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Ready *N*-alkylation of enantiopure aminophenols: synthesis of tertiary aminophenols

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Abstract—A regioselective indirect alkylation of aminophenols to enantiopure tertiary aminophenols, which are useful chiral ligands for metal-catalysed asymmetric reactions, is reported. This very simple synthetic methodology, through reduction or alkylation of an intermediate benzoxazine, was performed in mild conditions, suitable for the conservation of the configuration of the stereogenic centres. Some crystalline aminophenols show the phenomenon of 'crystallization-induced asymmetric transformation'. © 2001 Elsevier Science Ltd. All rights reserved.

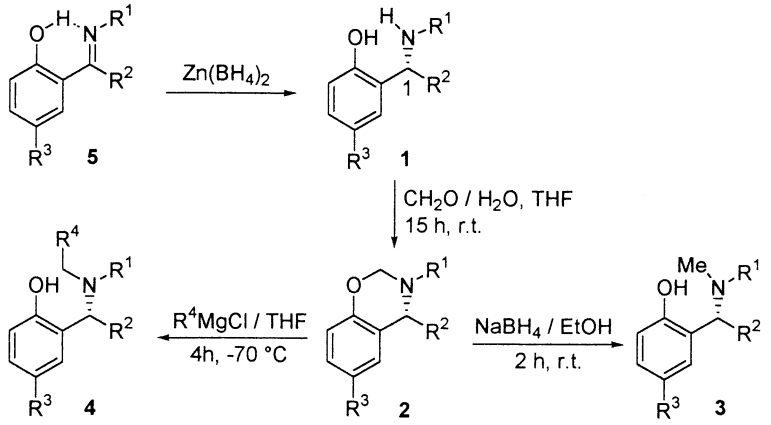
1. Introduction

Enantiopure aminophenols are important building blocks in organic synthesis. Moreover they are used as ligands for the preparation of chiral metal catalysts which are very useful in stereoselective organic synthesis.[1–5]

The search for new metal-catalysed asymmetric reactions has provided some fascinating insights into the effects imposed on the metal catalysts by chiral ligands. A practical consequence is the discovery of ligand-accelerated catalysis (LAC).[6] Thus, an existing catalysed process is improved by the addition of a specific ligand, which leads to a faster 'ligand-accelerated' reaction. The concept is especially valuable in reactions catalysed by early transition metals.[7]

In previous work, we have observed that a catalytic amount of enantiopure aminophenol **1** and aminonaphthol **8** considerably accelerate the addition of dialkylzincs to aldehydes, affording the corresponding alcohols in good enantiomeric purity.[1,4] The precatalyst aminophenol **1** is an accessible compound generally obtained by stereoselective reduction of the corresponding 2-imidoylphenol **5**.[1–3] The aminoalkylation of electron-rich aromatic compounds (the aromatic Mannich reaction) is a convenient route to enantiopure aminonaphthol **8** that is obtained enantiopure by a simple and straightforward condensation of 2-naphthol with benzaldehyde and *R*-(+)-1-phenylethylamine.[4,5]

Literature data showed that an increasing number of aliphatic substituents in the N atom of the ligand procures



Scheme 1.

Keywords: alkylation; aminophenols; benzoxazine.

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Table 1. Cyclization of aminophenols **1a–m** to 3,4-dihydro-2*H*-1,3-benzoxazines **2a–m** and their reduction to aminophenols **3a–m**

Entry	1	R^1	R^2	R^3	2	Yield[a] (%)	3	Yield[a] (%)	dr[b]
1	(*R*)-**1a**	R^{*c}	H	H	(*R*)-**2a**	95	(*R*)-**3a**	85	–
2	(*R*,*R*)-**1b**	R^{*c}	Me	H	(*R*,*R*)-**2b**[1]	91	(*R*,*R*)-**3b**	84	96:4
3	(*R*,*R*)-**1c**	R^{*c}	Et	H	(*R*,*R*)-**2c**	79	(*R*,*R*)-**3c**	60	98:2
4	(*R*,*R*)-**1d**	R^{*c}	$(CH_2)_2Ph$	H	(*R*,*R*)-**2d**	82	(*R*,*R*)-**3d**	72	98:2
5	(*R*,*R*)-**1e**	R^{*c}	Pr	H	(*R*,*R*)-**2e**	93	(*R*,*R*)-**3e**	76	99:1
6	(*R*,*R*)-**1f**	R^{*c}	*i*Bu	H	(*R*,*R*)-**2f**	92	(*R*,*R*)-**3f**	63	99:1
7	(*R*,*R*)-**1g**	R^{*c}	*t*Bu	H	(*R*,*R*)-**2g**	0			
8	(1*S*,1′*R*)-**1g**	R^{*c}	*t*Bu	H	(1*S*,1′*R*)-**2g**	62	(1*S*,1′*R*)-**3g**	0	–
9	(*R*,*R*)-**1h**	R^{*c}	$(CH_2)_2CH{=}CH_2$	H	(*R*,*R*)-**2h**	94	(*R*,*R*)-**3h**	75	99:1
10	(*R*,*R*)-**1i**	R^{*c}	Ph	H	(*R*,*R*)-**2i**[1]	90	(*R*,*R*)-**3i**	79[d]	84:16
11	(1*S*,1′*R*)-**1i**	R^{*c}	Ph	H	(1*S*,1′*R*)-**2i**[1]	87	(1*S*,1′*R*)-**3i**	60[d]	85:15
12	(*R*,*R*)-**1j**	R^{*c}	Me	OMe	(*R*,*R*)-**2j**	69	(*R*,*R*)-**3j**	65	97:3
13	(±)-**1k**	Me	Me	H	(±)-**2k**	60	(±)-**3k**	29	–
14	(±)-**1l**	*i*Pr	Me	H	(±)-**2l**	65	(±)-**3l**	61	–
15	(±)-**1m**	CH_2Ph	Et	H	(±)-**2m**	91	(±)-**3m**	87	–

[a] Isolated yield.
[b] (*R*,*R*)-**3**: (1*S*,1′*R*)-**3** dr was determined by ^1H NMR spectroscopy of the crude reaction mixture.
[c] R^*NH_2=(*R*)-1′-phenylethylamine.
[d] Combined yields of the two diastereomers.

high ees in the alkylation of aldehydes.[8–10] By reductive amination of the acylphenol, secondary aminophenol **1** only can be prepared. Therefore, a careful and chemoselective alkylation of the amino group of aminophenol **1** should be required that can be performed by a multistep procedure, but sometimes a complete loss of optical activity was observed. An alternative way is offered by oxazines that analogously to oxazolidines are useful substrates for nucleophilic additions as they act as acetal equivalents. Here we report the results of our work in exploring the usefulness of the reduction or alkylation of oxazine **2** to prepare enantiopure tertiary aminophenols.

2. Results and discussion

Our strategy starts from cyclization of the aminophenols **1a–m** to 1,3-benzoxazines **2a–m** with formaldehyde followed by reduction of the O–C2 bond with sodium borohydride to *N*-methylaminophenol **3**, or with the nucleophilic addition of organometallic compounds as Grignard reagents to prepare aminophenols **4** (Scheme 1). This strategy has been occasionally applied to β-aminoalcohols or aminonaphthols, through the intermediate oxazolidines[11] or naphthoxazines[8] but never has been applied to aminophenols **1a–m**.

Table 2. Alkylation of the benzoxazines **2b**,**i**,**j** to aminophenols **4**

Entry	2[a]	R^2	R^3	R^4	4[a]	Yield[b] (%)	dr[c]
1	(*R*,*R*)-**2b**	Me	H	Me	(*R*,*R*)-**4ba**	83	92:8
2	(*R*,*R*)-**2b**	Me	H	Bn	(*R*,*R*)-**4bb**	85	99:1
3	(*R*,*R*)-**2b**	Me	H	Ph	(*R*,*R*)-**4bc**	91	99:1
4	(*R*,*R*)-**2i**	Ph	H	Me	(*R*,*R*)-**4ia**	64[d]	80:20
5	(*R*,*R*)-**2i**	Ph	H	Bn	(*R*,*R*)-**4ib**	88[d]	71:29
6	(*R*,*R*)-**2i**	Ph	H	Ph	(*R*,*R*)-**4ic**	85[d]	81:19
7	(*R*,*R*)-**2j**	Me	OMe	Me	(*R*,*R*)-**4ja**	86	96:48
8	(*R*,*R*)-**2j**	Me	OMe	Bn	(*R*,*R*)-**4jb**	71	93:7
9	(*R*,*R*)-**2j**	Me	OMe	Ph	(*R*,*R*)-**4jc**	63	87:3

[a] R^1NH_2=(*R*)-1′-phenylethylamine.
[b] Isolated yield.
[c] (*R*,*R*)-**3**: (1*S*,1′*R*)-**3** dr was determined by ^1H NMR spectroscopy of the crude reaction mixture.
[d] Combined yields of the two diastereomers.

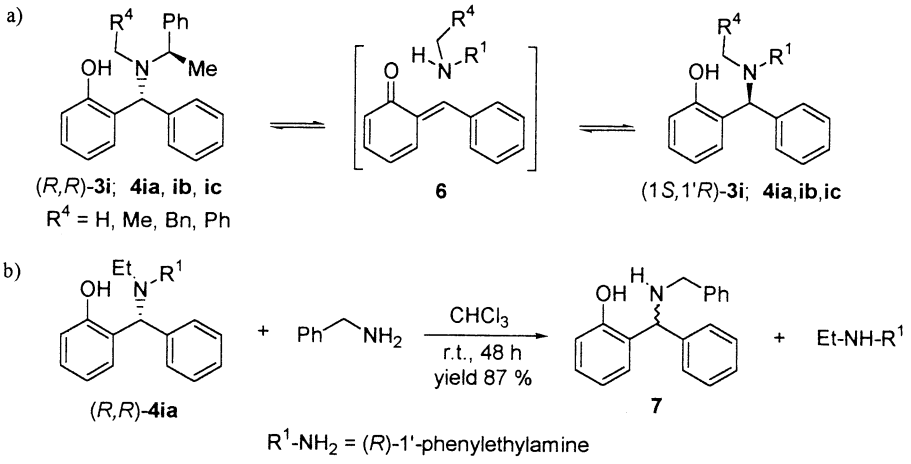
The synthesis of benzoxazines **2** proceeds readily with good yields and retention of configuration at the chiral centres[1,3–5] (see Table 1). Only in the case of aminophenol (*R*,*R*)-**1g** any trace of the corresponding oxazine was detected. Starting from the aminophenols **1a–j**, the benzoxazines were obtained only with formaldehyde; more bulky aldehydes such as acetaldehyde or phenylacetaldehyde failed.

The reduction with sodium borohydride of the intermediate benzoxazines **2a–m** to the *N*-methylaminophenols **3** occurs readily and with good yields except in the case of the *t*-butyloxazine (1*S*,1′*R*)-**2g**. Under these mild reaction conditions, the *N*-methylaminophenols **3** obtained retain the configuration of the chiral centre of the starting oxazines.[1,3–5] Only in the case of oxazines (*R*,*R*)-**2i** and (1*S*,1′*R*)-**2i** a partial epimerization to the C-1 chiral centre was observed with the final (*R*,*R*)- and (1*S*,1′*R*)-**3i** dr of 5.3 and 5.7, respectively (see Table 1).

Moreover, the oxazines (*R*,*R*)-**2b**,**i**,**j** undergo nucleophilic additions of Grignard reagents with the formation of tertiary aminophenols (*R*,*R*)-**4** (Table 2). The reactions take place readily at −70°C with good yields and retention of configuration at the chiral centres.[1,3–5] At higher temperature, there is a considerable epimerization at the C-1 chiral centre, because of the elevated basicity of the reaction medium. Even at the low temperature used for the alkylation, the aminophenols (*R*,*R*)-**4ia–ic**, in the same way as (*R*,*R*)-**3i**, with R^2=phenyl, were obtained with moderate dr=80:20–86:14.

The epimerization observed for these aminophenols **3** and **4** can occur easily by the elimination of the chiral amine through the formation of the intermediate **6** stabilized by the phenyl group (Scheme 2a). This hypothesis is supported by the following experimental evidence. When the aminophenol (*R*,*R*)-**4ia** was treated with benzylamine, exchange of the amines occurs in two days at room temperature (see Scheme 2b).

In addition, the solid and crystalline (1*S*,1′*R*)-**4ia**, dissolved in $CHCl_3$, shows an initial optical activity $[\alpha]_D^{20}$=+51.0 (*c*



Scheme 2.

1.7) which decreases in the time to a final value of $[\alpha]_D^{20}=-69.6$ after 43 h at room temperature. This mutarotation phenomenon was also observed for the aminophenol (1*S*,1′*R*)-**4ib**: from an initial $[\alpha]_D^{20}=+65.2$ (*c* 2.1, $CHCl_3$) to a final value of $[\alpha]_D^{20}=-88.0$ after 44 h at room temperature (see Fig. 1a).

The epimerization of these aminophenols was confirmed by ^1H NMR spectroscopy in $CDCl_3$ solution; in Fig. 1b, de variation vs time has been reported. The (*R*,*R*)-**4ia** and (*R*,*R*)-**4ib** are the final major diastereomers in $CHCl_3$ solution with dr of 80:20 and 71:19, respectively. Allowing the $CHCl_3$ solution of the (*R*,*R*)-**4ia**,**ib** diastereomers to evaporate slowly, the starting crystalline (1*S*,1′*R*)-**4ia**,**ib** were newly obtained. They again show the epimerization in $CHCl_3$ solution and these cycles can be repeated several times. This is a typical situation of 'asymmetric transformation of second kind' induced by the preferential crystallization of a diastereomer.[12–16] It is noteworthy that the two secondary diastereomers aminophenols (1*S*,1′*R*)- and (*R*,*R*)-**1i** are stable and do not epimerize in $CHCl_3$ solution. This may be due to a minor steric tension in the compounds respect to the corresponding tertiary aminonaphthols **4ia**,**ib**.

The aminonaphthol **8**, very similar to aminophenols **1**, shows useful application in stereoselective catalysis and is a very accessible product by a straightforward and stereoselective synthesis.[4,5] This aminonaphthol can be cyclized with formaldehyde to the respective naphthoxazine **9**, but differently from benzoxazines **2**, it is inert when treated with sodium borohydride or Grignard reagents (see Scheme 3).

3. Stereochemistry

The configuration of the unknown aminophenols **3** and **4** has been attributed on the basis of the general trend observed in the ^1H NMR spectroscopic chemical shift: the H-1, at the stereogenic centre C-1, of the (*R*,*R*)-**3** and (*R*,*R*)-**4** absorb at $\Delta\delta=0.07-0.26$ ppm upfield compared to the distereomers (1*S*,1′*R*)-**3** and (1*S*,1′*R*)-**4**. This trend can be explained considering the more stable conformations of the possible two diastereoisomers, obtained with PM3 semiempirical minimisation.[17] The phenyl group of the auxiliary amine exercises a shielding magnetic anisotropy[18] on the proton H-1 in the (*R*,*R*) diastereoisomer. Similar shielding effect can be observed on vicinal groups as the *N*-methyl group in

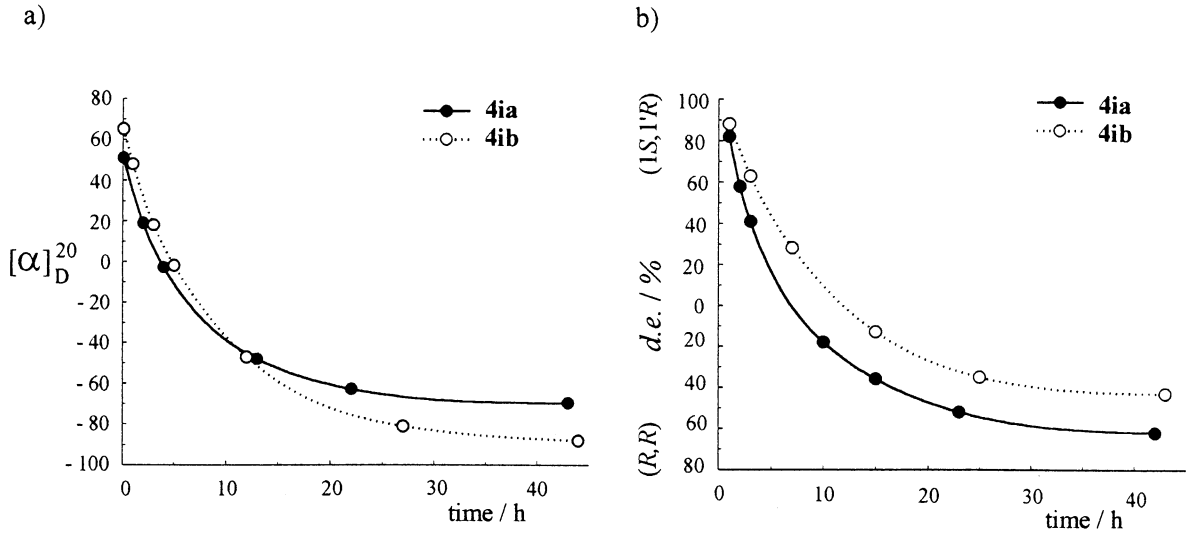
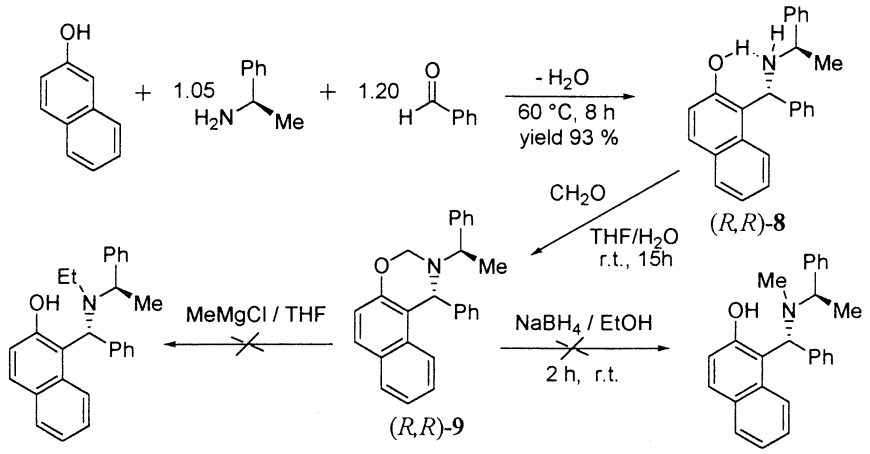


Figure 1. Trend of the variation of the optical activity and de observed for the aminophenols (*R*,*R*)- and (1*S*,1′*R*)-**4ia**,**ib** when dissolved in $CHCl_3$ or $CDCl_3$.



Scheme 3.

the case of (*R*,*R*)-**3i**, for which two equally stable conformations are obtained from conformational analysis.

4. Conclusions

In summary, a regioselective indirect alkylation of aminophenols **1a**–**m** to enantiopure tertiary aminophenol **3** and **4**, which are useful chiral ligand for metal-catalysed asymmetric reactions, is reported. This very simple synthetic methodology, through reduction or alkylation of the intermediate benzoxazines **2** was performed in mild conditions, suitable for the conservation of the configuration of the chiral centres. Some crystalline aminophenols show the phenomenon of crystallization-induced asymmetric transformation.

5. Experimental

5.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and at 50 or 75 MHz, respectively. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hz. IR spectra were recorded using FTIR apparatus. GC–MS analyses were performed with a gas chromatograph equipped with a methyl silicone capillary column and obtained by EI methods. Optical rotations were measured in a 1 dm cell at 20°C. All melting points are uncorrected. All reagents and solvents were distilled prior to use or were of commercial quality from freshly opened containers.

The 2-imidoyl phenols **5** were prepared by direct condensation of the appropriate *o*-acylphenol and (*R*)-(+)-1-methylbenzylamine (99%) according to described procedure.[19–21] The aminophenols **1a**–**m** were prepared by reduction of the corresponding 2-imidoyl phenols **5**.[1,3,4] The characterization of the newly prepared imidoylphenol (*R*)-**5j** and aminophenol (*R*,*R*)-**1j** follows.

5.1.1. 4-Methoxy-2-{[(1*R*)-1-phenylethyl]ethanimidoyl}-phenol [(*R*)-5j]. Yield 87%; yellow oil; IR (liquid film): 3028, 2970, 1610, 1581, 1500, 1283 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (d, 3H, J=6.6 Hz), 2.32 (s, 3H), 3.78 (s, 3H), 4.94 (q, 1H, J=6.6 Hz), 6.90–7.40 (m, 8H), 16.80 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 25.3, 56.1, 58.8, 112.8, 119.0, 119.2, 125.7, 126.3, 126.8, 127.1, 128.8, 144.3, 157.8, 169.8. Anal. calcd for $C_{17}H_{19}NO_2$ (269.3): C, 75.81; H, 7.11; N, 5.20%. Found: C, 75.62; H, 7.18; N, 5.42%.

5.1.2. 4-Methoxy-2-((1*R*)-1-{[(1*R*)-1-phenylethyl]amino}-ethyl)phenol [(*R*,*R*)-1j]. Yield 74%; oil; $[\alpha]_D^{20}$=+58.9 (*c* 2.9, $CHCl_3$); IR (liquid film): 3303, 1497, 1253, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (d, 3H, J=6.8 Hz), 1.41 (d, 3H, J=6.8 Hz), 1.86 (brs, 1H), 3.59 (q, 1H, J=6.8 Hz), 3.65 (q, 1H, J=6.8 Hz), 3.73 (s, 3H), 6.30–6.40 (m, 1H), 6.65–6.85 (m, 2H), 7.10–7.40 (m, 5H), 11.25 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 23.5, 55.4, 55.7, 56.3, 112.9, 114.2, 117.0, 126.3, 127.2, 127.5, 128.8, 143.6, 151.3, 152.5. Anal. calcd for $C_{17}H_{21}NO_2$ (271.4): C, 75.25; H, 7.80; N, 5.16%. Found: C, 75.13; H, 7.73; N, 5.28%.

5.2. General procedure for the preparation of the 3,4-dihydro-2*H*-1,3-benzoxazines 2a–m

To a solution of aminonaphthol **1** (2 mmol) in THF (3 mL) was added 35% aqueous formaldehyde (2.2 mmol). The solution was stirred for 15 h at room temperature. Solvent was removed and the residue dried under reduced pressure. The crude material was purified by filtration through a SiO_2 pad eluting with CH_2Cl_2.

5.2.1. 3-[(1*R*)-1-Phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*)-2a]. Oil, $[\alpha]_D^{20}$=+31.9 (*c* 6.2, $CHCl_3$); IR (film): 2960, 2925, 1850, 1481, 1228, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (d, 3H, J=6.6 Hz), 3.77 (d, 1H, J=16.6 Hz), 3.99 (q, 1H, J=6.6 Hz), 4.13 (d, 1H, J=16.6 Hz), 4.87 (d, 1H, J=10.3 Hz), 5.10 (dd, 1H, J=10.3, 1.7 Hz), 6.80–7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 48.7, 57.6, 80.1, 116.2, 120.5, 127.2, 127.3, 127.4, 127.5, 127.6, 128.5, 144.6, 154.8. Anal. calcd for $C_{16}H_{17}NO$ (239.3): C, 80.30; H, 7.16; N, 5.85. Found: C, 80.15; H, 7.32; N, 5.98.

5.2.2. (4*R*)-4-Ethyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*,*R*)-2c]. Oil; $[\alpha]_D^{20}=-12.9$ (*c* 2.8, $CHCl_3$); IR (liquid film): 2972, 2930, 1852, 1489, 1453, 1228, 1078, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, 3H, *J*=7.4 Hz), 1.48 (d, 3H, *J*=6.6 Hz), 1.54–1.90 (m, 2H), 3.28–3.38 (m, 1H), 3.85 (q, 1H, *J*=6.6 Hz), 5.00 (d, 1H, *J*=11.0 Hz), 5.14 (dd, 1H, *J*=11.0, 1.7 Hz), 6.75–7.45 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.1, 21.7, 31.1, 57.8, 59.0, 74.2, 116.3, 120.0, 125.1, 127.1, 127.3, 127.7, 128.2, 128.8, 145.2, 154.4. Anal. calcd for $C_{18}H_{21}NO$ (267.4): C, 80.86; H, 7.92; N, 5.24. Found: C, 80.75; H, 8.01; N, 5.09. **(4*S*)-4-Ethyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*S*,*R*)-2c]**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, 3H, *J*=7.2 Hz), 1.39 (d, 3H, *J*=6.6 Hz), 1.50–1.90 (m, 2H), 3.30–3.40 (m, 1H), 4.03 (q, 1H, *J*=6.6 Hz), 4.51 (dd, 1H, *J*=1.8, 10.8 Hz), 4.80 (d, 1H, *J*=10.8 Hz), 6.75–7.45 (m, 9H).

5.2.3. (4*R*)-4-Phenylethyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*,*R*)-2d]. Oil; $[\alpha]_D^{20}=-62.1$ (*c* 5.1, $CHCl_3$); IR (liquid film): 2954, 2927, 1477, 1231, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (d, 3H, *J*=6.6 Hz), 1.81–2.19 (m, 2H), 2.25–2.42 (m, 1H), 2.80–2.89 (m, 1H), 3.50–3.60 (m, 1H), 3.89 (q, 1H, *J*=6.6 Hz), 5.09 (d, 1H, *J*=11.0 Hz), 5.21 (dd, 1H, *J*=11.0, 1.6 Hz), 6.85–7.40 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 32.7, 40.3, 56.2, 59.2, 74.2, 116.4, 120.2, 124.8, 125.7, 127.3, 127.4, 127.8, 128.3, 128.4, 128.5, 128.7, 142.4, 145.1, 154.4. Anal. calcd for $C_{24}H_{25}NO$ (343.5): C, 83.93; H, 7.34; N, 4.08. Found: C, 84.16; H, 7.28; N, 4.23.

5.2.4. (4*R*)-3-[(1*R*)-1-Phenylethyl]-4-propyl-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*,*R*)-2e]. Oil; $[\alpha]_D^{20}=-25.9$ (*c* 5.8, $CHCl_3$); IR (liquid film): 2941, 2905, 1857, 1481, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (t, 3H, *J*=7.1 Hz), 1.00–2.30 (m, 4H), 1.49 (d, 3H, *J*=6.6 Hz), 3.40–3.50 (m, 1H), 3.84 (q, 1H, *J*=6.6 Hz), 5.02 (d, 1H, *J*=11.0 Hz), 5.15 (dd, 1H, *J*=11.0, 1.7 Hz), 6.80–7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 19.3, 21.6, 40.7, 56.0, 59.0, 74.2, 116.3, 120.1, 125.2, 127.1, 127.2, 127.7, 128.3, 128.7, 145.2, 154.4. Anal. calcd for $C_{19}H_{23}NO$ (281.4): C, 81.10; H, 8.24; N, 4.98. Found: C, 80.98; H, 8.19; N, 5.07.

5.2.5. (4*R*)-4-Isobutyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*,*R*)-2f]. Oil; $[\alpha]_D^{20}=-40.3$ (*c* 3.7, $CHCl_3$); IR (liquid film): 2925, 1853, 1491, 1226, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.44 (d, 3H, *J*=6.4 Hz), 0.85 (d, 3H, *J*=6.6 Hz), 1.20–1.37 (m, 1H), 1.51 (d, 3H, *J*=6.6 Hz), 1.66–1.90 (m, 2H), 3.49–3.58 (m, 1H), 3.84 (q, 1H, *J*=6.6 Hz), 5.04 (d, 1H, *J*=11.0 Hz), 5.16 (dd, 1H, *J*=11.0, 1.6 Hz), 6.80–7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 21.4, 23.8, 26.9, 48.3, 54.2, 59.1, 74.2, 116.3, 120.2, 125.5, 127.1, 127.2, 127.8, 128.3, 128.7, 145.1, 154.5. Anal. calcd for $C_{20}H_{25}NO$ (295.4): C, 81.31; H, 8.53; N, 4.74. Found: C, 81.45; H, 8.65; N, 4.59.

5.2.6. (4*S*)-4-(*tert*-Butyl)-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*S*,*R*)-2g]. Oil; $[\alpha]_D^{20}=+165.3$ (*c* 2.13, $CHCl_3$); IR (liquid film): 2945, 1857, 1282, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.36 (d, 3H, *J*=6.6 Hz), 3.76 (s, 1H), 3.90 (q, 1H, *J*=6.6 Hz), 4.55 (dd, 1H, *J*=11.0, 2.0 Hz), 5.04 (d, 1H, *J*=11.0 Hz), 6.80–7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 29.9, 37.4, 60.1, 61.9, 76.9, 116.8, 119.5, 121.9, 127.6, 128.0, 128.3, 128.9, 130.3, 145.1, 155.0. Anal. calcd for $C_{20}H_{25}NO$ (295.4): C, 81.31; H, 8.53; N, 4.74. Found: C, 81.16; H, 8.67; N, 4.95.

5.2.7. (4*R*)-4-But-3-enyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*,*R*)-2h]. Oil; $[\alpha]_D^{20}=-58.3$ (*c* 4.4, $CHCl_3$); IR (liquid film): 2951, 2907, 1869, 1480, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 (d, 3H, *J*=6.6 Hz), 1.60–2.00 (m, 3H), 2.20–2.40 (m, 1H), 3.44–3.54 (m, 1H), 3.86 (q, 1H, *J*=6.6 Hz), 4.80–4.96 (m, 2H), 5.03 (d, 1H, *J*=11.0 Hz), 5.16 (dd, 1H, *J*=11.0, 1.7 Hz), 5.58–5.80 (m, 1H), 6.80–7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 26.9, 30.3, 37.6, 55.8, 59.1, 74.2, 114.5, 116.4, 120.2, 127.2, 127.4, 127.7, 128.3, 128.7, 138.5, 145.0, 154.4. Anal. calcd for $C_{20}H_{23}NO$ (293.4): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.98; H, 7.75; N, 4.96.

5.2.8. (4*R*)-6-Methoxy-4-methyl-3-[(1*R*)-1-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*,*R*)-2j]. Crystals; mp 110–113°C (hexane); $[\alpha]_D^{20}=-52.35$ (*c* 1.4, $CHCl_3$); IR (nujol): 1497, 1283, 1046, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, 3H, *J*=7.0 Hz), 1.43 (d, 3H, *J*=6.6 Hz), 3.59 (q, 1H, *J*=7.0 Hz), 3.71 (s, 3H), 3.88 (q, 1H, *J*=6.6 Hz), 4.96 (d, 1H, *J*=11.1 Hz), 5.12 (dd, 1H, *J*=11.1, 1.6 Hz), 6.40–6.80 (m, 3H), 7.10–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 24.6, 52.8, 56.1, 59.2, 74.6, 113.6, 117.5, 126.7, 127.5, 127.6, 128.8, 129.0, 146.3, 148.8, 153.7. Anal. calcd for $C_{18}H_{21}NO_2$ (283.4): C, 76.29; H, 7.47; N, 4.94. Found: C, 76.07; H, 7.28; N, 4.75.

5.2.9. 3,4-Dimethyl-3,4-dihydro-2*H*-1,3-benzoxazine [2k]. Oil; IR (liquid film): 2973, 1487, 1446, 1273, 1248, 1214, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (d, 3H, *J*=7.0 Hz), 2.57 (s, 3H), 3.75 (q, 1H, *J*=7.0 Hz), 4.71 (d, 1H, *J*=10.1 Hz), 4.95 (d, 1H, *J*=10.1 Hz), 6.80–7.35 (m, 4H; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 40.2, 55.4, 79.9, 117.0, 120.9, 125.4, 128.1, 128.6, 153.6. Anal. calcd for $C_{10}H_{13}NO$ (163.2): C, 73.59; H, 8.03; N, 8.58. Found: C, 75.69; H, 7.86; N, 8.69.

5.2.10. 3-Isopropyl-4-methyl-3,4-dihydro-2*H*-1,3-benzoxazine [2l]. Oil; IR (liquid film): 2970, 1582, 1447, 1238, 1032, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (d, 3H, *J*=6.6 Hz), 1.17 (d, 3H, *J*=6.6 Hz), 1.48 (d, 3H, *J*=7.0 Hz), 3.07 (hept, 1H, *J*=6.6 Hz), 3.92 (q, 1H, *J*=7.0 Hz), 4.95 (s, 2H), 6.70–7.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 22.4, 25.2, 50.3, 52.6, 76.5, 117.2, 120.6, 127.5, 127.7, 128.4, 155.2. Anal. calcd for $C_{12}H_{17}NO$ (191.3): C, 75.35; H, 8.96; N, 7.32. Found: C, 75.21; H, 8.82; N, 7.51.

5.2.11. 3-Benzyl-4-ethyl-3,4-dihydro-2*H*-1,3-benzoxazine [2m]. Oil; IR (liquid film): 3063, 2962, 1582, 1486, 1220, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J*=7.3 Hz), 1.68–1.85 (m, 2H), 3.41 (t, 1H, *J*=7.3 Hz), 3.73 (d, 1H, *J*=13.4 Hz), 4.04 (d, 1H, *J*=13.4 Hz), 4.71 (dd, 1H, *J*=10.4, 1.5 Hz), 4.97 (d, 1H, *J*=10.4 Hz), 6.80–7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2, 30.9, 56.7, 58.9, 77.3, 116.5, 120.2, 124.6, 127.2, 127.5, 128.2, 128.7, 129.2, 138.6, 153.6. Anal. calcd for $C_{17}H_{19}NO$

(253.3): C, 80.60; H, 7.56; N, 5.53. Found: C, 80.45; H, 7.68; N, 5.36.

5.3. General procedure for the reduction of the benzoxazines 2a–m to aminophenols 3a–m

A solution of benzoxazine (1.0 mmol) in ethanol (5 mL) was treated with an excess of $NaBH_4$ (3.0 mmol, 0.113 g) and stirred at room temperature for 2 h. The reaction mixture, diluted with CH_2Cl_2 (50 mL), was treated with a saturated aqueous solution of ammonium chloride (10 mL). The organic layer was dried and evaporated. The residue, purified by flash chromatography (cyclohexane/ethyl acetate: 95/5 as eluent), gave the aminophenols **3a**–**m**.

5.3.1. 2-({Methyl[(1*R*)-1-phenylethyl]amino}methyl)-phenol [(*R*)-3a]. Oil; $[\alpha]_D^{20}=+9.1$ (*c* 4.85, $CHCl_3$); IR (liquid film): 2975, 1589, 1491, 1475, 1452, 1376, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (d, 3H, *J*=6.9 Hz), 2.21 (s, 3H), 3.63 (d, 1H, *J*=13.9 Hz), 3.78 (d, 1H, *J*=13.9 Hz), 3.80 (q, 1H, *J*=6.9 Hz), 6.70–7.45 (m, 9H), 11.75 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.7, 37.7, 58.5, 63.0, 116.4, 119.5, 122.5, 128.1, 128.5, 128.6, 128.9, 129.0, 141.0, 158.5. Anal. calcd for $C_{16}H_{19}NO$ (241.3): C, 79.63; H, 7.94; N, 5.80%. Found: C, 79.85; H, 7.82; N, 5.96%.

5.3.2. 2-((1*R*)-1-{Methyl[(1*R*)-1-phenylethyl]amino}ethyl)-phenol [(*R*,*R*)-3b]. Oil; $[\alpha]_D^{20}=+10.9$ (*c* 2.2, $CHCl_3$); IR (liquid film): 2974, 1492, 1453, 1374, 1257, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (d, 3H, *J*=6.7 Hz), 1.52 (d, 3H, *J*=6.8 Hz), 2.02 (s, 3H), 4.04 (q, 1H, *J*=6.8 Hz), 4.17 (q, 1H, *J*=6.7 Hz), 6.73–7.48 (m, 9H), 11.80 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 17.5, 23.0, 32.6, 58.9, 116.3, 119.1, 127.3, 127.4, 127.8, 128.4, 128.5, 129.3, 141.2, 158.6. Anal. calcd for $C_{17}H_{21}NO$ (255.3): C, 79.96; H, 8.29; N, 5.49%. Found: C, 80.13; H, 8.41; N, 5.31%.

5.3.3. 2-((1*R*)-1-{Methyl[(1*R*)-1-phenylethyl]amino}propyl)phenol [(*R*,*R*)-3c]. Oil; $[\alpha]_D^{20}=+12.7$ (*c* 10.2, $CHCl_3$); IR (liquid film): 3029, 1255, 1587, 1491, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, 3H, *J*=7.3 Hz), 1.49 (d, 3H, *J*=6.6 Hz), 1.75–2.00 (m, 2H), 2.12 (s, 3H), 3.58 (dd, 1H, *J*=8.9, 4.5 Hz), 4.25 (q, 1H, *J*=6.6 Hz), 6.80–7.50 (m, 9H), 11.70 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 16.2, 23.8, 32.9, 57.8, 68.0, 116.9, 119.2, 125.8, 128.0, 128.8, 128.9, 129.8, 129.9, 140.2, 158.2. Anal. calcd for $C_{18}H_{23}NO$ (269.4): C, 80.26; H, 8.61; N, 5.20%. Found: C, 80.39; H, 8.54; N, 5.38%.

5.3.4. 2-((1*R*)-1-{Methyl[(1*R*)-1-phenylethyl]amino}-3-phenylpropyl)phenol [(*R*,*R*)-3d]. Oil; $[\alpha]_D^{20}=-22.5$ (*c* 3.8, $CHCl_3$); IR (liquid film): 2973, 1588, 1493, 1471, 1453, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, 3H, *J*=6.6 Hz), 2.09 (s, 3H), 2.12–2.24 (m, 2H), 2.40–2.54 (m, 2H), 3.76 (t, 1H, *J*=6.6 Hz), 4.20 (q, 1H, *J*=6.6 Hz), 6.85–7.40 (m, 14H), 11.75 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9, 31.9, 32.6, 33.1, 57.6, 65.4, 116.7, 118.9, 125.3, 125.9, 127.1, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 129.0, 147.8, 157.7. Anal. calcd for $C_{24}H_{27}NO$ (345.5): C, 83.44; H, 7.88; N, 4.05%. Found: C, 83.59; H, 7.64; N, 3.84%.

5.3.5. 2-((1*R*)-1-{Methyl[(1*R*)-1-phenylethyl]amino}-butyl)phenol [(*R*,*R*)-3e]. Oil; $[\alpha]_D^{20}=-9.7$ (*c* 1.0, $CHCl_3$); IR (liquid film): 2959, 1587, 1454, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J*=7.2 Hz), 1.05–1.30 (m, 2H), 1.48 (d, 3H, *J*=7.0 Hz), 1.71–1.88 (m, 2H), 2.09 (s, 3H), 3.60–3.70 (m, 1H), 4.21 (q, 1H, *J*=7.0 Hz), 6.70–7.40 (m, 9H), 11.70 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 15.8, 20.1, 25.3, 32.5, 57.3, 65.9, 116.4, 118.7, 125.7, 127.1, 127.4, 128.2, 128.3, 129.0, 139.8, 157.6. Anal. calcd for $C_{19}H_{25}NO$ (283.4): C, 80.52; H, 8.89; N, 4.94%. Found: C, 80.63; H, 8.73; N, 4.97%.

5.3.6. 2-((1*R*)-3-Methyl-1-{methyl[(1*R*)-1-phenylethyl]-amino}butyl)phenol [(*R*,*R*)-3f]. Crystals; mp 53–55°C (hexane); $[\alpha]_D^{20}=-27.3$ (*c* 1.6, $CHCl_3$); IR (nujol): 2924, 2854, 1446,1400, 1377, 1258, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, 3H, *J*=6.5 Hz), 0.93 (d, 3H, *J*=6.3 Hz), 1.40–1.50 (m, 1H), 1.48 (d, 3H, *J*=6.6 Hz), 1.55–1.93 (m, 2H), 2.02 (s, 3H), 3.81 (dd, 1H, *J*=11.1, 3.6 Hz), 4.20 (q, 1H, *J*=6.6 Hz), 6.80–7.40 (m, 9H), 11.75 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 21.8, 24.3, 25.5, 32.8, 38.0, 57.3, 63.4, 116.6, 118.7, 126.1, 127.4, 128.1, 128.3, 128.4, 128.5, 128.6, 157.6. Anal. calcd for $C_{20}H_{27}NO$ (297.4): C, 80.76; H, 9.15; N, 4.71%. Found: C, 80.64; H, 9.28; N, 4.58%.

5.3.7. 2-((1*R*)-1-{Methyl[(1*R*)-1-phenylethyl]amino}pent-4-enyl)phenol [(*R*,*R*)-3h]. Oil; $[\alpha]_D^{20}=-9.3$ (*c* 2.9, $CHCl_3$); IR (liquid film): 2975, 1588, 1491, 1472, 1257, 913, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.47 (d, 3H, *J*=7.0 Hz), 1.85–1.95 (m, 4H), 2.09 (s, 3H), 3.60–3.72 (m, 1H), 4.21 (q, 1H, *J*=7.0 Hz), 4.90–5.05 (m, 2H), 5.65–5.85 (m, 1H), 6.80–7.40 (m, 9H), 11.70 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 29.9, 31.4, 33.0, 57.9, 65.9, 115.5, 117.1, 119.3, 125.8, 128.0, 128.7, 128.8, 128.9, 129.4, 129.5, 138.5, 158.1. Anal. calcd for $C_{20}H_{25}NO$ (295.4): C, 81.31; H, 8.53; N, 4.74%. Found: C, 81.16; H, 8.68; N, 4.90%.

5.3.8. 2-[(*S*)-{Methyl[(1*R*)-1-phenylethyl]amino}(phenyl)-methyl]phenol [(1*S*,1′*R*)-3i]. Oil; IR (liquid film): 2976, 1586, 1472, 1255, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, 3H, *J*=6.6 Hz), 2.34 (s, 3H), 3.85 (q, 1H, *J*=6.6 Hz), 4.95 (s, 1H), 6.80–7.60 (m, 14H), 12.75 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 33.4, 57.1, 73.2, 117.0, 119.4, 127.5, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.7, 129.0, 129.1, 129.7. Anal. calcd for $C_{22}H_{23}NO$ (317.4): C, 83.24; H, 7.30; N, 4.41%. Found: C, 83.41; H, 7.42; N, 4.24%. (*R*,*R*)-**3i**.[4]

5.3.9. 4-Methoxy-2-((1*R*)-1-{methyl[(1*R*)-1-phenylethyl]-amino}ethyl)phenol [(*R*,*R*)-3j]. Crystals; mp 65–68°C (hexane); $[\alpha]_D^{20}=+7.3$ (*c* 1.1, $CHCl_3$); IR (nujol): 2924, 2854, 2361, 1459, 1377, 1287 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (d, 3H, *J*=6.7 Hz), 1.51 (d, 3H, *J*=6.9 Hz), 2.00 (s, 3H), 3.78 (s, 3H), 4.02 (q, 1H, *J*=6.7 Hz), 4.10 (q, 1H, *J*=6.9 Hz), 6.60–6.80 (m, 2H), 7.20–7.40 (m, 6H), 12.50 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 17.2, 26.9, 32.6, 55.8, 59.1, 112.5, 113.9, 116.5, 118.5, 127.5, 127.8, 128.3, 128.5, 141.2, 152.6. Anal. calcd for $C_{18}H_{23}NO_2$ (285.4): C, 75.76; H, 8.12; N, 4.91%. Found: C, 75.93; H, 8.19; N, 4.78%.

5.3.10. 2-[1-(Dimethylamino)ethyl]phenol [(±)-3k]. Oil; IR (liquid film): 2979, 1586, 1401, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (d, 3H, J=6.8 Hz), 2.32 (s, 6H), 3.58 (q, 1H, J=6.8 Hz), 6.70–7.40 (m, 4H), 12.50 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2, 42.2, 65.2, 116.8, 119.4, 127.7, 128.1, 128.8, 157.9. Anal. calcd for $C_{10}H_{15}NO$ (165.2): C, 72.69; H, 9.15; N, 8.48%. Found: C, 72.86; H, 9.33; N, 8.29%.

5.3.11. 2-{1-[Isopropyl(methyl)amino]ethyl}phenol [(±)-3l]. Oil; IR (liquid film): 2973, 2874, 1589, 1479, 1463, 1259, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, 6 H, J=6.6 Hz), 1.40 (d, 3H, J=6.7 Hz), 2.20 (s, 3H), 3.17 (hept, 1H, J=6.6 Hz), 3.85 (q, 1H, J=6.7 Hz), 6.70–7.25 (m, 4H), 12.70 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 18.6, 31.4, 49.4, 62.0, 116.9, 119.3, 127.9, 128.6, 128.7, 157.9. Anal. calcd for $C_{12}H_{19}NO$ (193.3): C, 74.57; H, 9.91; N, 7.25%. Found: C, 74.32; H, 9.85; N, 7.37%.

5.3.12. 2-{1-[Benzyl(methyl)amino]propyl}phenol [(±)-3m]. Oil; IR (liquid film): 2973, 2794, 1586, 1490, 1454, 1254, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, 3H, J=7.4 Hz), 1.75–2.10 (m, 2H), 2.21 (s, 3H), 3.41 (dd, 1H, J=9.57, 3.75 Hz), 3.50 (d, 1H, J=13.0 Hz), 3.73 (d, 1H, J=13.0 Hz), 6.80–7.40 (m, 9H), 11.90 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8, 23.7, 38.6, 59.9, 71.5, 117.1, 119.2, 126.0, 127.9, 128.9, 129.0, 129.6, 129.9, 137.9, 157.5. Anal. calcd for $C_{17}H_{21}NO$ (255.4): C, 79.96; H, 8.29; N, 5.49%. Found: C, 79.79; H, 8.36; N, 5.37%.

5.4. General procedure for the alkylation of benzoxazines (*R*,*R*)-2b,i,j with Grignard reagents

To a solution of benzoxazines (*R*,*R*)-**2b,i,j** (1.0 mmol) in anhydrous THF (3.0 mL) under inert atmosphere, cooled to −60°C, was added dropwise the Grignard reagent (1.5 mmol, 1 M in THF) with stirring. The reaction mixture was stirred for 4 h with the temperature allowed to rise slowly to −10°C, and then was quenched with NH_4Cl saturated solution (5 mL) and extracted with CH_2Cl_2 (2×30 mL). The solution was dried with anhydrous Na_2SO_4 then filtered and the solvent evaporated under reduced pressure. Chromotographic separation of the crude oil obtained, with cyclohexane/ethyl acetate=90:10 as eluent afforded the alkylated aminophenols (*R*,*R*)-**4**; yields 63–94%.

5.4.1. 2-((1*R*)-1-{Ethyl[(1*R*)-1-phenylethyl]amino}ethyl)-phenol [(*R*,*R*)-4ba]. Oil; $[\alpha]_D^{20}$=−12.04 (*c* 3.5, $CHCl_3$); IR (liquid film): 3030, 2933, 1601, 1491, 1378, 1255, 1078, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.70 (t, 3H, J=7.2 Hz), 1.49 (d, 3H, J=6.8 Hz), 1.55 (d, 3H, J=6.8 Hz), 2.42–2.78 (m, 2H), 4.08 (q, 1H, J=6.8 Hz), 4.32 (q, 1H, J=6.8 Hz), 6.80–7.25 (m, 9H), 12.10 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5, 14.7, 15.4, 18.9, 41.5, 58.1, 116.3, 119.2, 126.5, 126.9, 127.5, 127.9, 128.4, 128.5, 142.3, 157.7. Anal. calcd for $C_{18}H_{23}NO$ (269.4): C, 80.26; H, 8.61; N, 5.20. Found: C, 80.43; H, 8.54; N, 5.38. **2-((1*S*)-1-{Ethyl[(1*R*)-1-phenylethyl]amino}ethyl)phenol [(*S*,*R*)-4ba]**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 3H, J=7.1 Hz), 1.37 (d, 3H, J=6.8 Hz), 1.45 (d, 3H, J=6.8 Hz), 2.40–2.70 (m, 2H), 4.01 (s, 1H, J=6.8 Hz), 4.15 (s, 1H, J=6.8 Hz), 6.80–7.25 (m, 9H), 12.10 (brs, 1H).

5.4.2. 2-((1*R*)-1-{Phenethyl[(1*R*)-1-phenylethyl]amino}-ethyl)phenol [(*R*,*R*)-4bb]. Crystals; mp 84–87°C (hexane); $[\alpha]_D^{20}$=+31.6 (*c* 2.5, $CHCl_3$); IR (nujol): 3021, 1455, 1251, 1376, 1107, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.52 (d, 3H, J=6.6 Hz), 1.55 (d, 3H, J=6.8 Hz), 2.00–2.28 (m, 2H), 2.62 (t, 2H, J=8.5 Hz), 4.08 (q, 1H, J=6.8 Hz), 4.39 (q, 1H, J=6.6 Hz), 6.60–7.40 (m, 14H), 11.62 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 19.2, 37.6, 51.1, 58.8, 60.1, 116.9, 119.9, 126.4, 127.5, 128.3, 128.5, 128.6, 128.7, 128.9, 129.1, 129.2, 140.3, 142.8, 158.0. Anal. calcd for $C_{24}H_{27}NO$ (345.5): C, 83.44; H, 7.88; N, 4.05. Found: C, 83.65; H, 7.75; N, 4.19.

5.4.3. 2-((1*R*)-1-{Benzyl[(1*R*)-1-phenylethyl]amino}ethyl)-phenol [(*R*,*R*)-4bc]. Oil; $[\alpha]_D^{20}$=+5.79 (*c* 2.64, $CHCl_3$); IR (liquid film): 3029, 1490, 1453, 1289, 1255, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, 3H, J=7.0 Hz), 1.62 (d, 3H, J=7.0 Hz), 3.48 (d, 1H, J=14.7 Hz), 4.01 (d, 1H, J=14.7 Hz), 4.12 (q, 1H, J=7.0 Hz), 4.22 (q, 1H, J=7.0 Hz), 6.80–7.40 (m, 14H), 11.05 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 18.4, 50.9, 57.9, 60.1, 116.5, 119.5, 126.9, 127.4, 127.5, 127.6, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 140.1, 157.1. Anal. calcd for $C_{23}H_{25}NO$ (331.4): C, 83.34; H, 7.60; N, 4.23%. Found: C, 83.53; H, 7.45; N, 4.08%.

5.4.4. 2-[(*S*)-{Ethyl[(1*R*)-1-phenylethyl]amino}(phenyl)-methyl]phenol [(*S*,*R*)-4ia]. Crystals; mp 130–132°C (hexane); $[\alpha]_D^{20}$=+51.0 (*c* 1.7, $CHCl_3$); IR (nujol): 3028, 2930, 1482, 1378, 1251, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, 3H, J=7.0 Hz), 1.47 (d, 3H, J=6.9 Hz), 2.70–3.00 (m, 2H), 4.05 (q, 1H, J=6.9 Hz), 5.03 (s, 1H), 6.60–7.40 (m, 14H), 12.10 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 18.3, 42.7, 60.3, 70.9, 117.1, 119.5, 127.9, 128.3, 128.5, 128.8, 129.0, 129.3, 129.4, 129.5, 130.1, 139.3, 143.2, 157.6. Anal. calcd for $C_{23}H_{25}NO$ (331.4): C, 83.34; H, 7.60; N, 4.23%. Found: C, 83.45; H, 7.52; N, 4.31%. **2-[(*R*)-{Ethyl[(1*R*)-1-phenylethyl]amino}(phenyl)-methyl]phenol [(*R*,*R*)-4ia]**: Oil; $[\alpha]_D^{20}$=−69.6 (*c* 1.7, $CHCl_3$, dr=4.0); ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (t, 3H, J=7.2 Hz), 1.45 (d, 3H, J=7.0 Hz), 2.55–2.75 (m, 2H), 4.21 (q, 1H, J=7.0 Hz), 4.90 (s, 1H), 6.60–7.60 (m, 14H), 12.50 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.7, 18.3, 42.1, 57.8, 72.2, 117.4, 119.8, 127.9, 128.4, 128.5, 128.7, 128.9, 129.1, 129.3, 129.5, 130.1, 141.3, 141.6, 157.7.

5.4.5. 2-[(*S*)-{Phenethyl[(1*R*)-1-phenylethyl]amino}-(phenyl)methyl]phenol [(*S*,*R*)-4ib]. Crystals; mp 112–114°C (hexane); $[\alpha]_D^{20}$=+65.2 (*c* 2.5, $CHCl_3$); IR (nujol): 3085, 3027, 2928, 1586, 1254, 992, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.52 (d, 3H, J=6.8 Hz), 1.98–2.10 (m, 1H), 2.23–2.37 (m, 1H), 2.80–2.90 (m, 2H), 4.24 (q, 1H, J=6.8 Hz), 5.05 (s, 1H), 6.50–7.60 (m, 19H), 11.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9, 38.1, 50.2, 58.8, 72.5, 117.5, 120.2, 126.4, 126.5, 127.5, 128.2, 128.3, 128.6, 128.7, 128.8, 129.0, 129.1, 129.3, 129.7, 130.0, 140.2, 141.0, 157.7. Anal. calcd for $C_{29}H_{29}NO$ (407.5): C, 85.47; H, 7.17; N, 3.44. Found: C, 85.32; H, 7.28; N, 3.21. **2-[(*R*)-{Phenethyl[(1*R*)-1-phenylethyl]amino}(phenyl)methyl]-phenol [(*R*,*R*)-4ib]**: Oil; $[\alpha]_D^{20}$=−88.0 (*c* 2.5, $CHCl_3$ dr=2.4); ^1H NMR (300 MHz, $CDCl_3$): δ 1.55 (d, 3H, J=7.0 Hz), 2.08–2.42 (m, 2H), 2.60–2.78 (m, 1H),

2.94–3.12 (m, 1H), 4.26 (q, 1H, *J*=7.0 Hz), 4.93 (s, 1H), 6.60–7.60 (m, 19H), 12.20 (brs, 1H).

5.4.6. 2-[(*R*)-{Benzyl[(1*R*)-1-phenylethyl]amino}(phenyl)-methyl]phenol [(*R*,*R*)-4ic]. Oil; $[\alpha]_D^{20}=-49.8$ (*c* 4.7, $CHCl_3$, dr=4.1); IR (liquid film): 3025, 1465, 1257, 1372, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.54 (d, 3H, *J*=7.2 Hz), 3.40 (d, 1H, *J*=14.6 Hz), 4.08 (d, 1H, *J*=14.6 Hz), 4.39 (q, 1H, *J*=7.2 Hz), 4.85 (s, 1H), 6.70–7.60 (m, 19H), 12.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 51.1, 58.1, 72.2, 117.0, 119.6, 126.3, 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.9, 129.4, 129.9, 138.5, 140.6, 156.9. Anal. calcd for $C_{28}H_{27}NO$ (393.5): C, 85.46; H, 6.92; N, 3.56. Found: C, 85.61; H, 6.84; N, 3.77%. **2-[(*S*)-{Benzyl[(1*R*)-1-phenylethyl]amino}(phenyl)methyl] phenol [(*S*,*R*)-4ic]**: Oil; ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (d, 3H, *J*=6.9 Hz), 3.64 (d, 1H, *J*=14.4 Hz), 3.91 (d, 1H, *J*=14.4 Hz), 4.31 (q, 1H, *J*=6.9 Hz), 5.11 (s, 1H), 6.70–7.60 (m, 19H), 12.00 (s, 1H).

5.4.7. 2-((1*R*)-1-{Ethyl[(1*R*)-1-phenylethyl]amino}ethyl)-4-methoxyphenol [(*R*,*R*)-4ja]. Oil; $[\alpha]_D^{20}=-7.65$ (*c* 2.2, $CHCl_3$, dr=28); IR (liquid film): 2928, 1492, 1453, 1378, 1286, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.67 (t, 3H, *J*=7.2 Hz), 1.46 (d, 3H, *J*=6.9 Hz), 1.52 (d, 3H, *J*=6.9 Hz), 2.42–2.72 (m, 2H), 3.77 (s, 3H), 4.04 (q, 1H, *J*=6.9 Hz), 4.26 (q, 1H, *J*=6.9 Hz), 6.60–7.40 (m, 8 H), 11.50 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 15.4, 18.8, 41.5, 55.7, 58.1, 59.0, 112.4, 113.7, 116.4, 127.5, 127.9, 128.4, 128.7, 128.9, 142.4, 152.6. Anal. calcd for $C_{19}H_{25}NO_2$ (299.4): C, 76.22; H, 8.42; N, 4.68. Found: C, 76.39; H, 8.49; N, 4.47.

5.4.8. 2-((1*R*)-1-{Phenethyl[(1*R*)-1-phenylethyl]amino}-ethyl)-4-methoxyphenol [(*R*,*R*)-4jb]. Oil; $[\alpha]_D^{20}=-3.22$ (*c* 2.1, $CHCl_3$, dr=14); IR (liquid film): 3021, 1489, 1264, 1341, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 (d, 3H, *J*=6.8 Hz), 1.53 (d, 3H, *J*=6.8 Hz), 1.98–2.24 (m, 2H), 2.62 (t, 2H, *J*=8.1 Hz), 3.80 (s, 3H), 4.06 (q, 1H, *J*=6.8 Hz), 4.33 (q, 1H, *J*=6.8 Hz), 6.60–7.50 (m, 13H), 11.10 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 17.7, 26.9, 37.1, 50.6, 55.9, 60.0, 112.8, 113.8, 116.6, 126.0, 127.6, 127.7, 128.0, 128.1, 128.2, 128.6, 135.5, 139.8, 151.2, 152.7. Anal. calcd for $C_{25}H_{29}NO_2$ (375.5): C, 79.96; H, 7.78; N, 3.73%. Found: C, 80.12; H, 7.63; N, 3.81%.

5.4.9. 2-((1*R*)-1-{Benzyl[(1*R*)-1-phenylethyl]amino}ethyl)-4-methoxyphenol [(*R*,*R*)-4jc]. Oil; $[\alpha]_D^{20}=+19.48$ (*c* 2.3, $CHCl_3$, dr=7.0); IR (liquid film): 3031, 1492, 1287, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, 3H, *J*=6.8 Hz), 1.60 (d, 3H, *J*=7.0 Hz), 3.48 (d, 1H, *J*=14.6 Hz), 3.76 (s, 3H), 3.97 (d, 1H, *J*=14.6 Hz), 4.08 (q, 1H, *J*=6.8 Hz), 4.19 (q, 1H, *J*=7.0 Hz), 6.70–7.50 (m, 13H), 10.40 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 18.8, 51.4, 56.3, 58.5, 60.3, 113.1, 114.6, 117.2, 127.3, 128.1, 128.7, 128.8, 128.9, 129.0, 129.1, 129.2, 129.5, 140.5, 151.3. Anal. calcd for $C_{24}H_{27}NO_2$ (361.5): C, 79.74; H, 7.53; N, 3.87. Found: C, 79.58; H, 7.68; N, 3.73.

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