Catalyst free, nitromethane assisted facile ring opening of epoxide with less reactive aromatic amines

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Abstract

Nucleophilic ring opening reactions of epoxides with aromatic amines are in the forefront of the synthetic organic chemistry research to build new bioactive scaffolds. Here, a convenient, green and highly efficient regioselective ring opening of sterically hindered (2R,3S)-3-(*N*-Boc-amino)-1-oxirane-4-phenylbutane with various poorly reactive aromatic amines are accomplished under microwave irradiation in nitromethane. All the reactions effectively implemented for various aromatic amines involves reuse of nitromethane that supports its dual role as a solvent and catalyst. The corresponding new β-alcohol analogs of hydroxyethylamine (HEA) are isolated in 41-98% yields. The reactions proceed under mild conditions for a broad range of less reactive and sterically hindered aromatic amines. Proton NMR and UV-visible spectroscopic studies suggest that the nucleophilicity of amines is influenced by nitromethane, which is substantiated by the extensive computational studies. Overall, this methodology elucidates the first time use of nitromethane as a solvent for the ring opening reactions under microwave conditions involving equimolar ratio of epoxide and aromatic amine without any catalyst, facile ring opening of complex epoxide by less reactive aromatic amines, low reaction time, less energy consumption, recycling of the solvent and simple workup procedures.

1. Introduction:

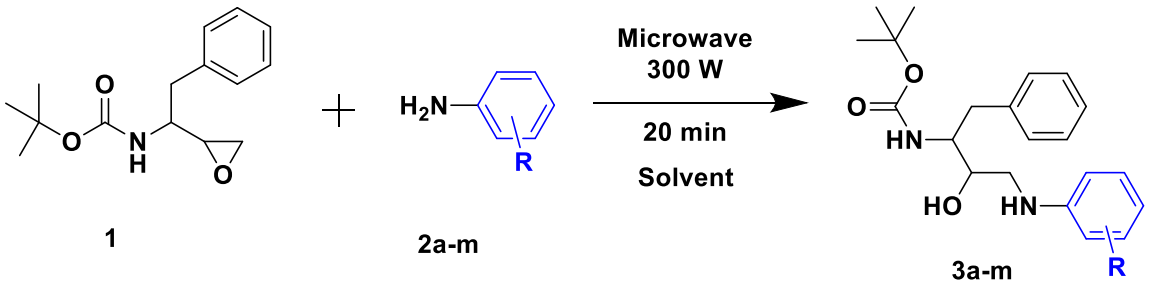
Epoxides are invaluable building blocks, both in synthetic organic chemistry and medicinal chemistry as they facilitate the introduction of multiple functional groups.[1-2] Nucleophilic ring opening of epoxides with amines is one the important pathway to develop new chemical scaffolds with versatile functional groups, including β-amino alcohols.[3] The β-amino alcohols are vital intermediates in medicinal chemistry and have been widely implemented for the synthesis of various biologically active compounds.[4-5] One of the most important scaffolds of β-amino alcohol is hydroxyethylamine (HEA)[6] that has been extensively explored as synthon for the discovery of antimalarials[7-8], anti-fungal[9], HIV protease inhibitors[10] and anti-Alzheimer agents[11-12] etc. In literature, quite a few routes are available for synthesis of HEA that involves the nucleophilic ring opening of epoxide with amines under conventional heating or microwave irradiation. However, these procedures suffer from several drawbacks *viz.* poor yields, high molar ratio of epoxide and aniline, failure of reaction in case of sterically hindered epoxide and less reactive aromatic amines, prolonged reaction time, and tedious work up.[13] The epoxide ring opening with less reactive aromatic amines is reported in the presence of catalysts such as zinc tetrafluoroborate hydrate in solvent free condition[14], $Sc(OSO_3C_{12}H_{25})_3$ with chiral bipyridine ligand at room temperature in water[15], zinc(II) perchlorate hexahydrate in solvent free condition[16], aluminium triflate[17], chiral zinc (II) and copper (II)[18], lanthanide iodo binaphtholates,[19] bismuth trichloride[20], tetrathiomolybdate[21], antimony (III) chloride in dichloromethane at room temperature[22], Cobalt(III) tetraphenylporphyrin chloride[23], and lewis pair in toluene as a solvent at room temperature.[24] The obstacles associated with the ring opening of complex epoxides have been tackled with the use of heterogenous catalysts and metal triflates under microwave irradiation.[3, 25-26] However, the use of moisture and air-sensitive catalysts, recovery of catalysts, requirement of stoichiometric amount of catalysts collectively limits the efficiency of these procedures. Of late, Zhengyin Du *et al*[27] reported a microwave assisted ring opening reaction of a simple epoxide with aniline (3:1 equivalents) in the absence of catalysts. To the date, the available methods do not include the ring opening reaction of complex epoxides with less reactive, and sterically hindered aromatic amines in equimolar ratios, particularly without use of any catalysts. Therefore, new highly efficient, catalyst free, and simpler procedures are need to be explored for nucleophilic ring opening reaction in organic synthesis. Herein, we report a facile method for the nucleophilic ring opening reactions of epoxide, (2R,3S)-3-(N-BOC-amino)-1-oxirane-4-phenylbutane with less nucleophilic aromatic amines in nitromethane under microwave irradiation. Steric and

electronic factors affecting ring opening of epoxide with aromatic amines in various solvents have been investigated, and the results are corroborated with the considerable computational studies.

2. Result and Discussion:

Synthesis and characterization

(2R, 3S)-3-(N-BOC-amino)-1-oxirane-4-phenylbutane (**1**) is one the popular epoxide employed to prepare the high-valued compounds *viz.* HEAs. The standard procedures for ring opening of the epoxide, **1** have been optimized that led to regioselective HEA analogs identified as scaffolds potent against malaria parasite[28-30] , plasmepsin inhibitors[31-33] , HIV inhibitors[34-35] etc.As a part of our ongoing research interest towards the search of new HEA scaffolds, synthesis of these analogs based on epoxide **1** was attempted following the standard conventional synthetic routes. Initially, ring opening reaction of epoxide **1** (1.0 mmol), with *p*-toluidine, **2a** (1.0 mmol) in iso-propanol (50 mL) was carried out for 12 hours at 80 °C as reported in the literature[36] however, thin layer chromatography (TLC) did not indicate any product formation.



2a, 3a R = 4-CH_3 **2h, 3h** R = 3-F
2b, 3b R = 4-F **2i, 3i** R = 3-CF_3
2c, 3c R = 4-CF_3 **2j, 3j** R = 2,4-F, F
2d, 3d R = 4-OCF_3 **2k, 3k** R = 4-$C(CH_3)_3$
2e, 3e R = 4-$COCH_3$ **2l, 3l** R = 4-OCH_3
2f, 3f R = 2-F **2m, 3m** R = 2,6-CH_3, CH_3
2g, 3g R = 2-CF_3

Scheme 1. Reaction of substrate **1** with substituted anilines (**2a-m**) to give product (**3a-m**).

Next, we attempted the reaction of epoxide **1** (1.0 mmol), with *p*-toluidine **2a** (1.0 mmol) under microwave irradiation following the reported procedures.[27] Various solvents were employed for this reaction such as ethanol, water, and mixture of ethanol and water with different molar ratios (Table 1, Entry 14-17) in the search for a suitable green solvent. The similar reaction performed in water indicated no product formation probably due the insolubility of the

reactants (Table 1, Entry 17). The maximum yield, 70% of the product **3a** was isolated when ethanol was used as a solvent (Table 1, Entry 14). Selection of the appropriate solvent was made on the basis of the optimization of the reaction in a broad range of polar solvents as depicted in Table 1. The unsuccessful reaction in aqueous media and less fruitful reaction in ethanol encouraged us to explore the organic polar solvents.[37]

Two factors, use of catalysts[15, 18-19] and high molar ratio of the epoxide[27] or amine[38] are broadly responsible for the efficiency of the ring opening reactions. Considering the complexities of these reactions, we attempted the ring opening reactions in the presence polar solvents (i.e. dimethylformamide, dimethyl sulfoxide and nitromethane) without any catalysts under microwave irradiation. We noted that the reaction was progressed competently in nitromethane, however no product formation was observed in dimethyl sulfoxide and dimethylformamide (Table 1, Entry 17-18). Reports are available to support nitromethane as good choice of solvent for the ring opening reactions with the limitations i.e. high molar ratio of epoxide and nucleophile (i.e. aniline), which is one of the major drawbacks of these reported reactions.[38]

Table 1. Optimisation of reaction conditions.

Entry No	Molar ratio of compound **1** and **2a**	Solvent	Power (W)	Time (min)	Yield (%) [a]
1.	1:1	Nitromethane	80	20	56
2.	1:1	Nitromethane	100	20	64
3.	1:1	Nitromethane	150	20	71
4.	1:1	Nitromethane	200	20	77
5.	1:1	Nitromethane	250	20	80
6.	1:1	Nitromethane	300	20	89
7.	1:1	Nitromethane	300	5	53
8.	1:1	Nitromethane	300	10	62
9.	1:1	Nitromethane	300	15	72
10.	1:1	Nitromethane	300	20	90

11.	1:1	Nitromethane	300	25	90
12.	1:1	Nitromethane	300	30	90
13.	1:1	Dimethyl sulfoxide	300	20	-
14.	1:1	Ethanol	300	20	70
15.	1:1	Ethanol:Water (1:1)	300	20	62
16.	1:1	Ethanol:Water (30:70)	300	20	41
17.	1:1	Water	300	20	-
18.	1:1	DMF	300	20	-
19.	1:1	Isopropanol[b]	-	-	-
20.	1:3	Nitromethane[c]	-	-	43
21.	2:1	Nitromethane	300	30	98
22.	1:1	Nitromethane[c]	-	-	21
23.	1:1	Nitromethane[d]	300	20	85
24	1:1	Nitromethane[e]	300	20	81
25	1:1	Nitromethane[f]	300	20	76

Reaction conditions: [a]isolated yield after recrystallization of product using ethyl acetate and hexane; [b]reaction performed under reflux condition for 12 h; [c]reaction performed at room temperature for 36 h; [d]reaction performed in nitromethane (II cycle); [e]reaction performed in nitromethane (III cycle); [f]reaction performed in nitromethane (IV cycle).

Therefore, nitromethane was selected for the ring opening *tert*-butyl(1-(oxiran-2-yl)-2-phenylethyl)carbamate (**1**) with *p*-toluidine (**2a**) (1.0 mmol) under microwave conditions and the yield of the product (**3a**) was significantly improved. The optimization of reaction conditions (i.e. power and time) for nitromethane are represented in Table 1. The yield of the products was dependent on the reaction time. As the reaction time increases from 5 min. to 20 min., the yield of the product increases from 53% to 90% (Table 1, Entry 7-10). The yield of **3a** was also increased with the increase in power of the microwave irradiation (Table 1, Entry 1-6, 12). Maximum yield, 90 % was observed at 300W in 20 min (Table 1, Entry 10) however, no further increment in yield was noted even after 25 - or 30-minutes reaction period (Table 1, Entry 11 and 12). Apart from reaction conditions, different molar ratios of the reactants were investigated. While increasing the molar ratio of epoxide from one to two equivalents, the yield of the product **3a** was significantly increased from 90% to 98 % (Table 1, Entry 12 and 21). The similar reaction was performed at room temperature (Table 1, Entry 20 and 22) that led to the poor yield of the product, which further supported the efficiency of microwave assisted ring

opening reaction. To explore the recyclability of the solvent, reactions were performed in recovered nitromethane for three consecutive cycles that afforded 85% (II recycle), 81% (III recycle) and 76% (IV recycle) yield of **3a** (Table 1, entry 23-25), indicating the reuse and recyclability of the solvent.

Next, the yields of the products (**3a**-**m**) were compared in nitromethane and ethanol as depicted in Table 2. The solvent effect showed that the yield of all the listed new analogs was much better in nitromethane (a polar aprotic solvent) over ethanol (a protic solvent) possibly due to the improved nucleophilicity[39-41] of aromatic amines in nitromethane as supported by the computational studies described in next section. Although nitromethane is not a green solvent in comparison to ethanol, it was selected as a suitable solvent considering the high yields. Notably, high yield of the products was obtained in nitromethane while using less nucleophilic anilines, however the similar reactions performed in ethanol led to reduced yields.

As an important part of the study, the effect of electron donating group (EDG) and electron withdrawing group (EWG) on aromatic amines was investigated in the presence of both ethanol and nitromethane as listed in Table 2. In nitromethane, the effect of EDG or EWG on the rate of the reaction was clearly noted in case of the reactants **2a** and **2c**. Reactant **2a** possessing methyl group at *para* position of aniline increased the electron density on $-NH_2$ and enhanced the yield of the product **3a** *i.e* 90% in comparison to the reactant **2c** with $-CF_3$ group at *para* position giving the product **3c** in 54% yield (Table 2, Entry 1 and 3). Further, the effect of one or two fluoro group present at different positions of aromatic amines influencing the rate of the reaction was also studied. The observed trend for the yield of the product **3b** > **3h** > **3f** > **3j** (*p* > *m* > *o* > *op*) may be attributed to -F group exerting -I and +M effect, the anomalous behaviour shown by **3f** may be due to the steric factor or involvement of H bonding between $-NH_2$ and -F group present at the *ortho* position. These results were further supported by the total charge on amino group *i.e* Q_{NH2} values calculated by the computational studies. It was observed that greater the positive charge on $-NH_2$, lower is the yield of the product (Table 2, Entry 2, 6, 8,10). The chemical composition of all the listed new HEA analogs (**3a-m**) was confirmed by standard spectroscopic methods (Fig. S2-S39, supporting information). An extensive NMR study (i.e. NOSY and DEPT) was also performed in order to confirm the regioselectivity. In ^{1}H NMR of **3a** ($CDCl_3$), a multiplet appeared at 7.25 ppm due to the proton of aromatic ring, also two doublets for two proton each one at 6.96 ppm and other at 6.52 ppm for *p*-toluidine ring protons. A doublet corresponding to the hydroxyl proton was appeared at 4.89 ppm. The

two-methylene moiety were appeared at 3.91-3.78 (m) and 3.22-3.07 (m) ppm, respectively. The methyl protons of *p*-toluidine were observed at 2.22 (s), which are slightly deshielded due to the ring current effect in comparison to other methyl protons of **3a**, which appeared at 1.40 (s) ppm. In addition, an extensive study of ^{19}F-NMR were performed for the fluorine containing analogs (Fig. 1).

The effect of -CF_3 group present in aromatic amines at *para* (**3c**), *ortho* (**3g**) and *meta* (**3i**) position on the rate of reaction was also studied. In ^{19}F NMR, the peaks for **3c**, **3g** and **3i** were observed at δ -61.0 ppm, -62.4 ppm and -62.8 ppm, respectively as shown in Fig. 1.[42] The most shielded peak appeared at -62.8 ppm for -CF_3 group (*meta* position, **3i**) causing the enhanced electron density at -NH_2 group, and hence resulted in higher yield (66%) over the *ortho* (**3g**, 41%) and *para* (**3c**, 54%) substituents.

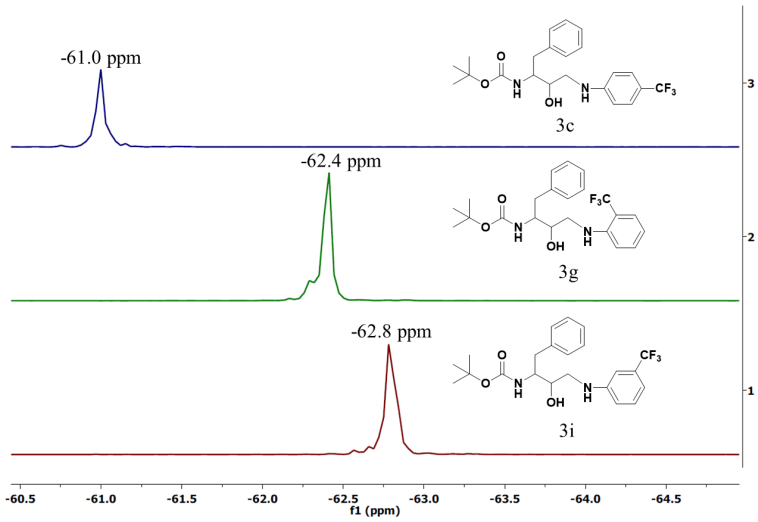
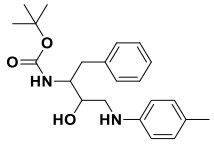
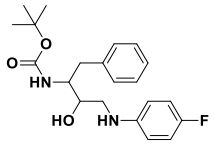
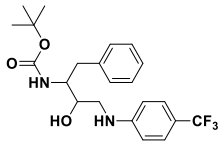
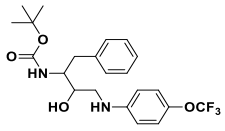
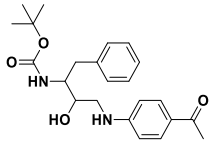
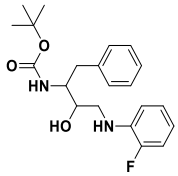
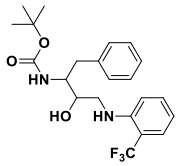
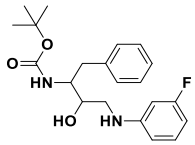
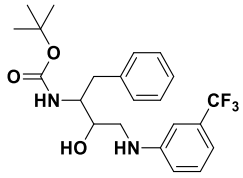
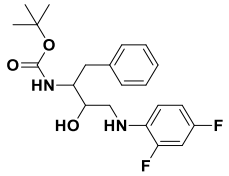
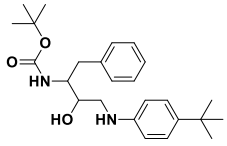
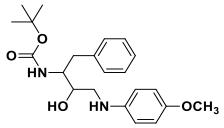
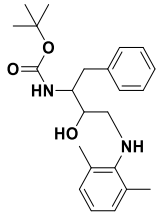


Fig. 1. Comparison of ^{19}F NMR spectra of **3c**, **3g** and **3i** having electron withdrawing group (CF_3) present at *para*, *ortho* and *meta* positions of aniline.

Table 2. Comparison of yields for products **3a-m** in ethanol and nitromethane and the charge on amino group of aromatic rings in nitromethane (Q_{NH2}).

Sr. No	Product	Structure	% Yield[a] in ethanol	% Yield[a] in nitromethane	Q_{NH2}, a.u. (nitromethane)
1.	**3a**		70	89	0.071

2.	**3b**		70	85	0.108
3.	**3c**		23	54	0.1513
4.	**3d**		26	61	0.1586
5.	**3e**		20	53	0.1796
6.	**3f**		37	56	0.1682
7.	**3g**		<5	41	0.2606
8.	**3h**		47	64	0.1129
9.	**3i**		39	66	0.1640
10.	**3j**		23	52	0.1983
11.	**3k**		59	80	0.0606

12.	**3l**		70	86	0.0863
13.	**3m**		37	64	0.0717

Reaction conditions: reaction performed using 1:1 molar ratio of **1** and **2a-m.** [a] isolated yield after recrystallization of product using ethyl acetate and hexane (1:9).

Computational Studies: Density Functional Theory (DFT) calculations were carried out that did not show significant dependence of the yields on the energy, orbital or charge characteristics of both the reactants (**1** and **2**) and the reaction products (**3**). The best dependence was observed on the sum of the partial charges of the atoms of the -NH_2 of reactants **2a-m** at the DFT B3LYP 6-311G(d,p) level of theory, however the correlation coefficient (R) was only 0.704 with the exclusion of the **2e** molecule.

Next, a computational analysis of the yields within the MERA model[43-45] showed that the yields in both ethanol and nitromethane solutions correlate well with the total charge of the -NH_2 of reactants **2a-m**. Dependencies are shown in Fig. 2. The values of R were calculated 0.827 for ethanol, and 0.815 for nitromethane solvent system. Compound **3m** was an outlier for both dependences, possibly due to the steric hindrance of methyl groups in the *ortho* positions. Without the compound **3m**, R equals 0.906 and 0.902, correspondingly. Compound **3m** is represented by filled markers as shown in Fig. 2. The calculated charges for -NH_2 and the yields of the products are shown in Table 2.

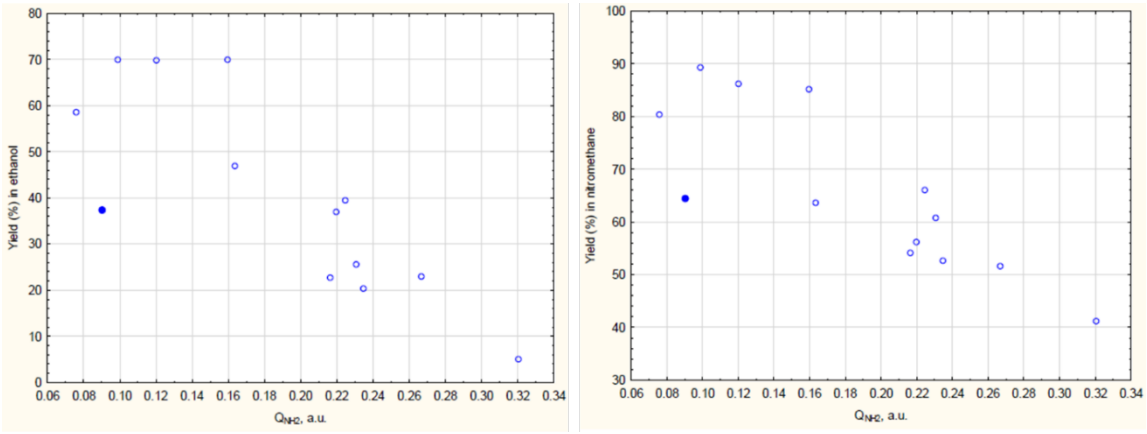


Fig. 2. The dependencies of the yields on the charge of the amino group (Q_{NH2}) of reactants **2a-m**: a) in ethanol; b) in nitromethane (• is **2m** compound).

It should be noted that the yields in ethanol and nitromethane were correlated very well (correlation coefficient 0.974) indicating the same mechanism of the process in different solvents, and the difference in yields could be related to the solvation effects.

The yields in both solvents can be described well by the equation:

$$\text{Yield} = 77.9 - 201 \cdot Q_{NH2} + \Delta$$

$\Delta = 25.1\%$, in the case of nitromethane; $\Delta = 0\%$, in the case of ethanol.

$R = 0.877$; standard deviation $S = 11\%$.

Therefore, the yields in nitromethane were greater than in ethanol by 25.1 ± 4.4%. The experimental (Yield (exp.)) and calculated by the equation (Yield (calc.)) are shown in Fig. 3a (the outlier, compound **2m** is represented by filled markers). Without compound **2m**, R = 0.927; S = 9.0%.

In order to clarify the energy characteristics of the reaction it was necessary to calculate the equilibrium constant K_e for each of the reaction using experimental yields by the formula

$$K_e = \frac{\text{Yield}/100}{C(1 - \text{Yield}/100)^2}$$

where C is the concentration of the reactants (1.9 mM).

Then it is possible to calculate the Gibbs free energy (ΔG) for each process using van 't Hoff equation, i.e.

$$\Delta G = -RT \cdot \ln K_e$$

The values of K_e and ΔG are presented in Table 3.

A comparison of the Gibbs free energies (ΔG) showed that they were lowered by 4.6 ± 1.4 kJ/mol in ethanol when compared with nitromethane leading to difference in yields. ΔG was also dependent on $-NH_2$ charge as per the following equation.

$$\Delta G = -22.7 + 37.5 \cdot Q_{NH2} + \Delta_1$$

Δ_1 = -4.55 kJ/mol, in the case of nitromethane; Δ_1 = 0 kJ/mol in the case of ethanol.

R = 0.870; S = 2.1 kJ/mol.

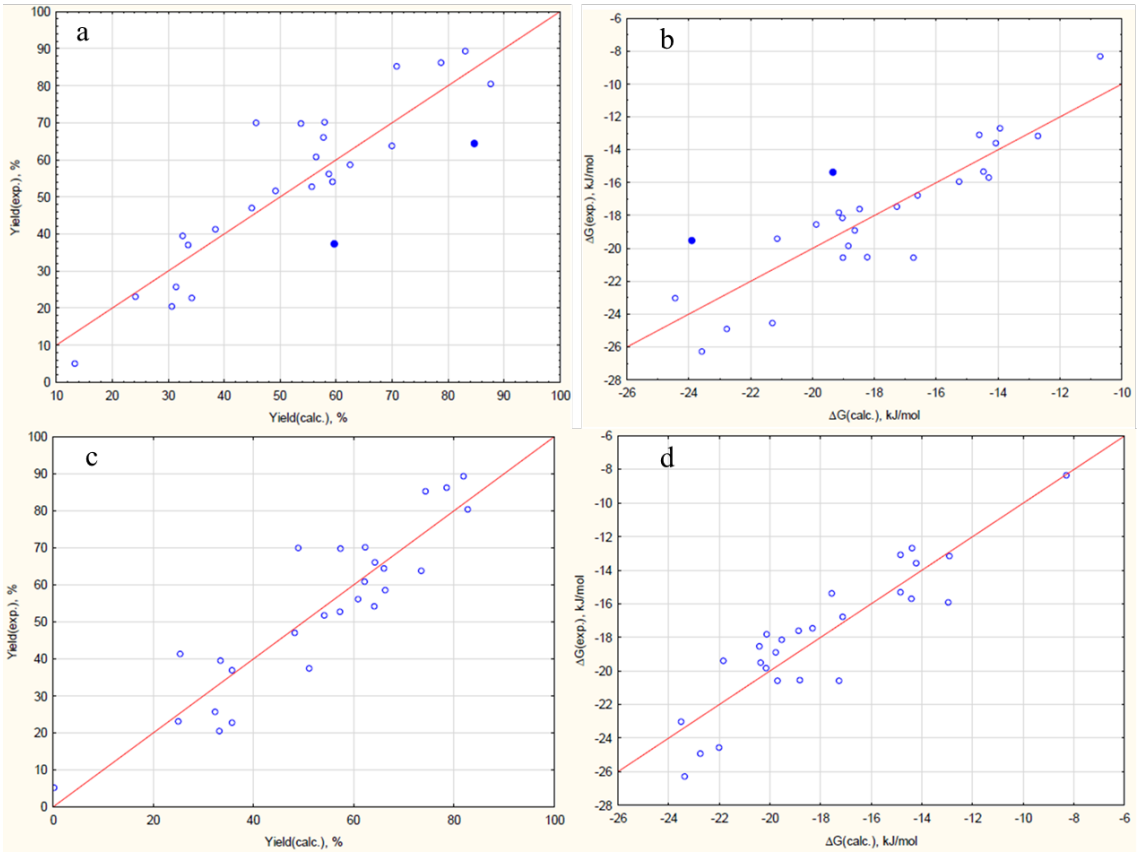


Fig. 3. Experimental and calculated. a) yields; b) free energies (• is **3m** compound); c) yields (excluding **3m**); d) Gibbs free energies (excluding **3m**).

Table 3. Equilibrium constants, Gibbs free energies (ET –in ethanol, NM – in nitromethane), Reactant-Accessible Area (RAA) and amino group charges in ethanol.

Compound	K_e (NM)	K_e (ET)	ΔG, kJ/mole (NM)	ΔG, kJ/mole (ET)	Q_{NH2}, a.u. (ET)	RAA, Å^2 (NM)	RAA, Å^2 (ET)
3a	4.073E+04	4.080E+03	-26.30	-20.60	0.0990	32.3345	30.8618
3b	2.029E+04	4.077E+03	-24.57	-20.60	0.1597	32.4125	30.9070
3c	1.346E+03	1.990E+02	-17.85	-13.11	0.216	32.3588	30.8691
3d	2.071E+03	2.426E+02	-18.92	-13.61	0.230	32.3354	30.8564

3e	1.234E+03	1.690E+02	-17.64	-12.71	0.2347	32.3090	31.0428
3f	1.532E+03	4.875E+02	-18.17	-15.33	0.2220	32.4282	30.9562
3g	6.257E+02	2.916E+01	-15.95	-8.36	0.3207	30.8295	29.5642
3h	2.530E+03	8.734E+02	-19.41	-16.78	0.1636	32.4309	30.9200
3i	3.009E+03	5.657E+02	-19.84	-15.70	0.2248	32.6209	30.8165
3j	1.157E+03	2.032E+02	-17.48	-13.17	0.2671	32.4326	30.9541
3k	1.096E+04	1.787E+03	-23.05	-18.55	0.0761	32.1514	30.7294
3l	2.349E+04	4.022E+03	-24.94	-20.56	0.120	32.3260	30.8547
3m	2.661E+03	4.991E+02	-19.54	-15.39	0.0905	30.5904	29.4223

The formation energy of products (**3a-m**) was also calculated and noted in the range of –30 ± 11 kJ/mol. Only compound **3g** and **3m** were out of this range probably due to the steric hindrance of *ortho* substituents. The formation energy of these complexes was noted as –2.2 and –0.8 kJ/mol, correspondingly, that explained their low yield.

Further, studies were carried out to investigate the possible effects of steric obstacles for **3m** and **3g**, the reactant-accessible area (RAA) of amino group was calculated within MERA approach. These values in ethanol and in nitromethane are presented in Table 3. It should be noted that the RAA of -NH_2 in nitromethane is greater by 1.45 ± 0.15 Å^2 than in ethanol. Therefore, ethanol increased the charge on -NH_2 and decreased its RAA in comparison to nitromethane. The smallest RAA was observed for **2g** and **2m** containing substituents at *ortho* position. The abnormal low yield of **3g** may be explained by both higher charge of -NH_2 and its low RAA provided by electronegative -CF_3 substituent at *ortho* position.

ΔG was also well related to the RAA and charges of -NH_2 in the corresponding solvents for these reactions:

$$\Delta G = 30 + 41.4 \cdot Q_{NH2} - 1.73 \cdot RAA$$

R = 0.905; S = 1.8 kJ/mol. The calculated and experimental yields and ΔG are shown in Fig. 3b and 3d.

As, mentioned above the yields were higher in nitromethane in comparison to ethanol, the ring opening of **1** was believed to proceed through the nucleophilic attack of aromatic amines (**2**)

on less hindered site (C atom), followed by proton transfer to yield regioselective products as shown in Fig. 4a. Nitromethane is enhancing the rate of reaction possibly due to weak van der Waals interactions with **2**. To further, explore the role of nitromethane in the reaction mechanism (Fig. 4a), ^{1}H-NMR, UV-visible and computational studies were carried out independently.

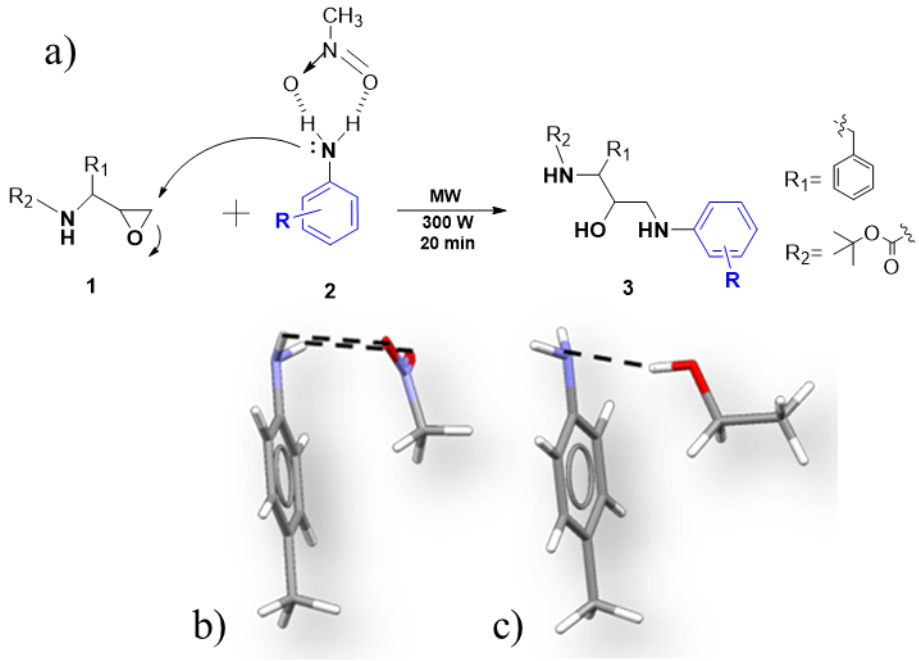


Fig. 4. a) Possible mechanism for the ring opening of the epoxide (**1**) with aromatic amines (**2**); Complexes of aromatic amine **2a** with b) nitromethane; c) ethanol.

In ^{1}H-NMR spectroscopic studies the weak van der Waals interactions[46] between nitromethane and aromatic amine was supported by the shifting of peaks of **2a** to the shielded region on addition of nitromethane. As shown in Fig. 5, the aromatic protons and methyl protons were shifted from δ 7.00 ppm to 6.93 ppm, 6.64 ppm to 6.57 ppm and 2.28 ppm to 2.21 ppm, respectively. However, there was no remarkable shifting for -NH_2 protons due to the broadening of the peak. In addition, a time dependent UV-visible studies for aromatic amine (**2a**) with nitromethane were carried out. A continuous increase in absorption band of **2a** on addition of equimolar amount of nitromethane (Fig. S44, supporting information), may be attributed to the intermolecular interactions.

Next, the complexes of reactants **2a-m** with ethanol and nitromethane were simulated using the MOPS algorithm with continual account of solvent influence.[47-49]. In case of nitromethane

complex (Fig. 4b), both the oxygen atoms of nitromethane exhibited interactions with both hydrogens of the -NH_2. However, the O...H distances were significantly greater and in the range 2.62 – 2.63 Å, which approximately corresponds to the sum of the van der Waals radii confirming the weak intermolecular interactions. While, in case of complex with ethanol (Fig. 4c), a typical hydrogen bond with a length of 2.11 – 2.12 Å was observed as the distance was substantially less than the sum of the van der Waals radii of hydrogen (ethanol) and nitrogen (-NH_2). The formation of hydrogen bonds led to increase in the positive charge on -NH_2 (Table 3) resulting in lesser yields. Also, the influence of hydrogen bond formation on the charges were in the good agreement as per the reported literature.[50-51] These observed studies further suggested that there could be an increase in the nucleophilicity of aromatic amines in nitromethane, as amines have been reported to possess the variable nucleophilic character with respect to the solvents.[39, 41] To confirm this hypothesis, more computational studies were carried out i.e. rate constant of these reactions was calculated along with the nucleophilicity of reactants **2a-m** in both nitromethane and ethanol.

Assuming that the process yields were obtained under kinetic conditions, we calculated the second-order rate constants of the processes using the following equation.

$$\frac{dC_1}{dt} = -kC_1C_2$$

where $\frac{dC_i}{dt}$ is the reaction rate, i.e. decreasing of the initial compound concentration C_1 in time t; k is the second-order rate constant; C_1 and C_2 are the current concentrations of **1** and **2**, respectively.

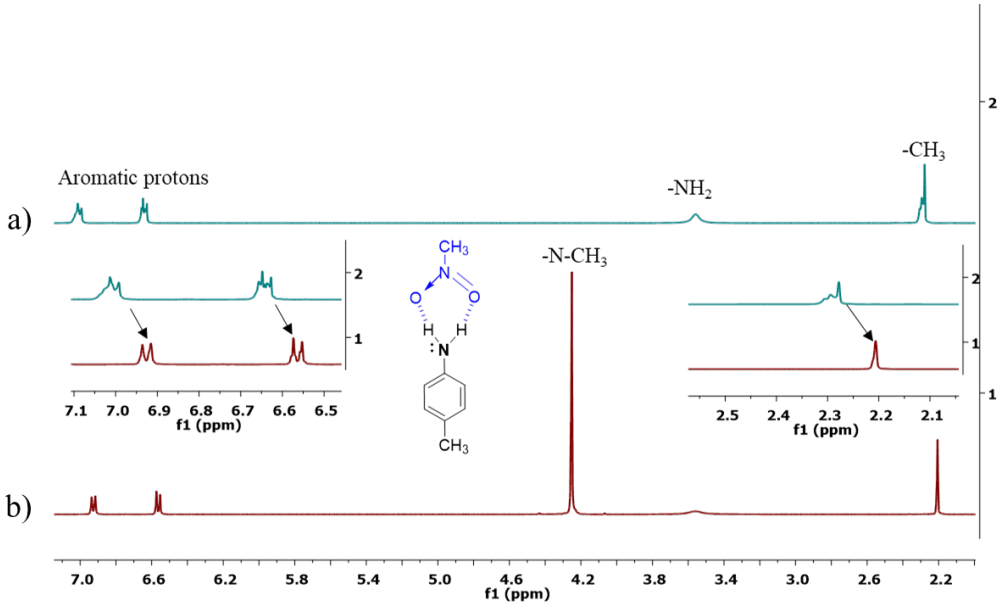


Fig. 5. ^{1}H-NMR spectra. a) **2a** in $CDCl_3$; b) **2a** with nitromethane in $CDCl_3$.

Since the concentrations of the components are equal (we denote them *C*), the equation is simplified

$$\frac{dC}{dt} = -kC^2$$

Integration of this equation leads to an equation by which it is possible to calculate the second-order rate constants

$$k = \frac{C_0 - C_1}{C_0 C_1 t}$$

where C_0 is the initial concentration.

Since $C = C_0 - C_p$ then

$$k = \frac{C_p}{C_0(C_0 - C_p)t}$$

Dividing the numerator and denominator by C_0, we obtain

$$k = \frac{C_p}{C_0(C_0 - C_p)t}$$

C_p / C_0 is called the extent of reaction ξ and equals Yield/100, then, finally, the equation has the form

$$k = \frac{\xi}{C_0(1-\xi)t} \qquad (1)$$

The second-order rate constants calculated by equation (1) were significantly higher in nitromethane than in ethanol (Table 4). The logarithms of the rate constants are also related to the charge of the amino group, however the reactants **2k** and **2m** strongly deviated from the dependence in both the solvents. As a result, the correlation coefficient of the logarithm of the rate constant with the charge of the -NH_2 was only 0.699. The reasons for the deviation of the **2m** have been discussed above. The reasons for the deviations of **2k** in this case were difficult to explain. The best two-factor model included two characteristics: the charge of the -NH_2 and the eigenvalue of the probability matrix of the association λ_{VDW}[52-53] of complexes of reactants with a solvent, is the following

$$\log k = 1.35 - 5.86 \cdot Q_{NH2} - 0.0071 \cdot \lambda_{VDW} \qquad (2)$$

R = 0.915; S = 0.21.

Table 4: Second-order rate constants, eigenvalues of the association probability matrix, and relative nucleophilicity of reactants (ET –in ethanol, NM – in nitromethane).

Reactant	k, L·mol^{-1}·s^{-1} NM	k, L·mol^{-1}·s^{-1} ET	λ_{VDW} NM	λ_{VDW} ET	N_{rel} NM	N_{rel} ET
2a	3.6452	1.0214	76.24	124.87	0.3889	-0.1165
2b	2.5129	1.0210	66.94	100.29	0.2417	-0.2980
2c	0.5157	0.1283	69.40	99.78	-0.0292	-0.6281
2d	0.6780	0.1505	81.08	118.67	-0.1550	-0.8455
2e	0.4873	0.1121	86.05	132.63	-0.3136	-0.9671
2f	0.5605	0.2564	76.20	107.34	-0.1769	-0.7013
2g	0.3068	0.0231	87.11	119.34	-0.7958	-1.3765
2h	0.7670	0.3868	68.52	100.81	0.2019	-0.3246
2i	0.8522	0.2855	72.22	103.02	-0.1086	-0.6986
2j	0.4670	0.1305	81.90	104.11	-0.3933	-0.9543
2k	1.7946	0.6180	105.32	168.72	0.2470	-0.2940

2l	2.7190	1.0127	91.89	129.95ss	0.1919	-0.2774
2m	0.7910	0.2608	100.34	150.04	0.2174	-0.2456

The calculated and experimental values are presented in Fig. 6a. The eigenvalues of the association probability matrix are presented in Table 4. It should be noted that the λ_{VDW} values in ethanol were significantly higher than in nitromethane leading to the stabilization of the reactants in ethanol and in turn led to decrease in their reactivity. In addition, just the reactants **2k** and **2m** had the maximum values of λ_{VDW}, which explains their deviations from the -NH_2 charge regularity.

According to Mayr and Patz[39-41], the nucleophilicity of the reactants is linearly related to the logarithm of the rate constant in accordance with the equation

$$\log k = s(N + E)$$

where N is the nucleophilicity of the nucleophilic reagent; E is the electrophilicity of an electrophilic reagent; s is a nucleophile-dependent slope parameter.

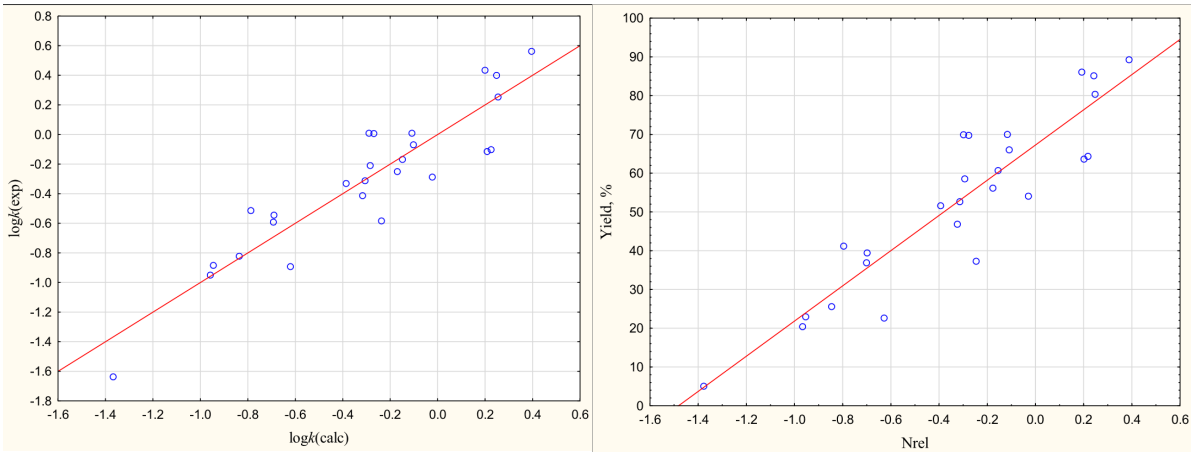


Fig. 6. a) The calculated log*k* (calc) and experimental log*k* (exp) values of the second-order rate constants logarithms; b) the relationship of the relative nucleophilicities of the reagents with the yields of products.

Then, in accordance with equation (2), the nucleophilicity of these reactions should also be exactly related to the charge of the -NH_2 and λ_{VDW}, since the values of s and E, in this case, are constant. However, exact nucleophilicity values cannot be determined since the electrophilicity

of the epoxide is unknown (Mayr and Patz often took s = 1). However, it is possible to calculate the relative nucleophilicity (N_{rel}), in accordance with equation (2), as

$$N_{rel} = 1.35 – 5.86 \cdot Q_{NH2} – 0.0071 \cdot \lambda_{VDW}$$

The obtained relative nucleophilicities are differ from the actual ones by the constant term E and presented in Table 4. It should be noted that the relative nucleophilicities of the reactants in nitromethane is much higher than in ethanol, in which they all have negative values. The relationship of the relative nucleophilicities of the reactants with the product yields for all solvents is shown in Fig. 6b. The correlation coefficient is 0.914.

Thus, the reaction yields supported by the charges of the -NH_2 of reactants **2a-m** in the solvent, in addition, the hydroxyl-containing solvent stabilizes the reactants of these reactions and subsequently decreases the yields. Together, NMR, UV-visible studies and relative nucleophilicities of the reactants in nitromethane supported the higher yield of products (**3a-m**). These facts also supported the dual role of nitromethane, acting as a solvent and a catalyst.

3. Conclusion:

In summary, we have demonstrated synthesis of β-alcohols (i.e. HEA analogs) using highly deactivated anilines as a nucleophile for the ring opening reactions of sterically hindered epoxide. A mild and highly efficient procedure was optimized in nitromethane. Notably, the yield of new analogs was observed much higher in nitromethane as compared to ethanol. The low yields observed for ortho-substituents may be due to the steric obstacles or H-bonding as supported by the reactant-accessible area (RAA) of -NH_2 group calculated by computational studies. Proton NMR, UV-visible studies and complexes stimulated using MOPS algorithm supported the role of nitromethane in the reaction mechanism for the epoxide ring opening. The rate constant and nucleophilicity of the reactants were much higher in nitromethane over ethanol owing to weak van der Waals interactions. To the best of our knowledge, nitromethane was implemented as a suitable solvent as well as a catalyst for the ring opening of epoxide in microwave irradiation. Largely, this method offers various advantages such as regioselectivity, use of 1:1 stoichiometric ratio of amine and epoxide, high yield of HEA analogs even for less nucleophilic aromatic amines and complex epoxides, low reaction time, less energy consumption, recycling of solvent, and simple workup procedures.

4. Experimental:

4.1 General Method:

All the reagents and solvents were purchased from commercial sources and used as received without further purification. All reactions were performed in oven-dried glassware. Epoxide (2R,3S)-3-(N-BOC-amino)-1-oxirane-4-phenylbutane (CAS No. 98760-08-8) was purchased from GLR Innovation (New Delhi, India) and aromatic amines were purchased from AVRA Synthesis Pvt. LTd. (Hyderabad, India). Nitromethane (AR grade) was purchased from Spectrochem (Mumbai, India) and Ethanol (absolute) was purchased from Changshu Hongsheng Fine Chemical Co., Ltd. (Jiangsu, China). The reaction was performed in "Start Synth Microwave Synthesis Labstation" microwave for organic synthesis. The melting point of the isolated compound was measured in "BUCHI Labortechnik AG CH-9230". The progress of reactions was monitored by using thin-layer chromatography (TLC). Nuclear magnetic resonance (NMR) spectra were obtained using a JEOL ECX-400P NMR Spectrometer. Chemical shifts were given in part per million downfield from internal standard, tetramethylsilane (TMS). The chemical structures of products were confirmed by a high-resolution Biosystems Q-Star Elite time-of-flight electrospray mass spectrometer.

4.2 General Procedure:

Aniline (**2a**-**m**) were employed for the regioselective ring opening of the epoxide (Scheme 1). The reaction was carried out in microwave oven at 300 W. In a 50 mL round-bottomed flask, aniline (**2a-m**) (1.9 mmol), tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (**1**) (1.9 mmol), and 5 mL of solvent (nitromethane or ethanol) was added. The contents were stirred in microwave for 20 minutes. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The obtained crude product was recrystalised in ethylacetate and hexane in 1:9 ratio that led to the desired product.

All synthesized analogs were characterized by IR, ^{1}H NMR, ^{13}C NMR and HR-MS techniques. The regioselectivity of the product was confirmed by ^{1}H NMR, ^{13}C NMR, NOSEY, DEPT-45 and DEPT-135 NMR.

4.3 Computational:

Geometry optimization individual molecules were carried out at the unrestricted DFT B3LYP 6-311G(d, p) level of theory. To simulate the solvate complexes, preliminarily the MOPS[32-34] algorithm was used, which search for the optimal geometry of a complex along all modes of

translational, vibrational, and rotational movement in the combined force field MM3/MERA with a continual account the solvent influence according to the MERA model. Energies, geometrical, surface and charge characteristics were calculated within MERA model. [29-31]

4.4 Tert-butyl (3-hydroxy-1-phenyl-4-(p-tolylamino)butan-2-yl)carbamate (3a):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and p-toluidine (393 mg, 1.9 mmol) provide the **3a** as a white solid (626 mg, 1.69 mmol, 89%). Rf = 0.38 (3:1 hexanes/ethyl acetate). Mp: 130-132 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.25 (m, 5H), 6.96 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 4.89, (d, J = 9.1 Hz, 1H), 3.91 – 3.78 (m, 2H), 3.22 – 3.07 (m, 2H), 2.98 – 2.84 (m, 2H), 2.76 (br, 1H), 2.22 (s, 3H), 1.40 (s, 9H). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 156.37 (s), 145.79 (s), 138.17 (s), 129.87 (s), 129.34 (s), 128.62 (s), 127.44 (s), 126.55 (s), 116.24 (s), 113.69 (s), 79.79 (s), 69.85 (s), 53.81 (s), 48.19 (s), 38.66 (s), 28.43 (s), 20.47 (s).

4.5 Tert-butyl (4-((4-fluorophenyl)amino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (3b):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 4-fluoroaniline (211 mg, 1.9 mmol) provide the **3b** as a white solid (602 mg, 1.61 mmol, 85%). Rf = 0.33 (3:1 hexanes/ethyl acetate). Mp: 129-131 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.24 (m, 5H), 6.84 (t, J = 8.7 Hz, 2H), 6.52 (dd, J = 9.0, 4.4 Hz, 2H), 4.85 (d, J = 9.1 Hz, 1H), 3.86 (dd, J = 15.9, 8.2 Hz, 1H), 3.79 – 3.74 (m, 1H), 3.11 (ddd, J = 18.1, 13.1, 5.0 Hz, 2H), 2.96 – 2.84 (m, 2H), 2.70 (br, 1H), 1.40 (s, 9H). ^{19}F NMR (376 MHz, $CdCl_3$) δ -127.22 (s). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 156.42 (s), 144.38 (s), 138.02 (s), 129.27 (s), 128.67 (s), 126.63 (s), 115.93 (s), 115.78 (d, J = 22.3 Hz), 114.39 (d, J = 7.4 Hz), 79.93 (s), 69.82 (s), 53.82 (s), 48.45 (s), 38.55 (s), 28.41 (s).

4.6 Tert-butyl (3-hydroxy-1-phenyl-4-((4-(trifluoromethyl)phenyl)amino)butan-2-yl)carbamate (3c):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 4-(trifluoromethyl)aniline (306 mg, 1.9 mmol) provide the **3c** as a white solid (435 mg, 1.02 mmol, 54%). Rf = 0.40 (3:1 hexanes/ethyl acetate). Mp: 154-156 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.30 – 7.17 (m, 5H), 6.62 (d, *J* = 8.4 Hz, 2H), 4.81 (d, *J* = 8.6 Hz, 1H), 3.86 (dt, *J* = 11.6, 6.8 Hz, 2H), 3.22 (ddd, *J* = 18.5, 13.4, 6.5 Hz, 2H), 2.92

(m, *J* = 20.8, 13.6, 8.1 Hz, 3H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.00 (s). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 129.17 (s), 128.72 (s), 126.73 (s), 112.83 (s), 69.76 (s), 54.15 (s), 28.37 (s).

4.7 Tert-butyl (3-hydroxy-1-phenyl-4-((4-(trifluoromethoxy)phenyl)amino)butan-2-yl)carbamate (**3d**):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 4-(trifluoromethoxy)aniline (336 mg, 1.9 mmol) provide the **3d** as a white solid (510 mg, 1.15 mmol, 61%). Rf = 0.40 (3:1 hexanes/ethyl acetate). Mp: 148-150 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.23 (m, 6H), 6.98 (d, J = 8.6 Hz, 2H), 6.54 (d, J = 8.9 Hz, 2H), 4.82 (d, J = 9.1 Hz, 1H), 3.92 – 3.72 (m, 2H), 3.15 (dt, J = 13.2, 10.6 Hz, 2H), 2.99 – 2.83 (m, 2H), 2.58 (br, 1H), 1.40 (s, 9H). ^{19}F NMR (376 MHz, $CdCl_3$) δ -58.47 (s). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 147.03 (s), 129.21 (s), 128.69 (s), 126.68 (s), 122.52 (s), 113.57 (s), 70.03 (s), 53.74 (s), 47.75 (s), 28.39 (s). ESI (HR-MS) m/z: $C_{22}H_{27}F_3N_2O_4$ calcd: 441.1956; found: 441.2028.

4.8 Tert-butyl (4-((4-acetylphenyl)amino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**3e**):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 1-(4-aminophenyl)ethan-1-one (256 mg, 1.9 mmol) provide the **3e** as a white solid (398 mg, 1.0 mmol, 53%). Rf = 0.23 (3:1 hexanes/ethyl acetate). Mp: 125-127 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.14 (m, 5H), 6.50 (d, *J* = 8.6 Hz, 2H), 4.97 (d, *J* = 9.0 Hz, 1H), 3.85 (dd, *J* = 40.9, 6.8 Hz, 2H), 3.31 – 3.26 (m, 2H), 3.20-3.15 (m, 1H), 2.96 – 2.83 (m, 2H), 2.46 (s, 3H), 1.39 (s, 9H). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 196.91 (s), 156.66 (s), 152.33 (s), 137.95 (s), 130.98 (s), 129.56 (s), 129.26 (d, *J* = 14.9 Hz), 128.59 (d, *J* = 15.3 Hz), 126.65 (s), 113.80 (s), 111.67 (s), 80.05 (s), 69.77 (s), 53.74 (s), 46.58 (s), 38.35 (s), 28.40 (s), 26.15 (d, *J* = 8.4 Hz). ESI (HR-MS) m/z $C_{23}H_{30}N_2O_4$ calcd: 399.2239; found: 399.2333.

4.9 Tert-butyl (4-((2-fluorophenyl)amino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**3f**):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 2-fluoroaniline (211 mg, 1.9 mmol) provide the **3f** as a white solid (398 mg, 1.06 mmol, 56%). Rf = 0.56 (3:1 hexanes/ethyl acetate). Mp: 124-126 °C. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.25 (m, 5H), 6.97 – 6.91 (m, 2H), 6.67 – 6.59 (m, 2H), 4.89 (d, J = 9.0 Hz, 1H), 3.86 (dd, J = 21.7, 13.7 Hz, 2H), 3.26 – 3.14 (m, 2H), 3.00 – 2.86 (m, 2H), 2.71 (br, 1H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.61 (s). ^{13}C NMR{^1H} (101 MHz, $CDCl_3$) δ 156.22 (s), 153.03 (s), 150.69 (s), 138.06 (s), 136.44 (s), 129.33 (s), 128.68 (s), 126.63 (s), 124.66 (s), 117.46 (s), 114.68 (d, J = 18.5 Hz), 112.59 (s), 79.89 (s), 69.89 (s), 54.00 (s), 47.52 (s), 38.60 (s), 28.41 (s). ESI (HR-MS) m/z$C_{21}H_{27}FN_2O_3$ calcd: 375.2039; found: 375.2089.

4.10 Tert-butyl (3-hydroxy-1-phenyl-4-((2-(trifluoromethyl)phenyl)amino)butan-2-yl)carbamate (3g):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 2-(trifluoromethyl)aniline (306 mg, 1.9 mmol) provide the **3g** as a white solid (339 mg, 0.78 mmol, 41%). Rf = 0.56 (3:1 hexanes/ethyl acetate). Mp: 100-102 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.7 Hz, 1H), 7.33 – 7.19 (m, 6H), 6.75 – 6.65 (m, 2H), 4.90 (d, J = 8.3 Hz, 1H), 4.71 (s, 1H), 3.89 – 3.80 (m, 2H), 3.24 (s, 2H), 2.93 (td, J = 20.8, 7.4 Hz, 2H), 2.80 (br, 1H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$ δ -62.41 (s). ^{13}C NMR{^1H} (101 MHz, $CdCl_3$) δ 156.37 (s), 145.55 (s), 137.97 (s), 133.18 (s), 129.28 (s), 128.71 (s), 126.66 (s), 116.58 (s), 112.25 (s), 79.96 (s), 69.72 (s), 54.18 (s), 47.24 (s), 38.49 (s), 28.39 (s). ESI (HR-MS) m/z: $C_{22}H_{27}F_3N_2O_3$ calcd: 425.2007; found: 425.2050.

4.11 Tert-butyl (4-((3-fluorophenyl)amino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (3h):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 3-fluoroaniline (211 mg, 1.9 mmol) provide the **3h** as a white solid (455 mg, 1.21 mmol, 64%). Rf = 0.56 (3:1 hexanes/ethyl acetate). Mp: 131-133 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 5H), 7.05 (dd, J = 15.0, 8.0 Hz, 1H), 6.40 – 6.32 (m, 2H), 6.27 (dt, J = 11.5, 2.2 Hz, 1H), 4.81 (d, J = 9.1 Hz, 1H), 3.91 – 3.75 (m, 2H), 3.15 (ddd, J = 18.7, 13.3, 6.6 Hz, 2H), 2.98 – 2.84 (m, 2H), 2.58 (br, 1H), 1.40 (s, 9H). ^{19}F NMR (376 MHz, $CdCl_3$) δ -112.68 (s). ^{13}C NMR{^1H} (101 MHz, $CDCl_3$) δ 165.34 (s), 156.51 (s), 149.91 (s), 137.95 (s), 130.36 (s), 129.22 (s), 128.70 (s), 126.67 (s), 109.13 (s), 104.40 (s), 100.03 (s), 80.03 (s), 69.95 (s), 53.71 (s), 47.46 (s), 38.42 (s), 28.39 (s).

4.12 Tert-butyl (3-hydroxy-1-phenyl-4-((3-(trifluoromethyl)phenyl)amino)butan-2-yl)carbamate (3i):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 3-(trifluoromethyl)aniline (306 mg, 1.9 mmol) provide the **3i** as a white solid (545 mg, 1.25 mmol, 66%). Rf = 0.51 (3:1 hexanes/ethyl acetate). Mp: 134-136 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.23 (m, 6H), 6.91 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 6.72 (d, J = 8.2 Hz, 1H), 4.84 (d, J = 9.0 Hz, 1H), 3.93 – 3.76 (m, 2H), 3.18 (dt, J = 32.1, 9.4 Hz, 2H), 2.90 (dd, J = 28.8, 7.6 Hz, 2H), 2.68 (br, 1H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, $CdCl_3$) δ -62.79 (s). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 156.59 (s), 148.29 (s), 137.88 (s), 129.73 (s), 129.18 (s), 128.71 (s), 126.70 (s), 116.31 (s), 114.22 (s), 109.24 (s), 80.12 (s), 69.85 (s), 53.81 (s), 47.15 (s), 38.35 (s), 28.37 (s). ESI (HR-MS) m/z: $C_{21}H_{27}FN_2O_3$ calcd: 375.2039; found: 393.2092.

4.13 Tert-butyl (4-((2,4-difluorophenyl)amino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**3j**):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 2,4-difluoroaniline (245 mg, 1.9 mmol) provide the **3j** as a white solid (388 mg, 0.99 mmol, 52%). Rf = 0.40 (3:1 hexanes/ethyl acetate). Mp: 110-112 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.44 – 7.08 (m, 5H), 6.74 (ddd, J = 20.5, 11.5, 4.8 Hz, 2H), 6.57 (td, J = 9.2, 5.5 Hz, 1H), 4.89 (d, J = 8.9 Hz, 1H), 3.93 – 3.74 (m, 2H), 3.24 – 3.09 (m, 2H), 3.00 – 2.85 (m, 2H), 2.76 (br, 1H), 1.42 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.04 (s), -131.07 (s). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 129.30 (s), 128.69 (s), 126.66 (s), 69.68 (s), 54.14 (s), 48.19 (s), 38.10 (s), 28.02 (s). ESI (HR-MS) m/z: $C_{21}H_{26}F_2N_2O_3$ calcd: 393.1945; found: 393.1298.

4.14 Tert-butyl (4-((4-(tert-butyl)phenyl)amino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**3k**):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 4-(tert-butyl)aniline (283 mg, 1.9 mmol) provide the **3k** as a white solid (630 mg, 1.52 mmol, 80%). Rf = 0.46 (3:1 hexanes/ethyl acetate). Mp: 106-108 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.23 (m, 7H), 6.56 (d, J = 8.7 Hz, 2H), 4.91 (d, J = 9.2 Hz, 1H), 3.91 – 3.75 (m, 2H), 3.22 – 3.09 (m, 2H), 2.91 (3, J = 13.6, 10.7 Hz, 3H), 1.41 (s, 9H), 1.26 (s, 9H).. ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 156.37 (s), 145.71 (s), 141.00 (s), 138.19 (s), 129.36 (s), 128.62 (s), 126.55 (s), 126.16 (s), 113.26 (s), 79.78 (s), 69.85 (s), 53.81 (s), 48.06 (s), 38.69 (s), 33.97 (s), 31.61 (s), 28.45 (s). ESI (HR-MS) m/z: $C_{25}H_{36}F_2N_2O_3$ calcd: 413.2759; found: 413.2799.

4.15 Tert-butyl (3-hydroxy-4-((4-methoxyphenyl)amino)-1-phenylbutan-2-yl)carbamate (**3l**):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 4-methoxyaniline (234 mg, 1.9 mmol) provide the **3l** as a white solid (632 mg, 1.63 mmol, 86%). Rf = 0.25 (3:1 hexanes/ethyl acetate). Mp: 110-112 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.30 – 7.14 (m, 5H), 6.77 – 6.56 (m, 4H), 4.89 (d, J = 9.3 Hz, 1H), 3.87 – 3.64 (m, 5H), 3.17 – 3.04 (m, 2H), 2.96 – 2.81 (m, 3H), 1.40 (s, 9H). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 156.34 (s), 152.69 (s), 142.13 (s), 138.16 (s), 129.34 (s), 128.56 (d, J = 11.9 Hz), 126.48 (d, J = 14.0 Hz), 120.51 (s), 114.99 (d, J = 11.8 Hz), 114.63 (s), 79.78 (s), 69.80 (s), 55.96 (s), 53.59 (s), 38.65 – 38.45 (m), 28.43 (s). ESI (HR-MS) m/z: $C_{21}H_{26}F_2N_2O_3$ calcd: 387.2239; found: 387.2262.

4.16 Tert-butyl (4-((2,6-dimethylphenyl)amino)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**3m**):

Using the general procedure, tert-butyl (1-(oxiran-2-yl)-2-phenylethyl) carbamate (500 mg, 1.9 mmol) and 2,6-dimethylaniline (230 mg, 1.9 mmol) provide the **3m** as a white solid (470 mg, 1.22 mmol, 64%). Rf = 0.47 (3:1 hexanes/ethyl acetate). Mp: 99-101 °C. ^{1}H NMR (400 MHz, $CdCl_3$) δ 7.33 – 7.17 (m, 5H), 6.97 (d, J = 7.5 Hz, 2H), 6.83 (t, J = 7.4 Hz, 1H), 4.87 (d, J = 9.1 Hz, 1H), 3.87 – 3.67 (m, 2H), 3.20 (s, 1H), 3.04 – 3.00 (dd, 2H), 2.94– 2.88 (m, 3H), 2.25 (s, 6H), 1.37 (s, 9H). ^{13}C NMR{^{1}H} (101 MHz, $CdCl_3$) δ 156.18 (s), 145.46 (s), 138.25 (s), 130.39 (s), 129.46 (s), 129.00 (s), 128.62 (s), 126.54 (s), 122.77 (s), 79.50 (s), 70.55 (s), 54.14 (s), 51.68 (s), 38.86 (s), 28.41 (s), 18.51 (s). ESI (HR-MS) m/z: $C_{21}H_{26}F_2N_2O_3$ calcd: 385.2446; found: 385.2496.

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