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$Sn(OTf)_2$ catalysed regioselective styrene oxide ring opening with aromatic amines

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ABSTRACT

$Sn(OTf)_2$ is an efficient and versatile catalyst for the highly regioselective opening of styrene oxide with aromatic amines, which allowed for the preparation of fourteen 2-arylamino-2-phenylethanols, some of them described here for the first time (**6g**, **6i**, **6j**, **6k** and **6m**). $Sn(OTf)_2$ also catalyses the opening of styrene oxide with aliphatic amines in moderate to high yields but with a lower degree of regioselectivity. 2-Akylamino-1-phenylethanols are the predominant products when moderate to high regioselectivity is observed (compounds **4b**, **4c** and **4d**). This is the first report of the use of $Sn(OTf)_2$ to catalyse the opening of an epoxide by aliphatic amines.

1. Introduction

Vicinal amino alcohol is a common structural component, which can be found in naturally occurring molecules,[1] synthetic pharmacologically active compounds,[2] ligands for catalysis[3] and more recently as organocatalysts.[4] The classical route for the preparation of such compounds is the direct aminolysis of 1,2-epoxides.[5] However, these reactions, which are typically carried out in the presence of a large excess of amines at elevated temperatures, often fail when poorly nucleophilic amines or hindered epoxides or amines are used and observed regioselectivities can be low. Several modifications of the classical procedures have been reported such as the use of metal amides,[6,7] Lewis acids[6–9] or lithium salts,[10] some of which include poorly nucleophilic counter-anions.[6,7,11] Many of these methods are catalytic, work for both aliphatic and aromatic amines and show improved regioselectivities, but there are reports of some catalyst systems, which fail to react with anilines bearing electron-withdrawing groups[9b,c,h] or foster the attack of aromatic amines on oxiranes, failing to promote the reaction with aliphatic amines.[8l,m,9a,b,d,h,12,13,16] There are also methods, which are only described employing aliphatic[11c,14,15] or aromatic[8a,b,d,h,i,k,m,9g,i,j] amines.

As part of a program to develop environmentally friendly and selective inhibitors for the fungus *Botrytis cinerea*,[17] we previously prepared amino alcohols with a clovane skeleton,[18] which show fungistatic activity against the fungus *B. cinerea*.[19] Treatment of caryophyllene oxide with aromatic amines in acetonitrile, under reflux, catalysed by $Sn(OTf)_2$ yielded amidinoclovanols as the main products and the above mentioned aminoclovanols as secondary products. Aliphatic amines failed to react under the previously described conditions, which is consistent with previous observations on the preparation of vicinal amino alcohols from *meso*-epoxides catalysed by $Sn(OTf)_2$.[16]

When evaluated against the phytopathogenic fungus *B. cinerea* while the above mentioned amidinoclovanols were inactive, the related aminoclovanols showed activities, which were related to the nature of the amino moiety. Further exploration of the influence of this amino moiety was hampered by the low yield of active compounds obtained. Therefore, a different epoxide should be chosen as the substrate in order to explore structure–activity relationships of amino alcohols with different substitution patterns in the amino moiety.

A suitable candidate for this exploration is styrene oxide, which is expected to react under similar conditions to those employed in the preparation of aminoclovanols and is also simple enough so as not to suffer rearrangement reactions. As a non-symmetrically substituted epoxide, styrene oxide displays a general tendency for regioselective attack on the benzylic position when aromatic amines are employed.[7,8,9e,10,11a,g–k,20] Aliphatic amines use to show a preferential attack on the non-benzylic unsubstituted position of the oxirane ring of styrene oxide, with a lower degree of regioselectivity.[8c,10e,11a,c,g–i]

Here we report on a highly regioselective preparation of amino alcohols through the opening of styrene oxide with aromatic amines catalysed by $Sn(OTf)_2$. The reactivity of aliphatic amines on styrene oxide mediated by this catalyst is also described.

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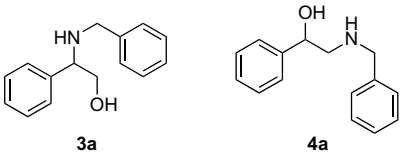
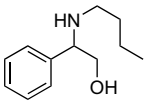
2. Results and discussion

Styrene oxide was treated with several representative aliphatic amines ($PhCH_2NH_2$, *n*-$BuNH_2$, diisopropylamine and pyrrolidine) under three different sets of reaction conditions (see Table 1). $Sn(OTf)_2$ catalysed the reaction of styrene oxide with the selected aliphatic amines under all of the reaction conditions evaluated. All compounds obtained were characterised by their MS and NMR spectra. The best yields were found in the case of those reactions carried out either in CH_3CN or in the absence of solvents. Regioisomeric mixtures of compounds were observed for all evaluated combinations of reagents and reaction conditions with selectivities ranging from almost nil for benzyl amine to the highly selective formation of the least substituted regioisomer **4b** for *n*-butyl amine under solvent-free conditions at 25 °C (Table 1, entry 6). The least substituted regioisomers **4c** and **4d** were also the main products when pyrrolidine and diisopropylamine were employed but their selectivities were lower than those exhibited by preparations of compound **4b** under solvent-free conditions. No amidine formation was observed when acetonitrile was used as a solvent.[18]

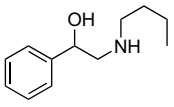


3a

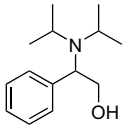
4a



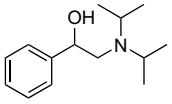
3b



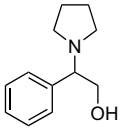
4b



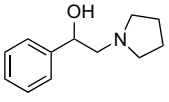
3c



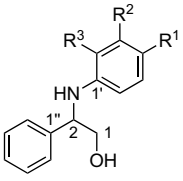
4c



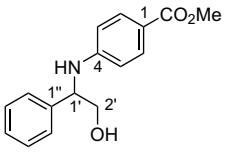
3d



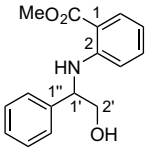
4d



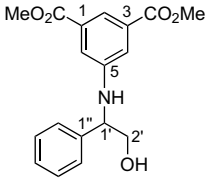
6a $R^1 = R^2 = R^3 = H$
6b $R^1 = OCH_3$; $R^2 = R^3 = H$
6c $R^1 = NO_2$; $R^2 = R^3 = H$
6d R^1 =H; $R^2 = NO_2$; $R^3 = H$
6e $R^1 = R^2 = H$; $R^3 = NO_2$
6f $R^1 = Br$; $R^2 = R^3 = H$
6g R^1 =H; $R^2 = Br$; $R^3 = H$
6h $R^1 = R^2 = H$; $R^3 = Br$



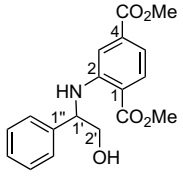
6i



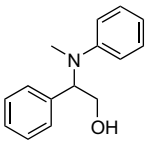
6j



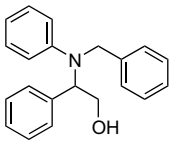
6k



6m



6n



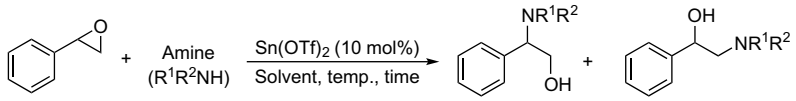
6p

In contrast, the reaction of aniline with styrene oxide catalysed by $Sn(OTf)_2$ regioselectively yielded the amino alcohol derived from the attack on the benzylic position of the epoxide. Although this reaction spread to a number of aromatic amines, either primary (**5a**–**m**) or secondary (**5n**, **5p**), none of the corresponding least substituted regioisomers could be detected (Table 2); this is an advantage of this method for the preparation of 2-arylamino-2-phenylethanols when compared with others described in the literature.[7,8a,c,9a,10b,e,11a,] Furthermore, anilines bearing electron-withdrawing groups do not fail to react in the evaluated reaction conditions. All compounds obtained were characterised by their MS and NMR spectra. For instance, the product obtained when methyl 4-aminobenzoate (**5i**) was used as starting material (compound **6i**) (80%) showed signals in its ^1H NMR at δH=3.80 (s, 3H), 3.91 (dd, *J*=6.3, 11.2 Hz, 1H), 3.99 (dd, *J*=4.0, 11.2 Hz, 1H), 4.56 (dd, *J*=4.0, 6.3 Hz, 1H), assigned to CO_2CH_3, H-2′a, H-2′b and H-1′, respectively. 2D COSY and HMBC studies and the observation of a fragment in the EIMS at *m*/*z* 240 corresponding to the loss of a CH_2OH unit from the molecular ion *m*/*z* 271, led to an assignment of the substitution on the phenylethyl moiety. These data led to the assignment of the structure of compound **6i** as methyl 4-(2′-hydroxyethyl-1′-phenyl-amino) benzoate.

Regarding the opening of styrene oxide by aromatic amines, reaction times were generally much shorter when no solvent was used. Unfortunately, however, the yields of isolated products were lower than those observed for reactions carried out in acetonitrile. Reaction mixtures were harder to purify due to the prevalence of inseparable mixtures. Reactions were much cleaner and the yields of isolated products were higher when the reactions were carried out in acetonitrile. This allowed for the preparation of some previously described amino alcohols (**6a**–**f**, **6h**) and of compounds **6g**, **6i**, **6j**, **6k** and **6m**, which are described here for the first time. Secondary alkyl aryl amines appear to behave as their primary aromatic counterparts yielding only products derived from the attack on the benzylic position even in the case of benzyl phenyl amine (**5p**). As observed with aliphatic amines, no amidine formation was detected when the reactions were carried out in acetonitrile.[18]

Some of the above described amino alcohols showed activities, which are comparable to or better than those showed by the

Table 1
Treatment of styrene oxide (**1**) with aliphatic amines catalysed by $Sn(OTf)_2$[a]



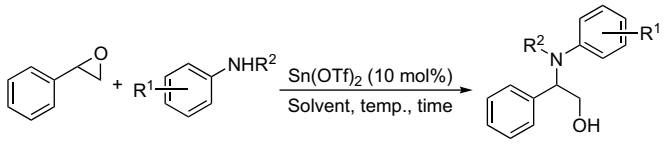
1 2 3 4

Entry	Amine (**2**)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	Products[b] (ratio)	Reference[c]
1	Benzyl amine (**2a**)	CH_3CN	80	24	33	**3a**+**4a** (50:50)	10b,11h
2	**2a**	CH_2Cl_2	40	24	33	**3a**+**4a** (50:50)	
3	**2a**	None	25	24	83	**3a**+**4a** (47:53)	
4	*n*-Butyl amine (**2b**)	CH_3CN	80	45	91	**3b**+**4b** (57:43)	10b
5	**2b**	CH_2Cl_2	40	45	11	**3b**+**4b** (47:53)	
6	**2b**	None	25	20	60	**3b**+**4b** (2:98)	
7	Diisopropylamine (**2c**)	CH_3CN	80	120	59	**3c**+**4c** (21:79)	10b
8	**2c**	CH_2Cl_2	40	105	51	**3c**+**4c** (39:61)	
9	**2c**	None	25	40	58	**3c**+**4c** (20:80)	
10	Pyrrolidine (**2d**)	CH_3CN	80	24	>99	**3d**+**4d** (25:75)	21
11	**2d**	CH_2Cl_2	40	24	83	**3d**+**4d** (40:60)	
12	**2d**	None	25	6	94	**3d**+**4d** (31:69)	

[a] Reaction conditions: styrene oxide (**1**) (1.5 mmol), aliphatic amine (**2**) (3 mmol), $Sn(OTf)_2$ (10 mol %), solvent (5 mL).
[b] Yields and product ratios obtained after chromatographic purification.
[c] References including spectroscopic data.

equivalent aminoclovanols. For example, compound **6c** exhibited an EC_{50} against *B. cinerea* after 6 days at 35 ppm while the comparable clovane derivative, 2β-(*p*-nitrophenylamino)clovan-2α-ol, displayed an EC_{50} against *B. cinerea*, after 6 days, at 70 ppm.[19b] The analysis of the structure–activity relationships will be discussed elsewhere.

Table 2
Treatment of styrene oxide (**1**) with aromatic amines catalysed by $Sn(OTf)_2$[a]



1 5 6

Entry	Amine (**5**)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	Product (**6**)	Reference[d]
1	Aniline (**5a**)	CH_3CN	25	24	92	**6a**	11h
2	**5a**	None	25	0.5	71		
3	4-Methoxyaniline (**5b**)	CH_3CN	25	24	90	**6b**	10b
4	**5b**	None	40	0.1	65		
5	4-Nitroaniline (**5c**)	CH_3CN	25	24	70	**6c**	10b
6	**5c**	None	25	0.1	41		
7	3-Nitroaniline (**5d**)	CH_3CN	25	24	72	**6d**	—
8	**5d**	None	25	0.1	74		
9	2-Nitroaniline (**5e**)	CH_3CN	25	24	56	**6e**	—
10	**5e**	None	25	0.1	39		
11	4-Bromoaniline (**5f**)	CH_3CN	80	24	53	**6f**	22
12	**5f**	None	25	0.1	55		
13	3-Bromoaniline (**5g**)	CH_3CN	25	24	82	**6g**	—
14	**5g**	None	25	0.3	75		
15	2-Bromoaniline (**5h**)	CH_3CN	80	24	70	**6h**[c]	23
16	**5h**	None	25	0.1	23		
17	Methyl 4-aminobenzoate (**5i**)	CH_3CN	80	24	80	**6i**	—
18	**5i**	None	25	0.1	33		
19	Methyl 2-aminobenzoate (**5j**)	CH_3CN	25	24	83	**6j**	—
20	**5j**	None	25	0.1	44		
21	Methyl 5-aminoisophthalate (**5k**)	CH_3CN	25	24	64	**6k**	—
22	**5k**	None	25	0.1	12		
23	Methyl 4-aminoterephthalate (**5m**)	CH_3CN	25	24	78	**6m**	—
24	**5m**	None	25	0.1	48		
25	Methyl phenyl amine (**5n**)	CH_3CN	25	24	82	**6n**	10b,11h
26	**5n**	None	25	1	56		
27	Benzyl phenyl amine (**5p**)	CH_3CN	25	24	62	**6p**[c]	24
28	**5p**	None	25	0.3	35		

[a] Reaction conditions: styrene oxide (**1**) (1.5 mmol), aromatic amine (**2**) (3 mmol), $Sn(OTf)_2$ (10 mol %), solvent (5 mL).
[b] Yield obtained after chromatographic purification.
[c] Prepared for first time by oxirane ring opening.
[d] References including spectroscopic data.

3. Conclusions

$Sn(OTf)_2$ is an efficient and versatile catalyst for the highly regioselective opening of styrene oxide with aromatic amines, permitting the preparation of novel 2-arylamino-2-phenylethanol derivatives (**6g**, **6i**, **6j**, **6k** and **6m**), together with nine others previously described. None of the regioisomeric amino alcohols was detected and anilines bearing electron-withdrawing groups do not fail to react in the evaluated reaction conditions. Reaction times were generally much shorter when no solvent was used, the regioselectivities were maintained, but yields were lower. $Sn(OTf)_2$ also catalyses the opening of styrene oxide with aliphatic amines ($PhCH_2NH_2$, *n*-$BuNH_2$, diisopropylamine and pyrrolidine) with moderate to high yields. 2-Akylamino-1-phenylethanols are the predominant regioisomers when moderate or high regioselectivity is observed (compounds **4b**, **4c** and **4d**).

4. Experimental

4.1. General

Melting points were measured with a Reichert-Jung Kofler block and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrophotometer. ^1H and ^{13}C NMR measurements were obtained on Varian Gemini 300 and INOVA 400 NMR spectrometers with $SiMe_4$ as the internal reference. NMR assignments were made by a combination of 1D and 2D techniques. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. In ^{13}C NMR the multiplicities refer to the resonances in the off-resonance spectra and were elucidated using distortionless enhancement by polarization transfer (DEPT) spectral editing technique with secondary pulses at 90° and 135°. Electron Impact mass spectra were recorded on a Finnigan Voyager mass spectrometer at 70 eV and high resolution mass spectrometry was carried out in a Finnigan MAT95S spectrometer. HPLC was performed using a Hitachi/Merck L-6270 apparatus equipped with a UV–vis detector (L 4250) and a differential refractometer detector (RI-71). TLC was performed on a Merck Kieselgel 60 F_{254}, 0.2 mm thick. Silica gel (Merck) was used for column chromatography. Purification by HPLC was conducted using a Si gel column (Hibar 60, 7 m, 1 cm wide, 25 cm long).

4.2. Standard procedure for the reaction of styrene oxide (1) with amines

Tin(II) triflate (73 mg, 0.166 mmol) was added to a magnetically stirred mixture of styrene oxide (**1**) (204 mg, 1.66 mmol) and methyl *p*-aminobenzoate (**5i**) (310 mg, 3.32 mmol) in anhydrous acetonitrile (5 mL), and the reaction was heated to 80 °C. After 24 h, once compound **1** was consumed (TLC), the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel to yield methyl 4-(2′-hydroxyethyl-1′-phenyl-amino) benzoate **6i** (368 mg, 1.358 mmol, 80% yield). Orange solid; mp 94–97 °C; IR (KBr) ν_{max} (cm^{-1}): 3399 (ν O–H, N–H), 2878 (ν C–H, N–CH_2), 1691 (ν C=O ester), 1605, 1525 (ν C=C aromatic ring); ^1H NMR (400 MHz, C_6D_6): δ (ppm) 3.80 (s, 3H, CO_2CH_3), 3.91 (dd, *J*=6.3, 11.2 Hz, 1H, H-2′b), 3.99 (dd, *J*=4.0, 11.2 Hz, 1H, H-2′a), 4.56 (dd, *J*=4.0, 6.3 Hz, 1H, H-1′), 5.05 (br s, 1H, O*H*), 6.51 (dd, *J*=2.6, 8.8 Hz, 2H, H-2, H-6), 7.22–7.35 (5H, H-2″, H-3″, H-4″, H-5″, H-6″), 7.77 (dd, *J*=2.6, 8.8 Hz, 2H, H-3, H-5); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 51.5 (q, CO_2CH_3), 59.2 (d, C-1′), 67.1 (t, C-2′), 112.5 (2C, d, C-2, C-6), 118.6 (s, C-1), 126.6 (2d, C-2″, C-6″), 127.8 (d, C-4″), 128.9 (2C, d, C-3″, C-5″), 131.3 (2C, d, C-3, C-5), 139.3 (s, C-1″), 151.1 (s, C-4), 167.4 (s, CO_2Me); HMBC (selected correlations): C-1→H-2, H-6, CO_2CH_3; C-1″→H-1′, H-2′a, H-2′b; C-4→H-1′, H-3, H-5; MS (EI) *m*/*z* (relative intensity): 271 $[M]^{+\bullet}$ (4), 240 $[M-CH_2OH]^+$ (100), 208 (17), 162 (27), 135 (19), 120 (28), 103 (26), 91 $[C_7H_7]^+$ (27), 77 $[C_6H_5]^+$ (18); HRMS *m*/*z*: observed 271.1200 $[M]^+$; $C_{16}H_{17}NO_3$ requires 271.1208.

4.3. Selected physical and spectroscopic data

4.3.1. 2-Diisopropylamino-2-phenylethanol (**3c**)

Yellow oil; IR (KBr) ν_{max} (cm^{-1}): 3406 (ν O–H), 2963 (ν C–H), 2870 (ν C–H, N–CH_2), 1602, 1493 (ν C=C aromatic ring), 1395, 1363 (δ_s CH_3 isopropyl); ^1H NMR (400 MHz, C_6D_6): δ (ppm) 0.88 (d, *J*=6.8 Hz, 6H, 2Me), 1.15 (d, *J*=6.8 Hz, 6H, 2Me), 3.37 (septuplet, *J*=6.8 Hz, 2H, H-1″, H-1‴), 3.48 (dd, *J*=5.7, 10.3 Hz, 1H, H-1a), 3.78 (dd, *J*=10.2, 10.3 Hz, H-1b), 4.02 (dd, *J*=5.7, 10.2 Hz, 1H, H-2), 7.25–7.37 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 21.7 (2c, 2Me), 24.5 (2c, 2Me), 45.2 (2d, C-1″, C-1‴), 59.6 (d, C-2), 61.3 (t, C-1), 127.3 (d, C-4′), 128.2 (2d, C-3′, C-5′), 129.2 (2d, C-2′, C-6′), 140.8 (s, C-1′); HMBC (selected correlations): C-1′→H-2; C-1″, C-1‴→H-2; MS (EI) *m*/*z* (relative intensity): 221 $[M]^{+\bullet}$ (4), 190 $[M-CH_2OH]^+$ (99), 148 (98), 131 (40), 104 (99), 91 $[C_7H_7]^+$ (64), 83 (100), 79 (54), 77 $[C_6H_5]^+$ (50), 47 (36); HRMS *m*/*z*: observed 221.1770 $[M]^+$; $C_{14}H_{23}NO$ requires 221.1780.

4.3.2. 2-(3′-Nitrophenylamino)-2-phenylethanol (**6d**)

Red solid; mp 89–91 °C; IR (KBr) ν_{max} (cm^{-1}): 3400 (ν O–H), 2932 (ν C–H, N–CH_2), 1619, 1527 (ν C=C aromatic ring, N=O); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.60 (br s, 1H, O*H*), 3.82 (dd, *J*=6.8, 11.2 Hz, 1H, H-1b), 4.00 (dd, *J*=4.0, 11.2 Hz, 1H, H-1a), 4.54 (dd, *J*=4.0, 6.8 Hz, 1H, H-2), 5.07 (br s, 1H, N*H*), 6.81 (ddd, *J*=0.7, 2.3, 8.1 Hz, 1H, H-6′), 7.19 (dd, *J*=8.2, 8.2 Hz, 1H, H-5′), 7.30 (m, 1H, H-4″), 7.36 (m, 5H, H-2′, H-2″, H-3″, H-5″, H-6″), 7.48 (ddd, *J*=0.6, 2.2, 8.0 Hz, 1H, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 59.6 (d, C-2), 66.9 (t, C-1), 107.6 (d, C-2′), 112.1 (d, C-4′), 119.3 (d, C-6′), 126.6 (d, 2C, C-2″, C-6″), 127.9 (d, C-4″), 128.9 (d, 2C, C-3″, C-5″), 129.6 (d, C-5′), 138.8 (s, C-1″), 148.0 (s, C-1′), 149.0 (s, C-3′); HMBC (selected correlations): C-1″→H-2, 2H-1; C-2″, C-6″→H-2; MS (EI) *m*/*z* (relative intensity): 258 $[M]^{+\bullet}$ (4), 227 $[M-CH_2OH]^+$ (100), 207 (18), 181 (40), 180 (26), 103 (16), 91 $[C_7H_7]^+$ (24), 77 $[C_6H_5]^+$ (14); HRMS *m*/*z*: observed 258.1009 $[M]^+$; $C_{14}H_{14}N_2O_3$ requires 258.1004.

4.3.3. 2-(2′-Nitrophenylamino)-2-phenylethanol (**6e**)

Red oil; IR (KBr) ν_{max} (cm^{-1}): 3372 (ν O–H), 2936 (ν C–H, N–CH_2), 1618, 1508, 1572 (ν C=C aromatic ring, N=O); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.56 (br s, 1H, OH), 3.92 (dd, *J*=6.7, 11.5 Hz, 1H, H-1b), 4.03 (dd, *J*=4.5, 11.5 Hz, 1H, H-1a), 4.71 (ddd, *J*=4.5, 6.0, 6.7 Hz, 1H, H-2), 6.62 (m, 2H, H-4′, H-6′), 7.20 (m, 1H, H-5′), 7.28 (m, 1H, H-4″), 7.38 (m, 4H, H-2″, H-3″, H-5″, H-6″), 8.18 (dd, *J*=1.6, 8.4 Hz, 1H, H-3′), 8.73 (d, *J*=6.0 Hz, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 59.2 (d, C-2), 66.8 (t, C-1), 115.1 (d, C-6′*), 115.8 (d, C-4′), 126.5 (d, 2C, C-2″, C-6″), 126.6 (d, C-3′), 127.9 (d, C-4″), 128.9 (d, 2C, C-3″, C-5″), 132.3 (s, C-2′), 136.0 (d, C-5′), 138.7 (s, C-1″), 144.6 (s, C-1′) *interchangeable signals; HMBC (selected correlations): C-1′→H-2; C-1″→H-2, 2H-1; C-2″, C-6″→H-2; C-2′→H-4′, H-6′; MS (EI) *m*/*z* (relative intensity): 258 $[M]^{+\bullet}$ (2), 227 $[M-CH_2OH]^+$ (100), 194 (46), 180 (32), 104 (23), 91 $[C_7H_7]^+$ (24), 77 $[C_6H_5]^+$ (30); HRMS *m*/*z*: observed 258.1015 $[M]^+$; $C_{14}H_{14}N_2O_3$ requires 258.1004.

4.3.4. 2-(3′-Bromo-phenyl-amino)-2-phenylethanol (**6g**)

Brown solid; mp 81–84 °C; IR (KBr) ν_{max} (cm^{-1}): 3404 (ν O–H), 2877 (ν C–H, N–CH_2), 1595, 1480 (ν C=C aromatic ring); ^1H NMR (400 MHz, C_6D_6): δ (ppm) 1.61 (s_a, 1H, O*H*), 3.79 (dd, *J*=6.6, 11.1 Hz, 1H, H-1b), 3.95 (dd, *J*=4.0, 11.1 Hz, 1H, H-1a), 4.47 (dd, *J*=4.2, 6.6 Hz, 1H, H-2), 4.73 (s_a, 1H, N*H*), 6.47 (ddd, *J*=0.8, 2.2, 8.2 Hz, 1H, H-6″), 6.73 (dd, *J*=1.9, 2.2 Hz, 1H, H-2″), 6.79 (ddd, *J*=0.8, 1.9, 7.9 Hz, 1H, H-4″), 6.93 (dd, *J*=7.9, 8.2 Hz, 1H, H-5″), 7.26–7.37 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 59.5 (d, C-2),

67.1 (t, C-1), 112.2 (d, C-6″), 116.4 (d, C-2″), 120.5 (d, C-4″), 123.0 (s, C-3″), 126.6 (2d, C-2′, C-6′), 127.7 (d, C-4′), 128.8 (2d, C-3′, C-5′), 130.4 (d, C-5″), 139.4 (s, C-1′), 148.5 (s, C-1″); HMBC (selected correlations): C-1″→H-2; C-2′, C-6′→H-2; MS (EI) *m/z* (relative intensity): 291/293 $[M]^{+\bullet}$ (5/4), 273/275 (8/6), 260/262 $[M-CH_2OH]^+$ (100/80), 182 (24), 180 (23), 155/157 $[C_6H_4Br]^+$ (24/20), 103 (20), 91 $[C_7H_7]^+$ (38), 77 $[C_6H_5]^+$ (32); HRMS *m/z*: observed 291.0255 $[M]^+$; $C_{14}H_{14}NOBr$ requires 291.0259.

*4.3.5. Methyl 2-(2′-hydroxyethyl-1′-phenyl-amino)benzoate (**6j**)*

Yellow solid; mp 78–80 °C; IR (KBr) ν_{max} (cm^{-1}): 3357 (ν O–H), 2877 (ν C–H, N–CH_2), 1684 (ν C=O ester), 1581, 1516 (ν C=C aromatic ring); 1255 (ν C–O–C ester); ^1H NMR (400 MHz, C_6D_6): δ (ppm) 2.63 (br s, 1H, O*H*), 3.86 (dd, *J*=6.6, 11.1 Hz, 1H, H-2′b), 3.90 (s, 3H, CO_2CH_3), 3.94 (dd, *J*=4.5, 11.1 Hz, 1H, H-2′a), 4.65 (dd, *J*=4.5, 6.6 Hz, 1H, H-1′), 6.49 (dd, *J*=1.1, 8.6 Hz, 1H, H-3), 6.57 (ddd, *J*=1.1, 7.1, 8.1 Hz, 1H, H-5), 7.18 (ddd, *J*=1.6, 7.1, 8.6 Hz, 1H, H-4), 7.26 (m, 1H, H-4″), 7.31–7.38 (4H, H-2″, H-3″, H-5″, H-6″), 7.91 (dd, *J*=1.6, 8.1 Hz, 1H, H-6), 8.49 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 51.5 (q, CO_2CH_3), 59.1 (d, C-1′), 67.2 (t, C-2′), 110.5 (s, C-1), 112.6 (d, C-3), 115.1 (d, C-5), 126.6 (2C, d, C-2″, C-6″), 127.4 (d, C-4″), 128.6 (2C, d, C-3″, C-5″), 131.4 (d, C-6), 134.4 (d, C-4), 139.9 (s, C-1″), 150.2 (s, C-2), 169.1 (s, CO_2CH_3); HMBC (selection of correlations): C-2→H-1′; C-1″→H-1′, H-2′a, H-2′b; C-2″, C-6″→H-1′; MS (EI) *m/z* (relative intensity): 271 $[M]^{+\bullet}$ (3), 253 $[M-OH]^+$ (15), 240 $[M-CH_2OH]^+$ (52), 224 (24), 208 (100), 180 (23), 151 $[NHC_6H_5CO_2Me]^+$ (22), 119 (30), 104 (24), 92 (24), 91 $[C_7H_7]^+$ (40), 77 $[C_6H_5]^+$ (36); HRMS *m/z*: observed 271.1215 $[M]^{+\bullet}$; $C_{16}H_{17}NO_3$ requires 271.1208.

*4.3.6. Dimethyl 5-(2′-hydroxyethyl-1′-phenyl-amino)-isophthalate (**6k**)*

Yellow solid; mp 136–141 °C; IR (KBr) ν_{max} (cm^{-1}): 3386 (ν O–H), 2871 (ν C–H, N–CH_2), 1718 (ν C=O ester), 1605, 1438 (ν C=C aromatic ring), 1246, 1024 (ν C–O–C ester); ^1H NMR (400 MHz, C_6D_6): δ (ppm) 2.21 (s_a, 1H, OH), 3.81 (dd, *J*=6.7, 11.2 Hz, 1H, H-2′b), 3.86 (s, 6H, CH_3-2‴, CH_3-2^{IV}), 3.97 (dd, *J*=4.1, 11.2 Hz, 1H, H-2′a), 4.60 (dd, *J*=4.1, 6.7 Hz, 1H, H-1′), 4.84 (s_a, 1H, N*H*), 7.27 (m, 1H, H-4″), 7.35 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.41 (d, *J*=1.6 Hz, 2H, H-4, H-6), 7.96 (t, *J*=1.6 Hz, 1H, H-2); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 52.2 (2c, CH_3-2‴, CH_3-2^{IV}), 59.5 (d, C-1′), 67.0 (t, C-2′), 118.5 (2d, C-4, C-6), 119.7 (d, C-2), 126.7 (2d, C-2″, C-6″), 127.8 (d, C-4″), 128.9 (2d, C-3″, C-5″), 131.1 (2s, C-1, C-3), 139.2 (s, C-1″), 147.5 (s, C-5), 166.7 (2s, C-1‴, C-1^{IV}); HMBC (selected correlations): C-1″→H-1′, 2H-2′; C-2″, C-6″→H-1′; C-1‴→H-2, H-6; C-1^{IV}→H-2, H-4; MS (EI) *m/z* (relative intensity): 329 $[M]^{+\bullet}$ (3), 311 (10), 298 $[M-CH_2OH]^+$ (100), 281 (20), 220 (18), 209 (19), 207 $[NHC_6H_4(CO_2Me)_2]^+$ (48), 193 $[C_6H_4(CO_2Me)_2]^+$ (17), 178 (20), 150 (10), 133 (12), 103 (16), 91 $[C_7H_7]^+$ (33), 77 $[C_6H_5]^+$ (14); HRMS *m/z*: observed 329.1291 $[M]^+$; $C_{18}H_{19}NO_5$ requires 329.1263.

*4.3.7. Dimethyl 2-(2′-hydroxyethyl-1′-phenyl-amino)-terephthalate (**6m**)*

Yellow solid; mp 147–149 °C; IR (KBr) ν_{max} (cm^{-1}): 3358 (ν O–H), 2877 (ν C–H, N–CH_2), 1691 (ν C=O ester), 1578, 1450 (ν C=C aromatic ring), 1245 (ν C–O–C ester); ^1H NMR (400 MHz, C_6D_6): δ (ppm) 3.81 (s, 3H, CH_3-2‴), 3.89 (dd, *J*=6.8, 11.2 Hz, 1H, H-2′b), 3.92 (s, 3H, CH_3-2^{IV}), 3.98 (dd, *J*=6.4, 6.8 Hz, 1H, H2′a), 4.74 (dd, *J*=6.4, 11.2 Hz, 1H, H-1′), 7.17 (dd, *J*=1.4, 8.4 Hz, 1H, H-5), 7.22 (d, *J*=1.4 Hz, 1H, H-3), 7.26 (m, 1H, H-4″), 7.36 (4H, H-2″, H-3″, H-5″, H-6″), 7.95 (d, *J*=8.4 Hz, 1H, H-6), 8.55 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 51.9 (q, CH_3-2^{IV}), 52.2 (q, CH_3-2‴), 58.9 (d, C-1′), 67.2 (t, C-2′), 113.76 (d, C-3), 113.83 (s, C-1), 115.6 (d, C-5), 126.7 (2C, d, C-2″, C-6″), 127.8 (d, C-4″), 128.9 (2C, d, C-3″, C-5″), 131.7 (d, C-6), 134.9 (s, C-4), 139.4 (s, C-1″), 150.0 (s, C-2), 166.6 (s, C-1^{IV}), 168.7 (s, C-1‴); HMBC (selected correlations): C-1″→H-1′; C-2→H-1′; C-1→CH_3-2‴; C-4→CH_3-2^{IV}; C-2″, C-6″→H-1′; C-1‴→H-6; C-1^{IV}→H-3, H-5; MS (EI) *m/z* (relative intensity): 329 $[M]^{+\bullet}$ (2), 311 (9), 298 $[M-CH_2OH]^+$ (72), 266 (100), 238 (14), 207 $[NHC_6H_4(CO_2Me)_2]^+$ (21), 177 (34), 150 (16), 119 $[PhCHCH_2OH]^+$ (18), 104 (22), 91 $[C_7H_7]^+$ (38), 77 $[C_6H_5]^+$ (18); HRMS *m/z*: observed 329.1280 $[M]^+$; $C_{18}H_{19}NO_5$ requires 329.1263.

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