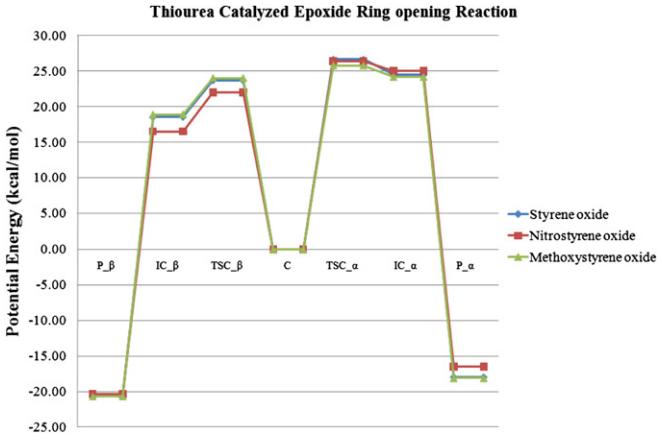


Figure 1. Comparison of the potential energy surface of the thiourea catalyzed epoxide ring opening reaction. C: Epoxide–thiourea complex, TSC: TS of catalyzed reaction, IC: Intermediate in the catalyzed reaction, P: Product (β-amino alcohol).

Table 7
Transition state barriers (kcal/mol) for the catalyzed and un-catalyzed epoxide ring opening reaction with anilne

R=	Ph			MeOPh			NO_2Ph		
	α	β	α−β	α	β	α−β	α	β	α−β
Un-catalyzed	39.24	33.61	5.63	38.51	34.04	4.47	39.28	32.04	7.59
Catalyzed	26.68	23.73	2.95	25.77	24.03	1.74	26.41	22.01	4.40
Difference	12.56	9.88		12.74	10.01		12.87	10.03	

Thiourea stabilizes the transition state leading to the products by about ~12 kcal/mol. The intermediates are stabilized to a similar extent. For the aliphatic class of epoxides the β-attack is favored over the α-attack (on kinetic scale) by ~2.5 kcal/mol in the un-catalyzed reaction. This difference is only marginally affected in the catalyzed reaction. (See Supplementary data).

The nucleophilic attack can take place on α as well as β carbons of the epoxide. In styrene epoxide the barrier for α-attack (39.24 kcal/mol) is only marginally larger than that of β-attack (33.61 kcal/mol) under un-catalyzed conditions. This indicates that there is a delicate balance between α and β nucleophilic attacks, supporting the observed experimental trends. This balance gets further delicate under the catalytic conditions as the difference between barriers in α and β paths gets reduced from 5.63 to 2.95 kcal/mol. Electron releasing groups like methoxy show a decrease in the difference of the reaction barrier (4.47 kcal/mol for un-catalyzed and 1.74 kcal/mol for catalyzed reaction), while electron withdrawing substituents like nitro lead to an increase in this difference (7.59 kcal/mol for un-catalyzed and 4.40 kcal/mol for catalyzed reaction).

In catalyzed reaction the barrier for the α-attack is reduced to a greater extent than that of β-attack (Table 7), showing that in the presence of thiourea catalyst the preference for α-attack is increased. These results are in accordance with our experimental observations (Fig. 2).

The nucleophilic attack follows an S_N2 mechanism thus as the nucleophile approaches the epoxide carbons C–O bond elongation takes place. The C–O bond elongation during α-attack is relatively larger than that of C–O bond elongation during β-attack. The O–C–C angles in the transition state structure are also significantly different during α-attack (~97°) in comparison to β-attack (~87°). The transition state is achieved relatively late in the case of α-attack (C···N distance ~1.92 Å) in comparison to the β-attack (C···N distance ~1.95 Å). All these geometric details indicate that the transition structures during α-attack are relatively more close to that of intermediates during the α-attack in comparison to β-attack.

Also the comparison of the C_α–O bond lengths in *p*-nitrostyrene oxide (2.12 Å), styrene oxide (2.16 Å) and *p*-methoxystyrene oxide (2.19 Å) during the α-attack shows the greatest elongation of C_α–O in *p*-methoxystyrene oxide. This shows that there is higher preference for α-attack in *p*-methoxystyrene oxide.

Thus from the above discussion it can be summarized that, the nucleophilic attack can take place at both α and β carbons in aromatic epoxides. On purely electrostatic count the attack at α position should be preferred. However, steric factors seem to counter the preference due to electrostatic factors. The barrier for the nucleophilic (aniline) attack at α position in styrene oxide is 26.68 kcal/mol and for the attack at β position is 23.73 kcal/mol, thus preference for β-attack is 2.95 kcal/mol in terms of energy. However, this preference gets reduced to 1.74 kcal/mol in *p*-methoxystyrene oxide but increases to 4.40 kcal/mol in the *p*-nitrostyrene oxide. Also the comparison of the bond lengths shows the marginal elongation of C_α–O in *p*-methoxystyrene oxide. This clearly indicates that the balance in the α/β product ratios gets opposite due to nitro and methoxy substitution.

3. Conclusion

In conclusion, we have developed a reactant economizing and environmentally benign process for the regioselective aminolysis of epoxides using equimolar quantities of reactants under solvent free conditions catalyzed by *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea catalyst. The study reveals the electronic control of regioselective ring opening of substituted styrene oxides as substantiated by ^{13}C NMR data and DFT based quantum chemical calculations at B3LPY/6-31+G(d) level.

4. Experimental

4.1. General

NMR spectra were obtained at 300 MHz (JEOL AL-300) using either $CDCl_3$ as solvents with Me_4Si in $CDCl_3$ as internal standard. The chemical shifts are reported in δ values relative to TMS and coupling constants (J) are expressed in hertz. Spectral patterns are designated as s=singlet; d=doublet; dd=doublet of doublets; q=quartet; t=triplet; br=broad; m=multiplet. Carbon NMR spectra were recorded on the same instrument (75.45 MHz) with total proton decoupling. High-resolution mass spectra (HRMS) were recorded with a Micromass Q-TOF mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on either (i) aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck, India) or (ii) glass plates (7.5×2.5 cm) coated with silica gel GF-254 (Spectrochem India) containing 13% calcium sulfate as binder and various combinations of ethyl acetate and hexane were used as eluents. Visualization of the spots was accomplished by exposing to UV light or iodine vapors. Column chromatography was performed on Acme's silica gel (60–120 mesh) using mixture of ethyl acetate and hexane as eluent. β-Amino alcohols **3aa**,[14a] **3ab**,[14b] **3ac**,[14c] **3ad**,[14a] **3ag**,[14a] **3ai**,[4b] **3aj**,[14b] **3ak**,[14d] **3al**,[14b] **3am**,[14e] and **3ha**[14a] were identified by comparing their spectral data with that reported in the literature.

Ab initio DFT calculations have been performed using B3LYP method and 6-31+G(d) basis set. Complete optimization of all the systems under consideration has carried out using Gaussian03 suite of programmes.[15] Analytical frequencies have been estimated by carrying out frequency calculations at the B3LYP/6-31+G(d) level to characterize the optimized structures as minima or transition state (one negative frequency) on the potential energy surface. The estimated zero point vibrational energy (ZPVE) values have been scaled by 0.9806[16] and employed in correcting the absolute energy values. Partial atomic charges have been estimated by performing Natural Bond Orbital (NBO) analysis.[17]

4.2. General procedure for the nucleophilic ring opening reaction

To a 10 ml RBF amine (1 mmol), epoxide (1 mmol) and thiourea catalyst were consecutively added and the resulting mixture was stirred at 60 °C for the time indicated. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was loaded on the chromatography column and eluted with mixture of ethyl acetate and hexane to obtain the pure regioisomers.

*4.2.1. 2-(3′-Chlorophenylamino)-2-phenylethanol (**3ae**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.50; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3404, 3062, 3028, 2926, 2875, 1597, 1485; ^1H NMR (300 MHz, $CDCl_3$): δ 1.60–1.95 (br s, 1H, OH), 3.74 (dd, J=6.6 and 11.1 Hz, 1H, CH_2), 3.93 (dd, J=4.2 and 11.1 Hz, 1H, CH_2), 4.45 (dd, J=4.2 and 6.6 Hz, 1H, CH), 6.39–6.43 (m, 1H, ArH), 6.53 (t, J=2.1 Hz, 1H, ArH), 6.61–6.64 (m, 1H, ArH), 6.98 (t, J=8.1 Hz, 1H, ArH), 7.25–7.36 (m, 6H, ArH, NH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 59.6, 67.2, 111.9, 113.5, 117.6, 126.6, 127.8, 128.7, 128.8, 130.1, 134.8, 139.4, 148.3; MS (m/z): 247, 249 (M^+, 3:1).

*4.2.2. 2-(4′-Fluorophenylamino)-2-phenylethanol (**3af**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.45; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3386, 3061, 3030, 2926, 2876, 1614, 1510; ^1H NMR (300 MHz, $CDCl_3$): δ 2.40–2.90 (br s, 2H), 3.64 (dd, J=6.9 and 11.4 Hz, 1H, CH_2), 3.84 (dd, J=4.2 and 11.4 Hz, 1H, CH_2), 4.32 (dd,

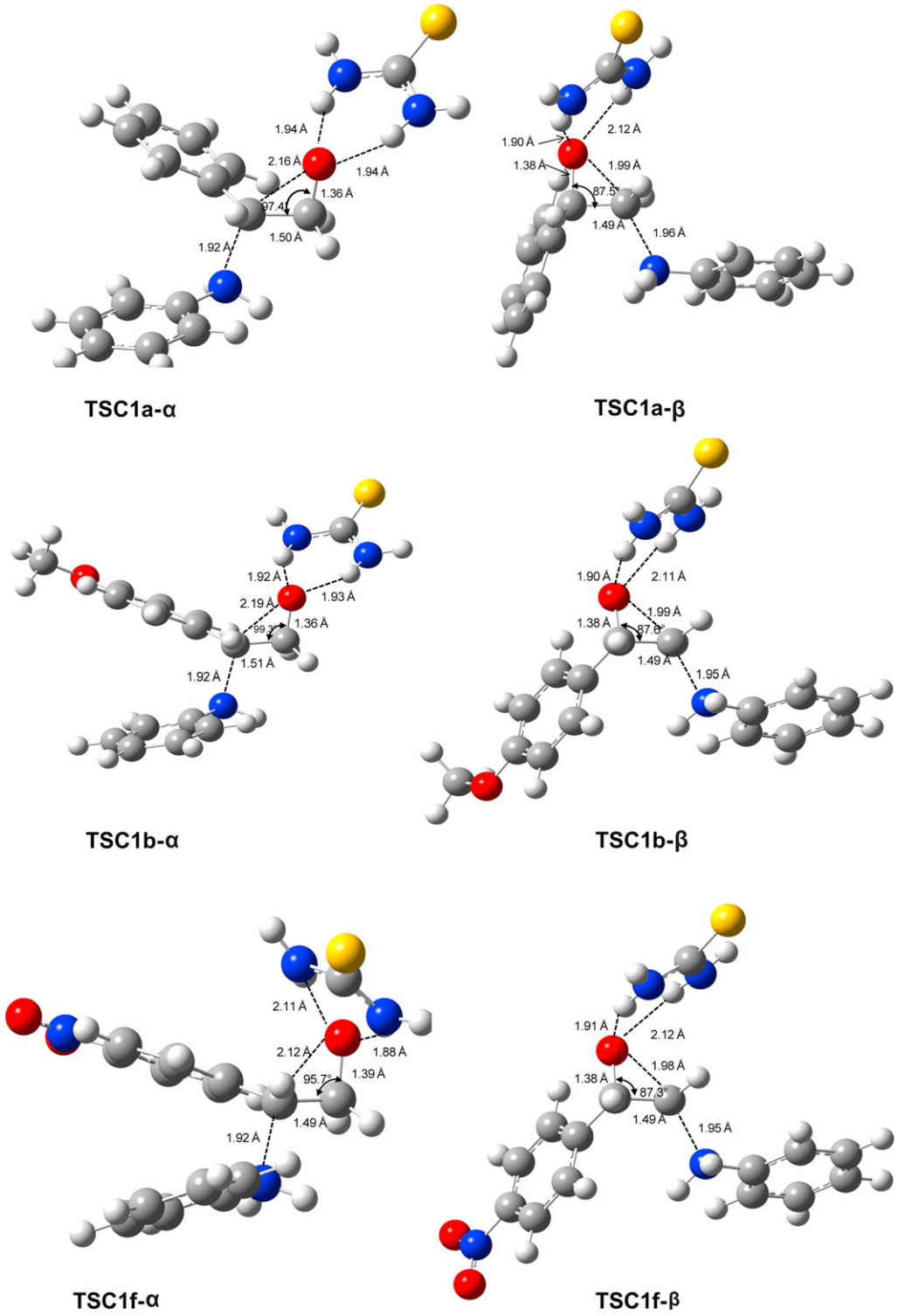


Figure 2. Structures of the transition states along the path of aniline attack on **1a**, **1b**, and **1f** epoxide–thiourea complex. The geometrical parameters are obtained at B3LYP/6-31+G(d) level, distances are in Å units and angles in degrees.

J=4.2 and 6.9 Hz, 1H, CH), 6.35–6.42 (m, 2H, ArH), 6.65–6.77 (m, 2H, ArH), 7.16–7.32 (m, 5H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): (52.8), 60.1, 67.1, (72.2), 114.9, 115.0, 115.4, 115.6, 115.9, 125.8, 126.7, 126.9, 127.7, 128.0, 128.5, 128.6, 128.8, 139.7, 143.2, 154.5, 157.6; HRMS: calculated for $C_{14}H_{14}FNO$ 254.0957 $[M+Na]^+$; found 254.0943.

*4.2.3. 2-(2′,4′-Dimethylphenylamino)-2-phenylethanol (**3ah**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.46; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3402, 3062, 3026, 3005, 2921, 2858, 1619, 1513; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (dd, *J*=7.2 and 11.1 Hz, 1H, CH_2), 3.94 (dd, *J*=4.2 and 11.1 Hz, 1H, CH_2), 4.70 (dd, *J*=4.2 and 7.2 Hz, 1H, CH), 6.22 (d, *J*=8.1 Hz, 1H, ArH), 6.57 (d, *J*=8.1 Hz, 1H, ArH), 6.68–6.71 (m, 1H, ArH), 7.20–7.34 (m, 5H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): (17.4), 17.6, 20.4, 52.2, 60.2, 67.4, 72.2, (111.1), 111.9, 122.7, (123.0), 125.8, 126.7, 127.2, 127.3, 127.4, 127.5, 127.9, 128.8, 130.1, 131.2, 140.4, 142.6,

143.1, 127.7, 128.0, 128.5, 128.6, 128.8, 139.7, 143.2, 154.5, 157.6; HRMS: calculated for $C_{16}H_{19}NO$ 264.1364 $[M+Na]^+$; found 264.1351.

*4.2.4. 2-(4′-Methoxyphenyl)-2-(phenylamino)ethanol (**3ba**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.48; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3395, 3051, 2933, 2836, 1603, 1510; ^1H NMR (300 MHz, $CDCl_3$): δ 3.20–3.50 (br s, 2H), 3.62 (dd, 1H, J=7.5, and 11.0 Hz, CH_2), 3.72 (s, 3H, OCH_3), 3.80 (dd, J=4.2 and 11.1 Hz, 1H, CH_2), 4.38 (dd, J=4.2 and 7.5 Hz, 1H, CH), 6.52–6.55 (m, 2H, ArH), 6.63–6.65 (m, 1H, ArH), 6.68–6.84 (m, 2H, ArH), 7.04–7.10 (m, 2H, ArH) 7.19–7.24 (m, 2H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 55.1, 59.2, 67.2, 113.8, 114.1, 117.7, 127.7, 129.0, 132.0, 147.2, 158.8; HRMS: calculated for $C_{15}H_{17}NO_2$ 266.1157 $[M+Na]^+$; found 266.1161.

*4.2.5. 2-(4′-Methylphenyl)-2-(phenylamino)ethanol (**3ca**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.55; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3395, 3021, 2923, 2870, 1602, 1504; ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.24–3.33 (br s, 2H, NH, OH), 3.63 (dd, J=7.2 and 11.1 Hz, 1H, CH_2), 3.82 (dd, J=4.2 and 11.1 Hz, 1H, CH_2), 4.40 (dd, J=4.2, and 7.2 Hz, 1H, CH), 6.53 (d, J=7.8 Hz, 2H, ArH), 6.65 (t, J=7.5 Hz, 1H, ArH), 7.04–7.11 (m, 4H, ArH), 7.14–7.25 (m, 2H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 21.0, 59.6, 67.2, 113.8, 117.7, 126.5, 129.0, 129.2, 129.4, 137.0, 137.1, 147.3; HRMS: calculated for $C_{15}H_{17}NO$ 250.1208 $[M+Na]^+$; found 250.1208.

*4.2.6. 2-(4′-Fluorophenyl)-2-(phenylamino)ethanol (**3da**).* The title compound was isolated by column chromatography (hexane/AcOEt 90:10) as yellow oil; R_f (hexane/AcOEt 85:15) 0.5; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3391, 2925, 2854, 1602, 1506; ^1H NMR (300 MHz, $CDCl_3$): δ 2.83–2.90 (br s, 2H), 3.67 (dd, J=7.2 and 11.0 Hz, 1H, CH_2), 3.88 (dd, J=4.2 and 11.0 Hz, 1H, CH_2), 4.44 (dd, J=4.2 and 7.2 Hz, 1H, CH), 6.51–6.54 (m, 2H), 6.65–6.71 (m, 1H), 6.97–7.19 (m, 4H), 7.29–7.35 (m, 2H); ^{13}C NMR (75.45 MHz, $CDCl_3$): 59.2, 67.2, 113.5, 113.8, 115.5, 115.7, 118.0, 128.2, 128.3, 129.1, 129.4, 135.7, 135.8, 147.0, 160.5, 163.8; HRMS: calculated for $C_{14}H_{14}FNO$ 254.0957 $[M+Na]^+$; found 250.0950.

*4.2.7. 2-(4′-Chlorolphenyl)-2-(phenylamino)ethanol (**3ea**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.48; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3385, 2955, 2924, 2853, 1602, 1503, 1491; ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (dd, J=7.2 and 11.0 Hz, 1H, CH_2), 3.88 (dd, J=4.2 and 11.0 Hz, 1H, CH_2), 4.43 (dd, J=4.2 and 7.2 Hz, 1H, CH), 6.50–6.53 (m, 2H, ArH), 6.66–6.71 (m, 1H, ArH), 7.06–7.12 (m, 2H, ArH), 7.28 (m, 5H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 59.3, 67.1, 113.5, 113.8, 118.1, 118.4, 127.2, 128.1, 128.7, 128.9, 129.1, 129.4, 133.2, 133.6, 133.7, 147.5; HRMS: calculated for $C_{14}H_{14}ClNO$ 286.0401 $[M+K]^+$; found 286.0878.

*4.2.8. 1-(4′-Nitrophenyl)-2-(phenylamino)ethanol (**4fa**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.48; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3406, 2923, 2853, 1602, 1517; ^1H NMR (300 MHz, $CDCl_3$): δ 3.06 (br s, 2H, NH and OH), 3.22 (dd, J=8.7 and 13.5 Hz, 1H, CH_2), 3.43 (dd, J=3.6 and 13.5 Hz, 1H, CH), 4.99 (dd, J=3.6 and 8.7 Hz, 1H, CH), 6.64 (m, 3H, ArH), 6.72–6.76 (m, 2H, ArH), 7.55 (d, J=8.7 Hz, 2H, ArH), 8.14–8.22 (m, 2H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 51.9, 71.4, 113.6, 118.8, 123.7, 126.6, 129.5, 147.3, 147.5, 149.0; HRMS: calculated for $C_{14}H_{14}N_2O_3$ 258.10; found 241$[M+H-H_2O]^+$.

*4.2.9. 1-(3′-Nitrophenyl)-2-(phenylamino)ethanol (**4ga**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.48; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3387, 2922, 2852, 1603, 1528; ^1H NMR (300 MHz, $CDCl_3$): δ 2.58 (br s, 1H), 3.26 (dd, J=8.7 and 13.5 Hz, 1H, CH_2), 3.47 (dd, J=3.6 and 13.5 Hz, 1H, CH_2), 5.02 (dd, J=3.6 and 8.7 Hz, 1H, CH), 6.64–6.75 (m, 3H, ArH), 7.14–7.30 (m, 2H, ArH), 7.54 (t, J=7.8 Hz, 1H, ArH), 7.74 (d, J=7.8 1H, Hz, ArH), 8.14–8.18 (m, 1H, ArH), 8.28 (s, 1H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 52.0, 71.4, 113.6, 118.8, 120.9, 122.8, 129.4, 129.5, 131.8, 144.4, 147.4, 148.6; HRMS: calculated for $C_{14}H_{14}N_2O_3$ 281.0902 $[M+Na]^+$; found 281.0896.

*4.2.10. 1-(2′-Methylphenoxy)-3-(phenylamino)propan-2-ol (**3ia**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.50; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3406, 3053, 2923, 2852, 1602, 1493; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 3.27 (dd, J=7.1 and 13.0 Hz, 1H, CH_2), 3.45 (dd, J=4.2 and 13.0 Hz, 1H, CH_2), 4.03 (d, J=4.9 Hz, 2H, CH_2), 4.19–4.32 (m, 1H, CH), 6.64–6.92 (m, 5H, ArH), 7.11–7.22 (m, 4H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 16.7, 47.3, 69.3, 70.6, 111.6, 113.8, 118.5, 121.5, 127.4, 129.8, 131.3, 148.2, 157.3; HRMS: calculated for $C_{16}H_{19}NO_2$ 280.1313 $[M+Na]^+$; found 280.1310.

*4.2.11. 1-(3′-Methylphenoxy)-3-(phenylamino)propan-2-ol (**3ja**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.45; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3383, 3054, 3025, 2923, 1602, 1497; ^1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 3.23 (dd, J=7.0 and 13.0 Hz, 1H, CH_2), 3.38 (dd, J=4.2 and 13.0 Hz, 1H, CH_2), (3.00–3.44, br s, 2H, NH and OH), 3.97–3.98 (m, 2H, CH_2), 4.12–4.22 (m, 1H, CH), 6.62–6.82 (m, 5H, ArH), 7.05–7.21 (m, 4H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 16.2, 46.7, 68.7, 69.9, 111.0, 113.2, 117.9, 120.9, 126.5, 126.8, 129.2, 130.7, 148.0, 156.3; $C_{16}H_{19}NO_2$ 280.1313 $[M+Na]^+$; found 280.1310.

*4.2.12. 1-(4′-Methylphenoxy)-3-(phenylamino)propan-2-ol (**3ka**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.48; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3399, 3028, 2922, 2855, 1604, 1510; ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 3.23 (dd, J=7.0 and 13.0 Hz, 1H, CH_2), 3.38 (dd, J=4.2 and 13.0 Hz, 1H, CH_2), 3.96 (m 2H, CH_2), 4.14–4.24 (m, 1H, CH), 6.62–6.82 (m, 5H, ArH), 7.05–7.21 (m, 4H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 20.6, 46.7, 68.9, 70.3, 113.4, 114.5, 118.1, 129.4, 130.2, 130.7, 148.2, 156.4; HRMS: calculated for $C_{16}H_{19}NO_2$ 258.1494 $[M+Na]^+$; found 258.1493.

*4.2.13. 1-(4′-Chlorophenoxy)-3-(phenylamino)propan-2-ol (**3la**).* The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; R_f (hexane/AcOEt 85:15) 0.47; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3404, 3053, 3022, 2926, 2854, 1602, 1492; ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (br s, 1H), 3.29 (dd, J=7.2 and 13.5 Hz, 1H, CH_2), 3.46 (dd, J=4.2 and 12.9 Hz, 1H, CH_2), 3.97–4.09 (m, 2H CH_2), 4.21–4.28 (m, 1H, CH), 6.62–6.86 (m, 5H, ArH), 7.13–7.25 (m, 4H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 46.5, 68.6, 70.3, 113.3, 115.8, 118.1, 126.1, 129.3, 129.4, 147.9, 157.0; HRMS: calculated for $C_{15}H_{16}ClNO_2$ 300.0767 $[M+Na]^+$; found 300.0780.

*4.2.14. 1-(Allyloxy)-3-(phenylamino)propan-2-ol (**3ma**).* The title compound was isolated by column chromatography (hexane/AcOEt 90:10) as yellow oil; R_f (hexane/AcOEt 85:15) 0.47; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3395, 3053, 3013, 2917, 2856, 1604; ^1H NMR (300 MHz, $CDCl_3$): δ 2.70–3.00 (br s, 1H), 3.14 (dd, J=7.2 and 12.9 Hz, 1H, CH_2), 3.30 (dd, J=4.2 and 12.9 Hz, 1H, CH_2), 3.45–3.57 (m, 2H, CH_2), 4.00–4.04 (m, 3H, CH_2, CH), 5.19–5.31 (m, 2H, CH_2 olefinic), 5.86–5.95 (m, 1H, CH), 6.61–6.74 (m, 3H, ArH), 7.14–7.24 (m, 2H, ArH); ^{13}C NMR (75.45 MHz, $CDCl_3$): 46.6, 68.9, 72.2, 72.3, 113.09, 117.4, 117.6, 129.1, 134.2, 148.1; HRMS: calculated for $C_{12}H_{17}NO_2$ 230.1157 $[M+Na]^+$; found 230.1013.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.02.053.

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