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Tetrahedron
Tetrahedron 63 (2007) 8727–8734

Synthesis of new tridentate chiral aminoalcohols by a multicomponent reaction and their evaluation as ligands for catalytic asymmetric Strecker reaction

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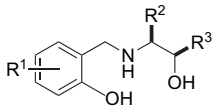
Received 22 March 2007; revised 30 May 2007; accepted 14 June 2007
Available online 21 June 2007

This paper is dedicated to late Dr. Vorawit Banphavichit

Abstract—A one-step, multicomponent Mannich-type reaction between phenols, paraformaldehyde, and β-aminoalcohols in the presence of LiCl afforded *N*-2-hydroxybenzyloxazolidines with high *ortho*-selectivity. Hydrolytic or reductive ring opening of the oxazolidines provided a series of *N*-salicyl-β-aminoalcohols in 84–92% overall yield. The synthesized compounds were evaluated as ligands for a titanium-catalyzed catalytic asymmetric Strecker reaction. The reaction employing 10 mol % of catalyst provided the Strecker products in excellent yields and up to 98% ee.

1. Introduction



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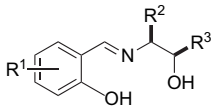

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1,2-Aminoalcohols are versatile chiral auxiliaries and ligands for catalytic asymmetric reactions.[1] A number of bidentate aminoalcohol ligands have been synthesized and utilized in many asymmetric reactions, especially in conjunction with dialkylzinc in asymmetric addition to carbonyl compounds and imines.[2] Relatively little work on tri- or multidentate aminoalcohols have been reported.[3] One of the most notable examples is the prolinol-based multidentate ligand.[4] We have recently shown that the *N*-salicyl β-aminoalcohol **1** is an effective ligand for titanium-catalyzed asymmetric Strecker reactions.[5] Similar ligands were shown to be effective for cyanosilylation of aldehydes[6] as well as Michael additions of malonate esters to cyclic enones.[7] A classical way of making this class of ligand is to reduce the Schiff base **2** derived from β-aminoalcohols or their ester precursors using an appropriate hydride transfer reagent.[5,8] However, this method delivered only moderate yields and, in our hands, the reduction failed with sterically hindered substrates. Furthermore, the limited commercial availability of substituted salicylaldehydes rendered this method of limited use. This prompted us to investigate a new methodology to synthesize this useful class of ligand.

We considered a Mannich-type reaction between a phenol, formaldehyde, and an aminoalcohol as a potential new route to eliminate major problems associated with the synthesis of **1**: namely, the limited variety of salicylaldehydes and low yields.[9] Although several hydroxyphenylbenzylamine derivatives have been made by this type of condensation,[9,10] very few examples employed aminoalcohols as the amine component.[11,12] Most importantly, no synthesis of chiral tridentate ligands of type **1** by this approach has been reported. It is therefore our objective to develop a synthetic route for ligand **1** employing this methodology, and to make a preliminary evaluation of their effectiveness as ligands for titanium-catalyzed asymmetric Strecker reactions.

2. Results and discussion

The conditions for the three-component Mannich-type reaction were optimized by reacting 4′-hydroxybiphenyl and phenol as representative phenols, (*S*)-valinol as a representative β-aminoalcohol, and excess of paraformaldehyde (10 equiv). The reaction proceeded poorly in both protic

Keywords: Enantioselective; Chiral ligand; Catalyst; Strecker reaction; Mannich reaction; Imine.
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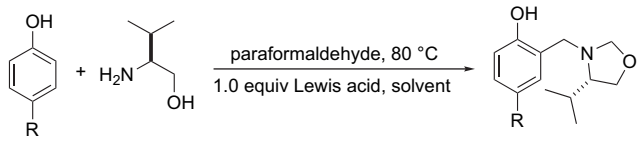
doi:10.1016/j.tet.2007.06.047

Table 1. Conditions for optimization of the three-component Mannich-type reaction



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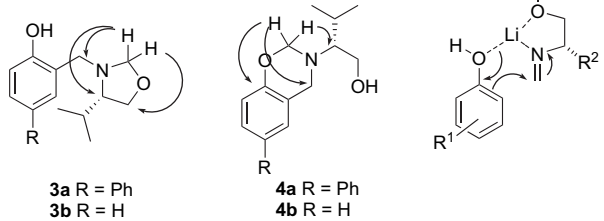
Entry	R	Lewis acid	Solvent	Yield (%)
1	C_6H_5	—	EtOH	46
2	C_6H_5	—	CH_3CN	31
3	C_6H_5	LiCl	EtOH	86
4	C_6H_5	LiCl	CH_3CN	45
5	C_6H_5	LiBr	EtOH	72
6	C_6H_5	LiOTf	EtOH	81
7	C_6H_5	$LiClO_4$	EtOH	83
8	C_6H_5	$MgCl_2$	EtOH	58
9	C_6H_5	$ZnCl_2$	EtOH	47
10	C_6H_5	$CuCl_2$	EtOH	38
11	H	—	EtOH	42
12	H	—	CH_3CN	28
13	H	LiCl	EtOH	86
14	H	LiCl	CH_3CN	48

(EtOH) and aprotic (MeCN) solvents. Addition of stoichiometric amounts of a Lewis acid resulted in significant improvement of the yield (Table 1). It was finally found that a combination of a lithium salt, preferably LiCl, as Lewis acid and ethanol as solvent was optimal. The reactions gave, instead of the expected ligand **1**, isolable intermediates, which have been identified as oxazolidines **3a** (from 4′-hydroxybiphenyl) and **3b** (from phenol). The structures of oxazolidines **3** were distinguished from the alternative benzoxazine structure **4** by NMR spectroscopy.[12] The latter was reported to be the product from condensation involving phenols and simple amines in the presence of 2 equiv of formaldehyde.[9a] Correlations between the aminal protons (δ_H=4.24 and 4.42 ppm in **3a**; 4.21 and 4.37 ppm in **3b**) and ^{13}C NMR signals of the aminoalcohol moiety (δ_C=68.3 and 70.7 ppm in **3a**; 68.2 and 70.6 ppm in **3b** for the α- and β-carbons, respectively), and the absence of correlations between these protons and aromatic carbons in HMBC experiments strongly supported the oxazolidine structures (Scheme 1). A very high *ortho*-selectivity with respect to the position of alkylation on the phenolic ring was observed with unsubstituted phenol. The high *ortho*-selectivity could be explained by the chelating effect of the lithium ion, making the alkylation at the *ortho*-position highly favored (Scheme 1). Substitution of phenol with anisole did not result in any product formation, indicating the critical role of the free phenolic OH in mediating the reaction.

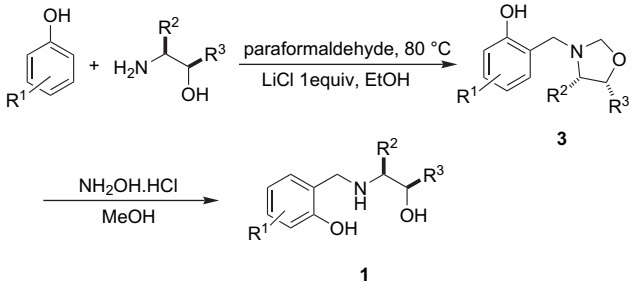


Scheme 1.

Next, we investigated the conditions for hydrolytic ring opening of the oxazolidines **3** to give the desired ligand **1**. Acid hydrolysis of oxazolidine or formacetal, e.g., aqueous HCl, was not efficient due to the reversible nature of the reaction. We have found that treatment of **3** with excess (10 equiv) of hydroxylamine hydrochloride in methanol, conditions previously applied for the cleavage of imines,[13] cleanly afforded the expected products **1**. The hydroxylamine probably works by trapping the liberated formaldehyde, therefore prevented the reverse reaction.

The two-step sequence, namely Mannich-type multicomponent reaction followed by oxazolidine ring opening, was applied to synthesize a number of chiral ligands **1** (Table 2). In most cases, the oxazolidine intermediates **3** were not isolated but the crude products from the Mannich reaction were directly hydrolyzed as described above to give **1** as the final products. In cases where comparisons are available, ligands **1** were obtained in consistently higher yields than those from the sodium borohydride reduction method (entries 1, 13–19, 23, and 24). Most of the phenols participated

Table 2. Synthesis of chiral aminoalcohols **1** from phenol and β-aminoalcohols by multicomponent Mannich-type reaction to form oxazolidines **3** followed by hydrolytic ring opening



Entry	Ligand	R^1	R^2	R^3	Yield[a] (%)
1	**1a**	4-C_6H_5	^{i}Pr	H	85
2	**1b**	H	^{i}Pr	H	87 (75)
3	**1c**	2-C_6H_5	^{i}Pr	H	86
4	**1d**	4-Me	^{i}Pr	H	86
5	**1e**	2-Me	^{i}Pr	H	88
6	**1f**	4-^{t}Bu	^{i}Pr	H	87
7	**1g**	2-^{t}Bu	^{i}Pr	H	84
8	**1h**	4-Cl	^{i}Pr	H	88
9	**1i**	2-Cl	^{i}Pr	H	84
10	**1j**	4-OMe	^{i}Pr	H	92
11	**1k**	2,4-diMe	^{i}Pr	H	83
12	**1l**	2,4-di^{t}Bu	^{i}Pr	H	87
13	**1m**	H	Ph	H	86 (73)
14	**1n**	H	^{i}Bu	H	85 (50)
15	**1o**	H	^{c}HexCH$_2$	H	84 (72)
16	**1p**	H	^{s}Bu	H	86 (74)
17	**1q**	H	Me	H	62 (51)
18	**1r**	H	H	Me	60 (49)
19	**1s**	H	$PhCH_2$	H	88 (74)
20	**1t**	3-C_6H_5	$PhCH_2$	H	86
21	**1u**	3-Cl	$PhCH_2$	H	85
22	**1v**	3-Me	$PhCH_2$	H	88
23	**1w**	H	^{t}Bu	H	85 (74)
24	**1x**	2,4-di^{t}Bu	^{t}Bu	H	85 (0)
25	**1y**	4-Me	^{t}Bu	H	84
26	**1z**	2-Me	^{t}Bu	H	89

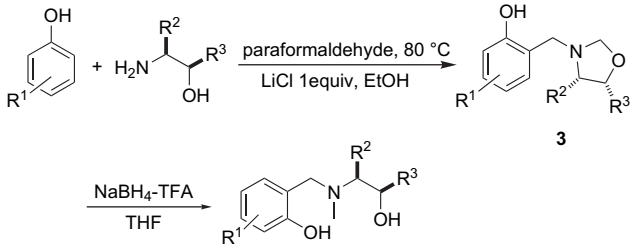
[a] Yields of pure ligands obtained from two-step reactions. Values in parentheses are the yields obtained by $NaBH_4$ reduction of Schiff bases **2** formed in situ between appropriate salicylaldehydes and aminoalcohols.

in the reaction well, except strongly deactivated phenols such as 4-nitrophenol. Both α- and β-naphthols gave only tarry materials. 2,2′-Dihydroxybiphenyl and binaphthol were inert under these conditions probably due to the chelating ability of these phenols, which inactivated the Lewis acid catalyst. It should be emphasized again that the Mannich reaction is very highly *ortho*-selective. *para*-Substituted products could neither be isolated nor observed in the crude reaction mixture. Even for 3-substituted phenol, only the less hindered *ortho*-position reacted (entries 20–22). Since a variety of phenols are commercially available, a great diversity of the salicyl moiety can easily be made. Furthermore, the reaction is also applicable for preparing highly sterically hindered ligands such as **1m** (entry 24), which could not be prepared by conventional methods due to the inertness of its Schiff base precursor toward a number of reducing agents.

It is known that oxazolidines may undergo a reductive ring opening with $NaBH_4$ in the presence of a Brønsted or a Lewis acid to give exclusively *N*-methylated aminoalcohols as a result of stereoelectronic effects.[14] The oxazolidines **3** when treated with $NaBH_4$/TFA should therefore provide the *N*-methylated ligands **5**. Some representative *N*-methylated ligands have been successfully synthesized in this way (Table 3). Although the yields of the ligands **5** were generally not as good as the corresponding NH ligands **1**, the method provided a very concise access to *N*-methylated ligands **5**, which are also potentially useful ligands for catalytic asymmetric reactions.

Strecker reaction of *N*-benzhydrylimine **6** with TMSCN in the presence of **1**-Ti(O^iPr)$_4$ and **5**-Ti(O^iPr)$_4$ complexes were performed under the conditions reported by Banphavichit et al. (Table 4).[5a] In cases where enantioselectivities were observed, the (*S*)-enantiomer of the Strecker product **7** was preferentially formed. When comparisons are available, practically identical enantioselectivities were obtained for ligands prepared by Mannich reaction and $NaBH_4$ reduction. The results confirmed previous observation that the bulkiness of the β-substituent on the chiral *N*-salicyl-β-aminoalcohol plays a significant role in determining the degree of enantioselectivity. The presence of substituents at *ortho*- or *meta*-positions on the salicyl moiety appeared to decrease the enantioselectivity, most notably when the substituent was sterically hindered. On the other hand, the presence of *para*-substituent was well tolerated. Although none of the new ligands provided better enantioselectivity than those already discovered,[5] the results suggest the possibilities of functionalization of the 4-position of the salicyl moiety, for example, immobilization of the ligand, without negative effects on the yield and enantioselectivity. It is noteworthy that even though all *N*-methylated ligands could catalyze the reaction, only very poor enantioselectivities were observed (Table 4). The presence of the free NH group in the ligand therefore appears to play a significant role in controlling the enantioselectivity of the reaction.

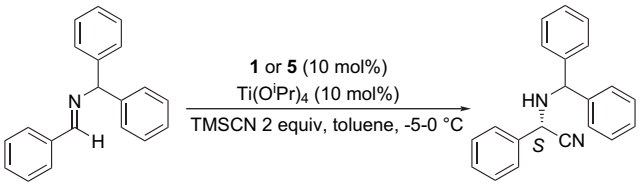
Table 3. Synthesis of *N*-methylated aminoalcohol **5** from phenols and β-aminoalcohols by multicomponent Mannich-type reaction to form oxazolidine **3** followed by reductive ring opening with TFA/$NaBH_4$



Entry	Ligand	R^1	R^2	R^3	Yield[a] (%)
1	**5a**	^{t}Bu	–$C_6H_4CH_2$–	[b]	61
2	**5b**	H	CH_2Ph	H	62
3	**5c**	2,4-di^{t}Bu	^{t}Bu	H	60
4	**5d**	4-Ph	Ph	H	60
5	**5e**	3-Me	^{i}Pr	H	57
6	**5f**	3-Ph	^{i}Pr	H	58

[a] Yields of pure ligands obtained from two-step reactions.
[b] (1*R*,2*S*) isomer.

Table 4. Evaluation of the ligands for asymmetric Strecker reaction



6 7

Entry	Ligand	Conversion[a] (%)	ee[b] (%)
1	**1a**	>99	98 (97)
2	**1b**	>99	97
3	**1c**	>99	41
4	**1d**	>99	97
5	**1e**	>99	79
6	**1f**	>99	93
7	**1g**	>99	5
8	**1h**	>99	93
9	**1i**	>99	43
10	**1j**	>99	94
11	**1k**	>99	47
12	**1l**	82	11
13	**1m**	>99	89 (89)
14	**1n**	>99	85 (84)
15	**1o**	>99	85 (85)
16	**1p**	>99	98 (98)
17	**1q**	>99	75 (73)
18	**1r**	>99	0 (0)
19	**1s**	>99	98 (98)
20	**1t**	>99	82
21	**1u**	>99	78
22	**1v**	>99	90
23	**1w**	>99	98 (98)
24	**1x**	78	14
25	**1y**	>99	97
26	**1z**	>99	83
27	**5a**	>99	0
28	**5b**	>99	24
29	**5c**	>99	0
30	**5d**	>99	11
31	**5e**	>99	14
32	**5f**	>99	8

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by ^{1}H NMR spectroscopy after addition of (*S*)-camphorsulfonic acid as chiral solvating agent.[5a] Values in parentheses are obtained from ligands prepared using $NaBH_4$ reduction method.[5a]

3. Conclusions

An efficient synthetic methodology for the preparation of *N*-salicyl-β-aminoalcohol ligands has been developed. The procedure was based on a multicomponent Mannich-type reaction to form an oxazolidine intermediate. Hydrolytic ring opening of the oxazolidines provided a series of chiral *N*-salicyl-β-aminoalcohol ligands **1** in high yields. Alternative reductive ring opening afforded the corresponding *N*-methylated ligands **5** in moderate yields. The 1:1 complexes of $Ti(O^iPr)_4$ and **1** were highly effective catalysts for enantioselective Strecker reactions of aldimines. Ligands **1** bearing a relatively sterically hindered substituent at the β-position (R^2) and without a substituent at the *ortho*-position of the salicyl moiety gave the Strecker product in excellent yields and enantioselectivities.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 melting point apparatus. The optical rotations were measured at ambient temperature with a Jasco P-1010 polarimeter. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-400 Plus operating at 400 (^1H) and 100 MHz (^{13}C), respectively. Infrared spectra were recorded on a Nicolet Impact 410 spectrometer, as a thin film on NaCl plates. The characteristic absorption is reported as broad (br), medium (m), or weak (w). High resolution mass spectra were recorded on a JEOL JMS-700T (Osaka City University, Japan) or Finnigan Mat High Resolution Mass Spectrometer (Chulabhorn Research Institute, Bangkok) using the Fast atom bombardment (FAB^+) ionization method. Elemental analysis results were analyzed on CHNS/O analyzer (Perkin–Elmer PE2400 Series II) at Scientific and Technological Research Equipment Centre, Chulalongkorn University.

Chemicals were purchased from standard suppliers and were used as received without purification. Commercial grade solvents for column chromatography were distilled before use. THF was distilled from sodium benzophenone ketyl radical prior to use. Toluene for the reactions was of AR grade and dried with activated 4 Å molecular sieves. Other solvents for the reactions were of AR grade and used without further purification. Unless otherwise stated, all reactions were performed in oven-dried glassware under ambient conditions.

4.2. General procedure for the synthesis of chiral *N*-salicyl-β-aminoalcohol ligands 1

A mixture of a phenol (0.5 mmol), paraformaldehyde (250 mg, 10 equiv), an appropriate aminoalcohol (0.5 mmol), and LiCl (0.5 mmol) was dissolved with 3 mL ethanol in a screw-capped test tube. The reaction mixture was heated in a heating block at 80 °C for 18 h. Ethanol was removed in vacuo and the crude products were purified by flash column chromatography using hexanes and ethyl acetate as eluant. At this stage, it is usually difficult to completely remove the contaminated phenols.

The partially purified oxazolidine was dissolved in methanol (5 mL) and treated with hydroxylamine hydrochloride (5.0 mmol, 10 equiv). The reaction mixture was vigorously stirred for 2 h or until the reaction went to completion (monitored by TLC). After a usual aqueous work-up, the crude product was purified by flash column chromatography using hexanes and ethyl acetate as eluant to obtain the chiral *N*-salicyl-β-aminoalcohols **1**.

Ligands **1b**, **1m–1s**, and **1w** have been previously synthesized and characterization data reported.[5]

4.3. Spectroscopic data of selected oxazolidine derivatives

4.3.1. *N*-(2′-Hydroxy-3′-biphenyl)methyl-(*S*)-4-isopropyloxazolidine (3a). Colorless oil; $[\alpha]_D^{28}$ +0.84 (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.92 and 1.15 (6H, 2×d, *J*=7.0 Hz, $CH(CH_3)_2$), 1.82 (1H, m, $CH(CH_3)_2$), 2.82 (1H, m, $NCHCH(CH_3)_2$), 3.59 (1H, dd, *J*=6.2, 8.6 Hz, $CHCH_aH_bO$), 3.96 and 4.05 (1H, AB system, *J*=14.0 Hz, $ArCH_2N$), 4.12 (1H, apparent t, *J*=8.6 Hz, $CHCH_aH_bO$), 4.24 (1H, A*B*, *J*=6.4 Hz, NCH_aH_bO), 4.42 (1H, *A*B, *J*=6.2 Hz, NCH_aH_bO), 6.97 (1H, d, *J*=8.6 Hz, Ar), 7.25 (1H, s, Ar), 7.32 (1H, m, Ar), 7.40–7.50 (3H, m, Ar), 7.56 (2H, d, *J*=7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): 18.7, 20.1, 30.9, 59.4, 68.3, 70.7, 84.6, 116.8, 126.6, 127.5, 127.8, 128.7, 132.6, 140.8, 157.2; IR (film, ν_{max}, cm^{-1}): 3020 (br), 2962 (w), 1606 (w), 1482 (w), 1266 (w); HRMS (FAB^+) calcd for $C_{19}H_{23}NO_2$: 297.1729, found: 297.1733.

4.3.2. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-4-isopropyloxazolidine (3b). Colorless oil; $[\alpha]_D^{28}$ −2.84 (*c* 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96 and 1.08 (6H, 2×d, *J*=7.0 Hz, $CH(CH_3)_2$), 1.79 (1H, m, $CH(CH_3)_2$), 2.80 (1H, m, $NCHCH(CH_3)_2$), 3.56 (1H, dd, *J*=7.0, 8.6 Hz, $CHCH_aH_bO$), 3.88 and 3.99 (1H, AB system, *J*=13.2 Hz, $ArCH_2N$), 4.15 (1H, apparent t, *J*=7.8 Hz, $CHCH_aH_bO$), 4.21 (1H, A*B*, *J*=6.2 Hz, NCH_aH_bO), 4.37 (1H, *A*B, *J*=6.2 Hz, NCH_aH_bO), 6.83 (1H, apparent t, *J*=7.8 Hz, Ar), 6.90 (1H, d, *J*=7.8 Hz, Ar), 7.01 (1H, d, *J*=7.8 Hz, Ar), 7.23 (1H, apparent t, *J*=7.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 20.0, 30.9, 59.3, 68.2, 70.6, 84.6, 116.4, 119.4, 122.2, 128.8, 129.2, 157.6; IR (film, ν_{max}, cm^{-1}): 3080 (br), 2962 (br), 1591 (w), 1486 (m), 1254 (m); HRMS (FAB^+) calcd for $C_{13}H_{19}NO_2$: 221.1416, found: 221.1420.

4.4. Physical properties and spectroscopic and analytical spectra of new ligands

4.4.1. *N*-(2′-Hydroxy-5′-biphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1a). White crystalline solid (121 mg, 85%); mp 132–133 °C; $[\alpha]_D^{24}$ −19.4 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.03 and 1.05 (6H, 2×d, *J*=6.8 Hz, $2\times CH_3$), 2.05 (1H, m, $CH(CH_3)_2$), 2.65 (1H, m, CHNH), 3.73 (1H, A*B*X, J_{AB}=11.2, J_{BX}=6.4 Hz, CH_aH_bOH), 3.87 (1H, *A*BX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 4.15 (1H, A*B*, *J*=13.6 Hz, CH_aH_bNH), 4.18 (1H, *A*B, *J*=13.6 Hz, CH_aH_bNH), 7.01 (1H, d, *J*=8.4 Hz, Ar), 7.32 (2H, m, Ar), 7.45 (3H, m, Ar), 7.55 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.7, 19.3, 28.6, 51.2, 61.1, 64.1, 116.0, 119.1, 123.5, 126.7, 127.5, 128.0, 129.1, 129.3, 138.5, 155.3; IR (film, ν_{max}, cm^{-1}): 3410 (br), 2959 (w), 1597 (w), 1461

(m), 1429 (m), 1235 (w), 1074 (w); Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; Found: C, 75.78; H, 8.22; N, 4.75%.

4.4.2. *N*-(2′-Hydroxy-3′-biphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1c). White crystalline solid (123 mg, 86%); mp 135–136 °C; $[\alpha]_D^{24}$ +19.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03 and 1.05 (6H, 2×d, J=6.8 Hz, 2×CH_3), 2.05 (1H, m, CH(CH_3)$_2$), 2.65 (1H, m, CHNH), 3.73 (1H, ABX, J_{AB}=11.2, J_{BX}=6.4 Hz, CH_aH_bOH), 3.87 (1H, ABX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 4.16 (2H, s, CH_2NH), 6.90 (1H, t, J=8.4 Hz, Ar), 7.01 (1H, d, J=8.4 Hz, Ar), 7.32 (2H, m, Ar), 7.45 (2H, m, Ar), 7.55 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 19.3, 28.6, 51.2, 61.1, 64.1, 119.1, 123.7, 126.8, 127.7, 128.1, 129.2, 129.4, 130.0, 138.6, 155.1; IR (film, ν_{max}, cm^{-1}): 3303 (br), 2961 (w), 1602 (w), 1460 (m), 1272 (w), 1074 (w); Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; Found: C, 75.74; H, 8.11; N, 5.15%.

4.4.3. *N*-(2′-Hydroxy-5′-methylphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1d). White crystalline solid (96 mg, 86%); mp 58–59 °C; $[\alpha]_D^{24}$ +18.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 and 1.02 (6H, 2×d, J=6.8 Hz, 2×CH_3), 1.95 (1H, m, CH(CH_3)$_2$), 2.27 (1H, s, CH_3), 2.50 (1H, m, CHNH), 3.62 (1H, ABX, J_{AB}=11.2, J_{BX}=6.4 Hz, CH_aH_bOH), 3.81 (1H, ABX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 3.97 (2H, s, CH_2NH), 5.22 (br s, NH and OH), 6.76 (1H, d, J=8.0 Hz, Ar), 6.82 (1H, s, Ar), 6.99 (1H, d, J=8.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 19.2, 20.5, 28.6, 50.8, 60.9, 64.0, 116.1, 123.0, 128.3, 128.9, 129.1, 155.5; IR (film, ν_{max}, cm^{-1}): 3303 (br), 2960 (w), 1606 (w), 1500 (w), 1257 (w), 1045 (w); Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.62; H, 9.46; N, 6.27%.

4.4.4. *N*-(2′-Hydroxy-3′-methylphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1e). White crystalline solid (98 mg, 88%); mp 56–57 °C; $[\alpha]_D^{24}$ +17.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 and 1.04 (6H, 2×d, J=6.8 Hz, 2×CH_3), 1.98 (1H, m, CH(CH_3)$_2$), 2.29 (1H, s, CH_3), 2.51 (1H, m, CHNH), 3.64 (1H, ABX, J_{AB}=11.2, J_{BX}=6.0 Hz, CH_aH_bOH), 3.82 (1H, ABX, J_{AB}=11.2, J_{AX}=4.0 Hz, CH_aH_bOH), 4.00 (2H, s, CH_2NH), 5.24 (br s, NH and OH), 6.74 (1H, apparent t, J=7.2 Hz, Ar), 6.88 (1H, d, J=7.2 Hz, Ar), 7.03 (1H, d, J=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.8, 18.8, 19.2, 28.6, 51.0, 61.0, 64.2, 118.8, 122.6, 125.3, 125.9, 130.0, 156.1; IR (film, ν_{max}, cm^{-1}): 3416 (br), 2960 (w), 1597 (m), 1460 (m), 1262 (m), 1226 (m), 1079 (m), 1044 (m); Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.93; H, 9.47; N, 6.20%.

4.4.5. *N*-(5′-*tert*-Butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1f). Colorless oil (115 mg, 87%); $[\alpha]_D^{24}$ +18.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 and 1.03 (6H, 2×d, J=6.8 Hz, 2×CH_3), 1.31 (9H, s, 3×CH_3), 1.98 (1H, m, CH(CH_3)$_2$), 2.55 (1H, m, CHNH), 3.66 (1H, ABX, J_{AB}=11.2, J_{BX}=6.4 Hz, CH_aH_bOH), 3.83 (1H, ABX, J_{AB}=11.2, J_{AX}=4.0 Hz, CH_aH_bOH), 4.03 (2H, s, CH_2NH), 5.24 (br s, NH and OH), 6.81 (1H, d, J=8.4 Hz, Ar), 7.04 (1H, s, Ar), 7.22 (1H, d, J=8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 19.2, 28.6, 31.6, 34.0, 51.2, 61.0, 64.2, 115.8, 122.3, 125.2, 125.6, 141.9, 155.5; IR (film, ν_{max}, cm^{-1}): 3305 (br), 2959 (w), 1605 (w), 1500 (m), 1390 (w), 1259 (w), 1125 (w), 1045 (w); Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28; Found: C, 72.30; H, 10.23; N, 5.14%.

4.4.6. *N*-(3′-*tert*-Butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1g). Colorless oil (111 mg, 84%); $[\alpha]_D^{24}$ +15.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 and 1.05 (6H, 2×d, J=6.8 Hz, 2×CH_3), 1.48 (9H, s, 3×CH_3), 1.99 (1H, m, CH(CH_3)$_2$), 2.55 (1H, m, CHNH), 3.68 (1H, ABX, J_{AB}=11.2, J_{BX}=5.6 Hz, CH_aH_bOH), 3.84 (1H, ABX, J_{AB}=11.2, J_{AX}=4.0 Hz, CH_aH_bOH), 4.03 (1H, AB, J=13.6 Hz, CH_aH_bNH), 4.08 (1H, AB, J=13.6 Hz, CH_aH_bNH), 6.78 (1H, apparent t, J=7.6 Hz, Ar), 6.94 (1H, d, J=7.2 Hz, Ar), 7.25 (1H, d, J=8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.0, 19.3, 28.7, 29.6, 34.7, 51.2, 61.0, 63.8, 118.5, 123.4, 126.1, 126.7, 137.1, 157.0; IR (film, ν_{max}, cm^{-1}): 3315 (br), 2958 (w), 1592 (w), 1439 (m), 1240 (w), 1083 (w); Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28; Found: C, 72.24; H, 10.34; N, 5.28%.

4.4.7. *N*-(5′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1h). White crystalline solid (107 mg, 88%); mp 98–100 °C, $[\alpha]_D^{24}$ +18.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 and 1.02 (6H, 2×d, J=6.8 Hz, 2×CH_3), 1.95 (1H, m, CH(CH_3)$_2$), 2.53 (1H, m, CHNH), 3.65 (1H, ABX, J_{AB}=11.2, J_{BX}=6.4 Hz, CH_aH_bOH), 3.83 (1H, ABX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 4.00 (2H, s, CH_2NH), 5.13 (br s, NH and OH), 6.78 (1H, d, J=8.8 Hz, Ar), 6.99 (1H, s, Ar), 7.25 (1H, d, J=8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.7, 19.3, 28.5, 50.2, 60.7, 64.0, 117.7, 123.6, 124.2, 128.2, 128.7, 156.8; IR (film, ν_{max}, cm^{-1}): 3302 (br), 2962 (w), 1707 (w), 1589 (w), 1481 (m), 1262 (m), 1182 (w), 1088 (w); Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.54; N, 5.75; Found: C, 59.13; H, 7.62; N, 5.77%.

4.4.8. *N*-(3′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1i). White crystalline solid (102 mg, 84%); mp 90–92 °C, $[\alpha]_D^{24}$ +13.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 and 0.95 (6H, 2×d, J=6.8 Hz, 2×CH_3), 1.94 (1H, m, CH(CH_3)$_2$), 2.56 (1H, m, CHNH), 3.62 (1H, ABX, J_{AB}=11.6, J_{BX}=6.8 Hz, CH_aH_bOH), 3.77 (1H, ABX, J_{AB}=11.2, J_{AX}=3.2 Hz, CH_aH_bOH), 4.01 (2H, s, CH_2NH), 6.50 (1H, apparent t, J=7.6 Hz, Ar), 6.90 (1H, d, J=7.6 Hz, Ar), 7.19 (1H, d, J=8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.4, 19.4, 28.2, 49.9, 60.3, 64.4, 119.6, 121.5, 123.1, 127.6, 129.6, 153.7; IR (film, ν_{max}, cm^{-1}): 3292 (br), 2965 (w), 1710 (w), 1589 (w), 1451 (m), 1288 (w); Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.44; N, 5.75; Found: C, 59.14; H, 7.49; N, 5.62%.

4.4.9. *N*-(2′-Hydroxy-5′-methoxyphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1j). Yellow viscous oil (110 mg, 92%); $[\alpha]_D^{24}$ +7.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 and 1.00 (6H, 2×d, J=6.8 Hz, 2×CH_3), 1.94 (1H, m, CH(CH_3)$_2$), 2.49 (1H, m, CHNH), 3.61 (1H, ABX, J_{AB}=11.2, J_{BX}=6.4 Hz, CH_aH_bOH), 3.74 (3H, s, OCH_3), 3.80 (1H, ABX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 3.98 (2H, s, CH_2NH), 4.98 (br s, NH and OH), 6.59 (1H, s, Ar), 6.74 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.7, 19.2, 28.5, 50.8, 55.8, 60.8, 64.1, 113.6,

114.3, 116.7, 123.8, 151.6, 152.5; IR (film, ν_{max}, cm^{-1}): 3304 (br), 2958 (w), 2361 (w), 1605 (w), 1498 (m), 1252 (m), 1151 (w), 1042 (w); Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85; Found: C, 64.96; H, 8.75; N, 5.85%.

4.4.10. *N*-(3′,5′-Dimethyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1k). Colorless oil (98 mg, 83%); $[\alpha]_D^{24}$ +13.0 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.93 (6H, apparent t, J=7.2 Hz, 2×CH_3), 2.14 and 2.16 (6H, 2×s, 2×CH_3), 2.58 (1H, m, CHNH), 3.60 (1H, ABX, J_{AB}=11.6, J_{BX}=6.8 Hz, CH_aH_bOH), 3.74 (1H, ABX, J_{AB}=11.6, J_{AX}=3.6 Hz, CH_aH_bOH), 3.91 (1H, AB, J=13.2 Hz, CH_aH_bNH), 4.00 (1H, AB, J=13.2 Hz, CH_aH_bNH), 6.67 (1H, s, Ar), 6.83 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.9, 18.3, 19.3, 20.3, 27.9, 49.7, 60.1, 64.1, 120.5, 125.9, 127.5, 128.9, 131.6, 153.6; IR (film, ν_{max}, cm^{-1}): 3305 (br), 2959 (w), 1613 (w), 1480 (m), 1242 (m), 1153 (w), 1043 (w); Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90; Found: C, 70.70; H, 9.76; N, 5.82%.

4.4.11. *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methylbutanol (1l). White crystalline solid (140 mg, 87%); mp 55–57 °C; $[\alpha]_D^{24}$ +17.3 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.06 and 1.09 (6H, 2×d, J=7.2 Hz, 2×CH_3), 1.38 (9H, s, C(CH_3)$_3$), 1.52 (9H, s, C(CH_3)$_3$), 2.03 (1H, m, CH(CH$_3$)$_2$), 2.56 (1H, m, CHNH), 3.72 (1H, ABX, J_{AB}=11.2, J_{BX}=5.6 Hz, CH_aH_bOH), 3.88 (1H, ABX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 4.05 (1H, AB, J=13.6 Hz, CH_aH_bNH), 4.12 (1H, AB, J=13.6 Hz, CH_aH_bNH), 6.98 (1H, s, Ar), 7.33 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1, 19.2, 28.7, 29.7, 31.8, 34.2, 35.0, 51.8, 61.3, 64.0, 122.7, 123.1, 123.2, 136.1, 140.7, 154.5; IR (film, ν_{max}, cm^{-1}): 3316 (br), 2958 (m), 1605 (w), 1475 (m), 1237 (m), 1165 (w), 1083 (w); Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36; Found: C, 74.90; H, 10.97; N, 4.48%.

4.4.12. *N*-(2′-Hydroxy-4′-phenylphenyl)methyl-(*S*)-2-amino-3-phenylpropanol (1t). White crystalline solid (145 mg, 87%); mp 134.8–136.3 °C; $[\alpha]_D^{24}$ +26.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.83 (1H, ABX, J_{AB}=13.6, J_{BX}=7.2 Hz, CH_aH_bPh), 2.92 (1H, ABX, J_{AB}=13.6, J_{AX}=6.4 Hz, CH_aH_bPh), 3.01 (1H, m, CHNH), 3.55 (1H, ABX, J_{AB}=11.2, J_{BX}=5.2 Hz, CH_aH_bOH), 3.75 (1H, ABX, J_{AB}=11.2, J_{AX}=4.0 Hz, CH_aH_bOH), 4.04 (2H, s, CH_2NH), 5.16 (br s, NH and OH), 7.03 (2H, m, Ar), 7.12 (1H, s, Ar), 7.20 (2H, m, Ar), 7.26 (1H, m, Ar), 7.34 (3H, m, Ar), 7.43 (2H, m, Ar), 7.59 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.2, 49.8, 59.3, 62.4, 115.1, 118.0, 121.8, 126.7 (overlapping signals), 126.9, 127.3, 128.7, 129.2, 138.0, 140.8, 142.0, 158.2; IR (film, ν_{max}, cm^{-1}): 3315 (br), 3028 (br), 2925 (w), 1602 (w), 1567 (m), 1486 (m), 1458 (m), 1306 (w), 1205 (w), 1039 (m); Anal. Calcd for $C_{21}H_{22}NO_2$: C, 79.25; H, 6.95; N, 4.20; Found: C, 78.94; H, 6.92; N, 4.21%.

4.4.13. *N*-(4′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenylpropanol (1u). White crystalline solid (121 mg, 83%); mp 143.6–144.5 °C; $[\alpha]_D^{24}$ +35.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.80 (1H, ABX, J_{AB}=13.6, J_{BX}=7.6 Hz, CH_aH_bPh), 2.88 (1H, ABX, J_{AB}=13.6, J_{AX}=6.4 Hz, CH_aH_bPh), 2.97 (1H, m, CHNH), 3.54 (1H, ABX, J_{AB}=10.8, J_{BX}=4.8 Hz, CH_aH_bOH), 3.71 (1H, ABX, J_{AB}=11.2, J_{AX}=4.0 Hz, CH_aH_bOH), 3.98 (2H, s, CH_2NH), 6.74 (1H, d, J=8.0 Hz, Ar), 6.84 (2H, m, Ar), 7.17 (2H, m, Ar), 7.24 (1H, m, Ar), 7.31 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.3, 49.8, 59.5, 62.4, 116.9, 119.2, 121.1, 126.7, 128.6, 128.9, 129.1, 134.0, 137.8, 158.9; IR (film, ν_{max}, cm^{-1}): 3322 (br), 2985 (w), 1595 (m), 1347 (w), 1259 (w), 1036 (m); Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80; Found: C, 65.78; H, 6.15; N, 4.85%.

4.4.14. *N*-(2′-Hydroxy-4′-methylphenyl)methyl-(*S*)-2-amino-3-phenylpropanol (1v). White crystalline solid (116 mg, 86%); mp 136.3–137.5 °C; $[\alpha]_D^{24}$ +28.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.24 (1H, s, CH_3), 2.80 (1H, ABX, J_{AB}=13.6, J_{BX}=7.6 Hz, CH_aH_bPh), 2.88 (1H, ABX, J_{AB}=13.6, J_{AX}=6.4 Hz, CH_aH_bPh), 2.97 (1H, m, CHNH), 3.52 (1H, ABX, J_{AB}=11.2, J_{BX}=5.2 Hz, CH_aH_bOH), 3.71 (1H, ABX, J_{AB}=11.2, J_{AX}=4.0 Hz, CH_aH_bOH), 3.95 (2H, s, CH_2NH), 5.07 (br s, NH and OH), 6.75 (2H, m, Ar), 6.96 (1H, d, J=8.0 Hz, Ar), 7.18 (2H, m, Ar), 7.24 (1H, m, Ar), 7.31 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 37.5, 50.2, 59.6, 62.4, 116.5, 122.2, 126.4, 128.3, 128.6, 129.1, 129.5, 138.2, 155.6; IR (film, ν_{max}, cm^{-1}): 3322 (br), 2921 (w), 1617 (w), 1587 (w), 1454 (m), 1348 (w), 1284 (w), 1109 (m), 1046 (m); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16; Found: C, 75.23; H, 7.78; N, 5.25%.

4.4.15. *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethylbutanol (1x). White crystalline solid (143 mg, 85%); mp 57–59 °C; $[\alpha]_D^{24}$ +16.7 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.06 (9H, s, C(CH_3)$_3$), 1.34 (9H, s, C(CH_3)$_3$), 1.49 (9H, s, C(CH_3)$_3$), 2.40 (1H, ABX, J_{AX}=3.6, J_{BX}=5.2 Hz, CHC(CH$_3$)$_3$), 3.77 (1H, ABX, J_{AB}=11.2, J_{BX}=5.2 Hz, CH_aH_bOH), 4.02 (1H, ABX, J_{AB}=12.0, J_{AX}=3.6 Hz, CH_aH_bOH), 4.19 (2H, d, J=13.2 Hz, CH_2NH), 6.95 (1H, s, Ar), 7.29 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.6, 29.7, 31.7, 34.2, 34.3, 35.0, 53.6, 61.6, 67.5, 122.9, 123.1, 123.3, 136.1, 140.6, 154.6; IR (film, ν_{max}, cm^{-1}): 2957 (w), 1478 (w), 1363 (w), 1237 (w), 1114 (w); Anal. Calcd for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.17; Found: C, 75.18; H, 11.04; N, 4.15%.

4.4.16. *N*-(2′-Hydroxy-5′-methylphenyl)methyl-(*S*)-2-amino-3,3-dimethylbutanol (1y). White crystalline solid (100 mg, 84%); mp 62–64 °C; $[\alpha]_D^{24}$ +7.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.03 (9H, s, 3×CH_3), 2.27 (1H, s, CH_3), 2.41 (1H, ABX, J_{AX}=3.6, J_{BX}=5.6 Hz, CHC(CH$_3$)$_3$), 3.72 (1H, ABX, J_{AB}=11.2, J_{BX}=6.0 Hz, CH_aH_bOH), 3.98 (1H, ABX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 4.14 (2H, d, J=13.6 Hz, CH_2NH), 4.76 (br s, NH and OH), 6.79 (1H, d, J=8.0 Hz, Ar), 6.85 (1H, s, Ar), 7.01 (1H, d, J=8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 27.5, 34.2, 53.0, 61.4, 67.7, 116.1, 123.0, 128.2, 129.0, 129.2, 155.6; IR (film, ν_{max}, cm^{-1}): 3420 (br), 2958 (m), 1597 (m), 1469 (m), 1263 (m), 1226 (m), 1085 (m), 1042 (m); Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90; Found: C, 70.89; H, 9.80; N, 5.98%.

4.4.17. *N*-(2′-Hydroxy-3′-methylphenyl)methyl-(*S*)-2-amino-3,3-dimethylbutanol (1z). White crystalline solid

(106 mg, 89%); mp 60–62 °C; $[\alpha]_D^{24}$ +6.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.05 (9H, s, 3×CH_3), 2.31 (1H, s, CH_3), 2.38 (1H, AB*X*, J_{AX}=3.6, J_{BX}=6.0 Hz, C*H*C(CH_3)$_3$), 3.68 (1H, A*B*X, J_{AB}=11.2, J_{BX}=6.0 Hz, CH_aH_bOH), 3.97 (1H, *A*BX, J_{AB}=11.2, J_{AX}=3.6 Hz, CH_aH_bOH), 4.03 (1H, A*B*, *J*=13.6 Hz, CH_aH_bNH), 4.15 (1H, *A*B, *J*=13.6 Hz, CH_aH_bNH), 5.21 (br s, N*H* and O*H*), 6.76 (1H, apparent t, *J*=7.6 Hz, Ar), 6.89 (1H, d, *J*=7.2 Hz, Ar), 7.10 (1H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.9, 27.5, 34.2, 53.3, 61.5, 67.9, 118.8, 122.9, 125.3, 126.0, 130.0, 156.2; IR (film, ν_{max}, cm^{-1}): 3427 (br), 2958 (w), 1597 (w), 1470 (m), 1263 (w), 1227 (w), 1084 (w), 1042 (w); Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90; Found: C, 70.72; H, 9.90; N, 5.85%.

4.5. General procedure for the synthesis of chiral *N*-salicyl-β-aminoalcohol ligands 5

The oxazolidine was prepared starting from the multicomponent reaction between a phenol, paraformaldehyde, and an aminoalcohol as described in the general procedure for the synthesis of **1**.

Sodium borohydride (2.5 mmol) was dissolved in anhydrous THF (10 mL) at 0 °C with vigorous stirring. Then trifluoroacetic acid (2.5 mmol) was added dropwise to a suspension of metal hydride. A solution of the partially purified oxazolidine in anhydrous THF (3 mL) was added dropwise to a cooled mixture. After the addition, the reaction mixture was stirred for 1 h at room temperature. The suspension was cooled and decomposed off cautiously by 10% sodium hydroxide aqueous solution. The mixture was concentrated and extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The oily residue was purified by flash column chromatography using hexanes and ethyl acetate as eluant to obtain chiral *N*-methyl-*N*-salicyl-β-aminoalcohols **5**.

4.6. Physical properties and spectroscopic and analytical spectra of new ligands

4.6.1. *N*-(5′-*tert*-Butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(1*R*,2*S*)-1-aminoindan-2-ol (5a). White crystalline solid (57 mg, 52%); mp 82–84 °C; $[\alpha]_D^{24}$ +18.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.35 (9H, s, C(CH_3)$_3$), 2.37 (3H, s, NCH_3), 3.03 (1H, A*B*X, J_{AB}=17.6, J_{BX}=4.8 Hz, ArCH_a*H*$_b$CHOH), 3.28 (1H, *A*BX, J_{AB}=17.6, J_{AX}=8.8 Hz, ArC*H*$_a$H$_b$CHOH), 4.17 (2H, AB, *J*=13.8 Hz, CH_2NH), 4.46 (1H, d, *J*=7.6 Hz, NC*H*CHOH), 4.93 (1H, m, NCHC*H*OH), 6.95 (1H, d, *J*=8.8 Hz, Ar), 7.08 (1H, s, Ar), 7.34 (3H, m, Ar), 7.45 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.6, 34.0, 38.1, 40.5, 58.8, 68.5, 73.1, 115.9, 120.3, 125.6, 125.8, 125.9, 126.5, 127.2, 129.0, 137.4, 141.2, 142.2, 155.2; IR (film, ν_{max}, cm^{-1}): 3316 (br), 2921 (w), 1591 (w), 1472 (w), 1256 (w), 1089 (w); HRMS (FAB^+) calcd for $C_{21}H_{28}NO_2$ ($M\cdot H^+$): 326.2120, found: 326.2120.

4.6.2. *N*-(2′-Hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-phenylpropanol (5b). White crystalline solid (84 mg, 62%); mp 63–65 °C; $[\alpha]_D^{24}$ −35.5 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.41 (3H, s, NCH_3), 2.60 (1H, A*B*X, J_{AB}=13.6, J_{BX}=9.2 Hz, CH_aH_bPh), 2.98 (1H, *A*BX, J_{AB}=13.6, J_{AX}=4.8 Hz, CH_aH_bPh), 3.19 (1H, m, C*H*NH), 3.71 (2H, m, CH_2OH), 3.88 (1H, A*B*, *J*=13.6 Hz, CH_aH_bN), 4.01 (1H, A*B*, *J*=13.6 Hz, CH_aH_bNH), 6.83 (2H, m, Ar), 7.01 (1H, d, *J*=8.0 Hz, Ar), 7.20 (2H, m, Ar), 7.27 (2H, m, Ar), 7.34 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.7, 35.7, 57.9, 60.9, 66.2, 116.2, 119.2, 121.9, 126.5, 128.7, 128.8, 128.9, 129.0, 129.1, 138.9, 157.7; IR (film, ν_{max}, cm^{-1}): 3397 (br), 2935 (w), 1591 (m), 1488 (m), 1257 (m), 1031 (w); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.29; H, 7.90; N, 4.88%.

4.6.3. *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3,3-dimethylbutanol (5c). Colorless oil (63 mg, 60%); $[\alpha]_D^{24}$ +8.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.08 (9H, s, C(CH_3)$_3$), 1.32 (9H, s, C(CH_3)$_3$), 1.47 (9H, s, C(CH_3)$_3$), 2.49 (3H, s, NCH_3), 2.71 (1H, AB*X*, J_{AX}=3.6, J_{BX}=11.6 Hz, C*H*C(CH_3)$_3$), 4.02 (1H, A*B*X, J_{AB}=11.6, J_{BX}=3.6 Hz, CH_aH_bOH), 4.10 (1H, *A*BX, J_{AB}=11.6, J_{AX}=6.4 Hz, CH_aH_bOH), 4.14 (1H, A*B*, *J*=13.2 Hz, CH_aH_bN), 4.21 (1H, *A*B, *J*=13.6 Hz, CH_aH_bN), 6.91 (1H, s, Ar), 7.25 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.6, 29.6, 31.7, 34.2, 34.9, 35.2, 38.2, 60.2, 62.0, 73.3, 121.6, 122.7, 123.8, 135.3, 140.4, 154.3; Anal. Calcd for $C_{22}H_{39}NO_2$: C, 75.59; H, 11.25; N, 4.01; Found: C, 75.13; H, 11.28; N, 4.01%.

4.6.4. *N*-(2′-Hydroxy-5′-phenylphenyl)methyl-*N*-methyl-(*R*)-2-amino-2-phenylethanol (5d). White crystalline solid (70 mg, 60%); mp 136–138 °C; $[\alpha]_D^{24}$ −96.8 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.33 (3H, s, NCH_3), 3.76 (1H, A*B*, *J*=13.6 Hz, CH_aH_bNH), 3.91 (1H, A*B*, *J*=13.6 Hz, CH_aH_bNH), 3.96 (1H, AB*X*, J_{AX}=5.6, J_{BX}=8.0 Hz, PhC*H*N), 4.02 (1H, A*B*X, J_{AB}=11.2, J_{BX}=5.4 Hz, CH_aH_bOH), 4.23 (1H, *A*BX, J_{AB}=11.6, J_{AX}=8.4 Hz, CH_aH_bOH), 6.97 (1H, d, *J*=8.4 Hz, Ar), 7.22 (1H, s, Ar), 7.33 (3H, m, Ar), 7.44 (5H, m, Ar), 7.55 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.4, 58.0, 62.1, 69.2, 115.9, 116.6, 122.0, 126.5, 126.6, 127.4, 127.5, 128.5, 128.7, 129.1, 132.4, 134.9, 140.9, 157.4; HRMS (FAB^+) calcd for $C_{22}H_{24}NO_2$ ($M\cdot H^+$): 334.1807, found: 334.1808.

4.6.5. *N*-(2′-Hydroxy-5′-methylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methylbutanol (5e). Colorless oil (51 mg, 57%); $[\alpha]_D^{24}$ +12.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.03 and 1.11 (6H, 2×d, *J*=6.8 Hz, 2×CH_3), 2.06 (1H, m, C*H*(CH_3)$_2$), 2.32 (3H, s, CH_3Ar), 2.39 (3H, s, NCH_3), 2.58 (1H, m, C*H*N), 3.88 (1H, A*B*X, J_{AB}=12.0, J_{BX}=7.2 Hz, CH_aH_bOH), 3.95 (1H, *A*BX, J_{AB}=11.6, J_{AX}=3.2 Hz, CH_aH_bOH), 4.02 (2H, s, CH_2NH), 6.64 (1H, d, *J*=7.2 Hz, Ar), 6.71 (1H, s, Ar), 6.91 (1H, d, *J*=7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.1, 21.2, 21.4, 26.7, 35.9, 59.2, 70.3, 116.6, 118.6, 119.9, 128.6, 138.9, 157.2; HRMS (FAB^+) calcd for $C_{14}H_{24}NO_2$ ($M\cdot H^+$): 238.1807, found: 238.1808.

4.6.6. *N*-(2′-Hydroxy-4′-phenylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methylbutanol (5f). White crystalline solid (60 mg, 58%); mp 126–128 °C; $[\alpha]_D^{24}$ −11.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.05 and 1.13 (6H, 2×d, *J*=6.8 Hz, 2×CH_3), 2.06 (1H, m, C*H*(CH_3)$_2$), 2.45 (3H, s, NCH_3), 2.66 (1H, m, C*H*N), 3.91 (1H, A*B*X,

J_{AB}=11.6, J_{BX}=7.2 Hz, CH_aH_bOH), 3.98 (1H, *A*BX, J_{AB}= 11.6, J_{AX}=3.2 Hz, CH_aH_bOH), 4.11 (2H, s, CH_2NH), 7.06–7.15 (3H, m, Ar), 7.28 (1H, s, Ar), 7.36 (1H, m, Ar), 7.45 (1H, apparent t, J=7.2 Hz, Ar), 7.61 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.2, 21.2, 21.5, 26.8, 36.0, 59.3, 70.5, 114.7, 118.0, 120.6, 127.0, 127.3, 128.7, 129.3, 140.8, 142.2, 158.0; HRMS (FAB^+) calcd for $C_{19}H_{26}NO_2$ ($M\cdot H^+$): 300.1964, found: 300.1967.

Acknowledgements

This work was supported by the Thailand Toray Science Foundation (T.V.) and the Thailand Research Fund under the Royal Golden Jubilee Ph.D. Project (V.B.). We thank Ms. Wanna Bannarukkul and Mr. Nitirat Chimnoi for their technical assistance.

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