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Diastereoselective intermolecular coupling of chiral α-imino amides with ketones by electroreduction

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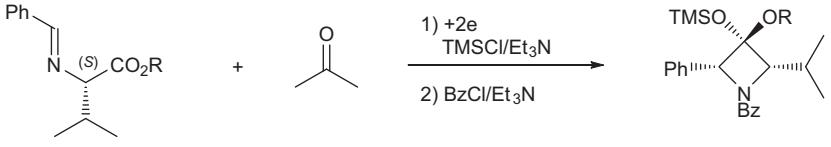
ABSTRACT

The electroreductive intermolecular coupling of chiral α-imino *N*,*N*-dialkylamides derived from (*S*)-α-amino *N*,*N*-dialkylamides and aromatic aldehydes with ketones in the presence of chlorotrimethylsilane and triethylamine gave β-amino alcohols with moderate to good (*R*)-stereoselectivity.

1. Introduction

The reductive coupling of imines with carbonyl compounds is a promising method for the synthesis of β-amino alcohols. A number of methods have been reported for this purpose using metal reducing agents such as $NbCl_3(DME)$,[1] Cp_2Zr,[2] Li-naphthalene,[3] $TiCl_3$,[4] and SmI_2,[5] and electroreduction.[6] Several of these[2,5c–f] have accomplished the diastereoselective imino pinacol coupling of chiral imines with carbonyl compounds for the asymmetric synthesis of optically active β-amino alcohols, which are useful as chiral ligands and auxiliaries.[7] On the other hand, we have reported the electroreductive intramolecular coupling of aromatic α-, β-, and γ-imino esters in the presence of chlorotrimethylsilane (TMSCl) and triethylamine (TEA).[8] However, the electroreduction of chiral α-imino esters prepared from (*S*)-α-amino acids with acetone only gave intramolecularly coupled azetidines,[8a] while the desired intermolecularly coupled products, β-amino alcohols, could not be obtained (Eq. 1). Therefore, we investigated the other chiral imines derived from (*S*)-α-amino acids as substrates for the reductive coupling with carbonyl compounds. Herein we report that the electroreductive intermolecular coupling of chiral (*S*)-α-imino *N*,*N*-dialkylamides with ketones gave the corresponding β-amino alcohols with moderate to good (*R*)-stereoselectivity (Eq. 2). This reaction provides a synthetic method for a new class of chiral β-amino alcohols from readily available optically active α-amino acids.



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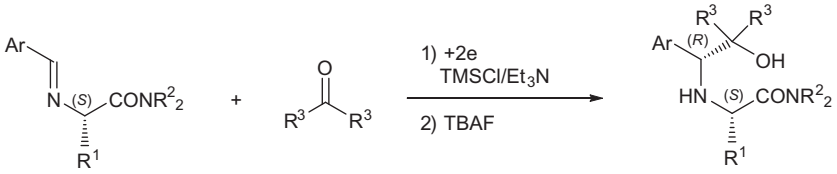

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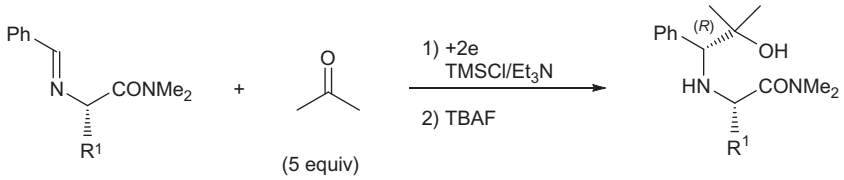
Table 1
Electroreductive coupling of (*S*)-α-benzylideneamino *N*,*N*-dimethylamides with acetone



Run	Imines	R^1	Products	% yield[a]	(*R*):(*S*)[b]
1	**1a**	*i*-Pr	**2a**	68	72:28
2	**3a**	*sec*-Bu	**4a**	62	72:28
3	**5**	*i*-Bu	**6**	65	60:40
4	**7**	Bn	**8**	55	54:46
5	**9**	$CH_2CH_2CO_2Me$	**10**	57	63:37

[a] Isolated yields.
[b] Determined by separation.

I II

2. Results and discussion

Chiral imines were prepared by the condensation of (*S*)-α-amino *N*,*N*-dialkylamides, derived from readily available (*S*)-α-amino acids, with aromatic aldehydes. The electroreduction of the chiral aromatic imines with acetone (5 equiv) was carried out in 0.3 M Bu_4NClO_4 in THF containing TMSCl (5 equiv) and Et_3N (5 equiv) at a constant current of 100 mA (300 C) employing a divided cell and platinum electrodes, according to our previously reported method.[8] The resulting silyl ethers were desilylated with TBAF in THF to give the corresponding chiral β-amino alcohols as mixtures of two diastereomers. The results of the electroreductive coupling of (*S*)-α-benzylideneamino *N*,*N*-dimethylamides, prepared from several (*S*)-α-amino acids with acetone and subsequent desilylation of the resulting trimethylsilyl ethers, are summarized in Table 1. From chiral imines **1a** (R^1 = *i*-Pr) and **3a** (R^1 = *sec*-Bu), β-amino alcohols **2a** and **4a** were obtained with the same (*R*):(*S*) ratio of 72:28 and in 68% and 62% yields, respectively (runs 1 and 2). Other chiral imines **5** (R^1 = *i*-Bu), 7 (R^1 = Bn), and 9 (R^1 = $CH_2CH_2CO_2Me$) afforded β-amino alcohols **6**, **8**, and **10** in low-

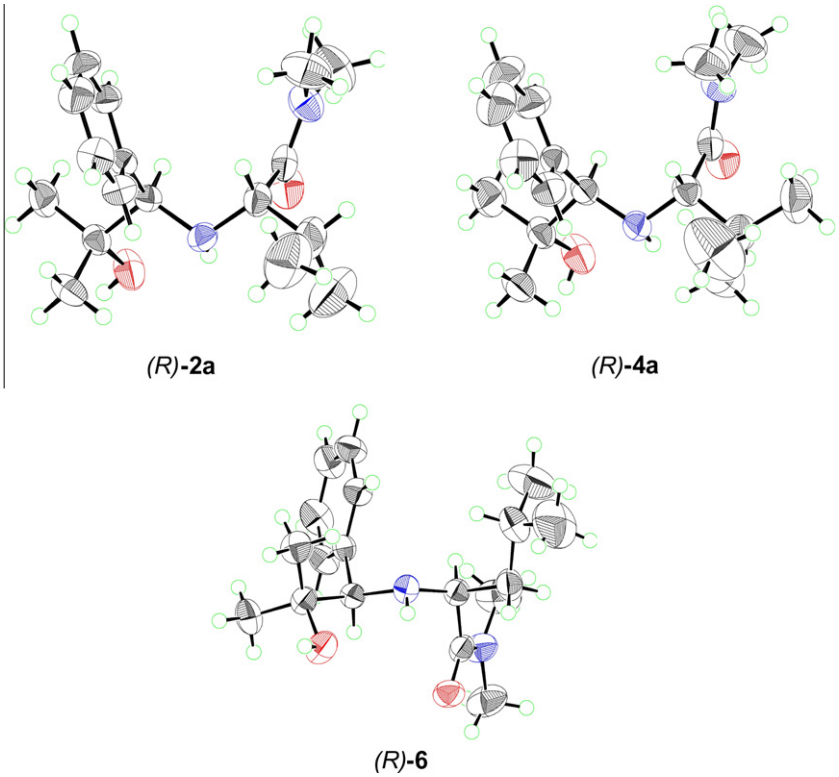


Figure 1. X-ray crystal structures of (*R*)-**2a**, (*R*)-**4a**, and (*R*)-**6**.

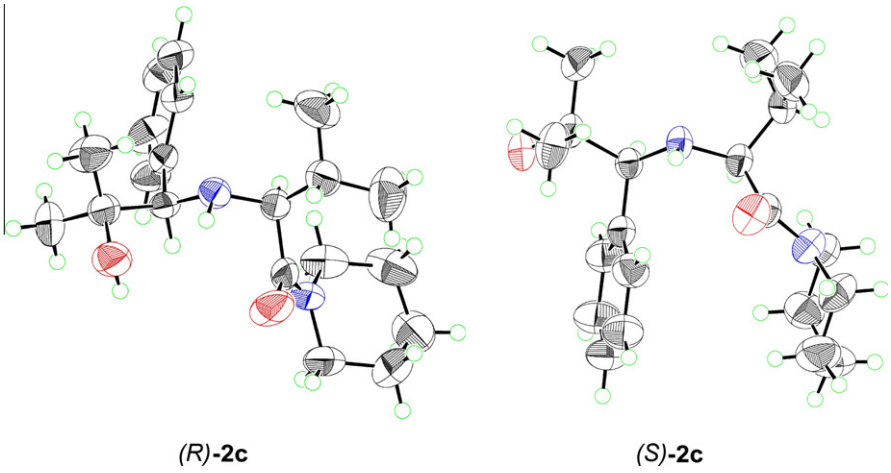


Figure 2. X-ray crystal structures of (*R*)-**2c** and (*S*)-**2c**.

er diastereomeric ratios than for **1a** and **3a** (runs 3–5). The diastereomers of the resulting β-amino alcohols could be separated by column chromatography and the absolute configuration of the newly-formed stereogenic center in the major isomers of **2a**, **4a**, and **6** was determined to be (*R*) by X-ray crystallographic analysis (Fig. 1). Therefore, it was likely that the sense of the newly-formed stereogenic center in the major isomers of **8** and **10** was also (*R*). The by-products of the electroreductive intermolecular coupling were simply reduced amines **I** (10–15%) and *N*-α-trimethylsilylated products **II** (5–10%). Similar to previous reports for the electroreductive intramolecular coupling,[8] the presence of TMSCl was essential for the present intermolecular coupling. Although the presence of Et_3N was not absolutely necessary, the absence of Et_3N brought about a slight decrease of the yields of the coupled products; the electroreduction of **1a** with acetone in the absence of Et_3N gave **2a** in a 55% yield [(*R*):(*S*) = 72:28].

(*S*)-α-Benzylideneamino *N*,*N*-diethylamides **1b** (R^1 = *i*-Pr) and **3b** (R^1 = *sec*-Bu) and piperidine amide **1c** were employed for the electroreductive coupling with acetone (Eqs. 3 and 4). Cross coupled products **2b**,**c** and **4b** were obtained in 60–65% yields with the same (*R*):(*S*) ratio of 75:25, which was slightly higher than with *N*,*N*-dimethylamides **2a** and **4a** [(*R*):(*S*) = 72:28]. The diastereomers of **2b**,**c** and **4b** could be separated by column chromatography and the stereostructures of both diastereomers of **2c** were assigned by X-ray crystallographic analysis (Fig. 2).

Next, several aromatic imines derived from (*S*)-valine *N*,*N*-diethylamide were subjected to reductive coupling with acetone to study the effect of the aromatic substituent on the diastereoselectivity in the cross coupling (Table 2). Substitution of the electron donating *para*-methoxy group slightly decreased the (*R*):(*S*) ratio in β-amino alcohol **12** (run 1), whereas electron withdrawing *meta*-methoxy and *para*-cyano substituents increased the (*R*)-selectivity in **14** and **16** (runs 2 and 3). 1- and 2-Naphthyl imines **17** and **19** also gave β-amino alcohols **18** and **20**, respectively, with increased (*R*):(*S*) ratios (runs 4 and 5). Of these coupling products shown in Table 2, the stereostructures of (*R*)-12, (*S*)-14, and (*R*)-20 were confirmed by X-ray crystallography (Fig. 3).

The electroreduction of **1a**,**b** with cyclopentanone and cyclohexanone also gave the corresponding β-amino alcohols **21a**,**b** and **22a**,**b**, respectively (Eqs. 5 and 6). Although the diastereoselectivities in **21a**,**b** and **22a**,**b** were higher than those in the cross coupled products with acetone **2a**,**b**, the yields, especially of **22a**,**b**, were much lower than those of **2a**,**b**. Incidentally, the electroreductive coupling of **1b** with *n*-butyraldehyde afforded β-amino alcohol **23** in good yield (Eq. 7). However, **23** was obtained as a mixture of four possible diastereomers (ca. 1:1:1:1). In addition, the electroreduction of **1b** with benzaldehyde gave a homo-coupled product of benzaldehyde (pinacol) as the only product and no cross-coupled product was detected.

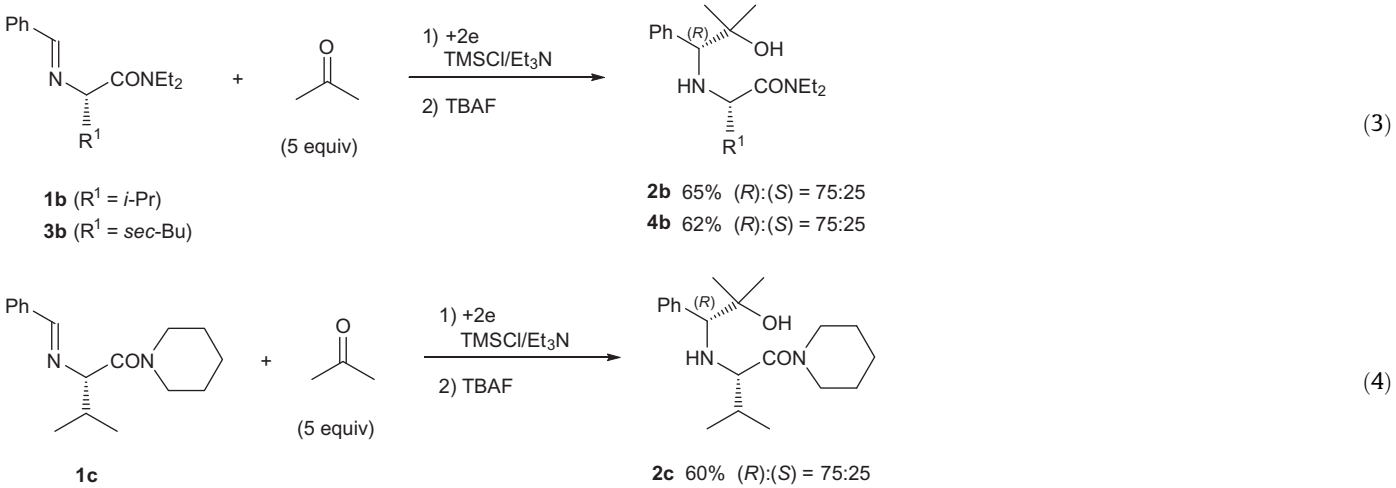
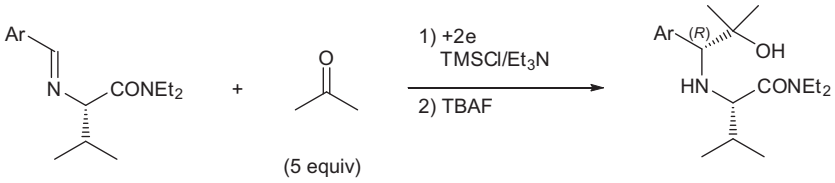
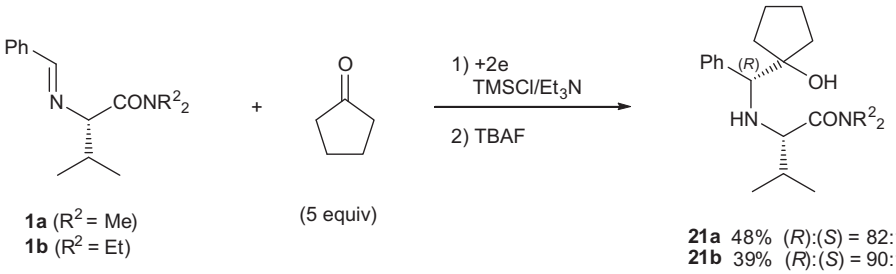


Table 2
Electroreductive coupling of (*S*)-α-arylideneamino *N*,*N*-diethylamides with acetone



Run	Imines	Ar	Products	% Yield[a]	*R*:*S*[b]
1	**11**	*p*-$MeOC_6H_4$	**12**	68	72:28
2	**13**	*m*-$MeOC_6H_4$	**14**	64	80:20
3	**15**	*p*-NCC_6H_4	**16**	50	89:11
4	**17**	1-Naphthyl	**18**	55	88:12
5	**19**	2-Naphthyl	**20**	58	84:16

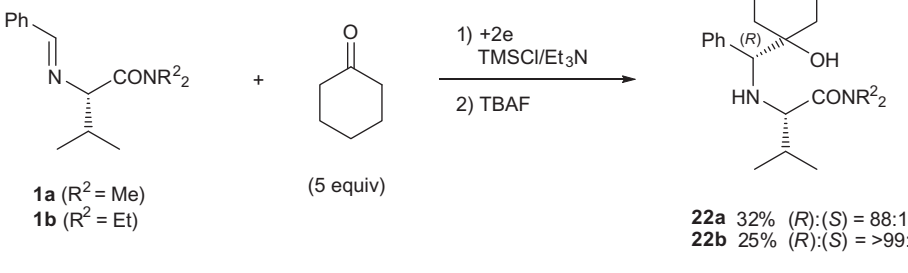
[a] Isolated yields.
[b] Determined by separation.



1a (R^2 = Me)
1b (R^2 = Et)

21a 48% (*R*):(*S*) = 82:18
21b 39% (*R*):(*S*) = 90:10

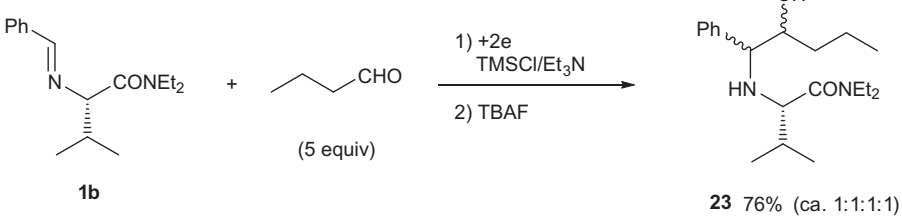
(5)



1a (R^2 = Me)
1b (R^2 = Et)

22a 32% (*R*):(*S*) = 88:12
22b 25% (*R*):(*S*) = >99:1

(6)



1b

23 76% (ca. 1:1:1:1)

(7)

A plausible mechanism for the electroreductive coupling of imine **1a** with acetone is shown in Scheme 1. As previously reported,[8a] **1a** forms complex **A** with TMSCl. Anion **B** generated by the two-electron transfer to **A** attacks acetone through transition state TS; this is followed by the O-silylation of the resulting adduct **C** to give *N*,*O*-disilylated **D**. The TMS ether **E** is obtained by N-desilylation of **D** during workup and subsequent *O*-desilylation of **E** with TBAF affords β-amino alcohol **2a**. Substitution of the electron withdrawing group on the phenyl group stabilizes anion **B** and therefore increases the stereoselectivity in the nucleophilic addition of **B** to acetone (Table 1, runs 2 and 3). The naphthyl groups stabilize anion **B** more strongly by a resonance effect than a phenyl group and thus the stereoselectivity increases (Table 1, runs 4 and 5). In order to study the (*R*)-stereoselectivity in the

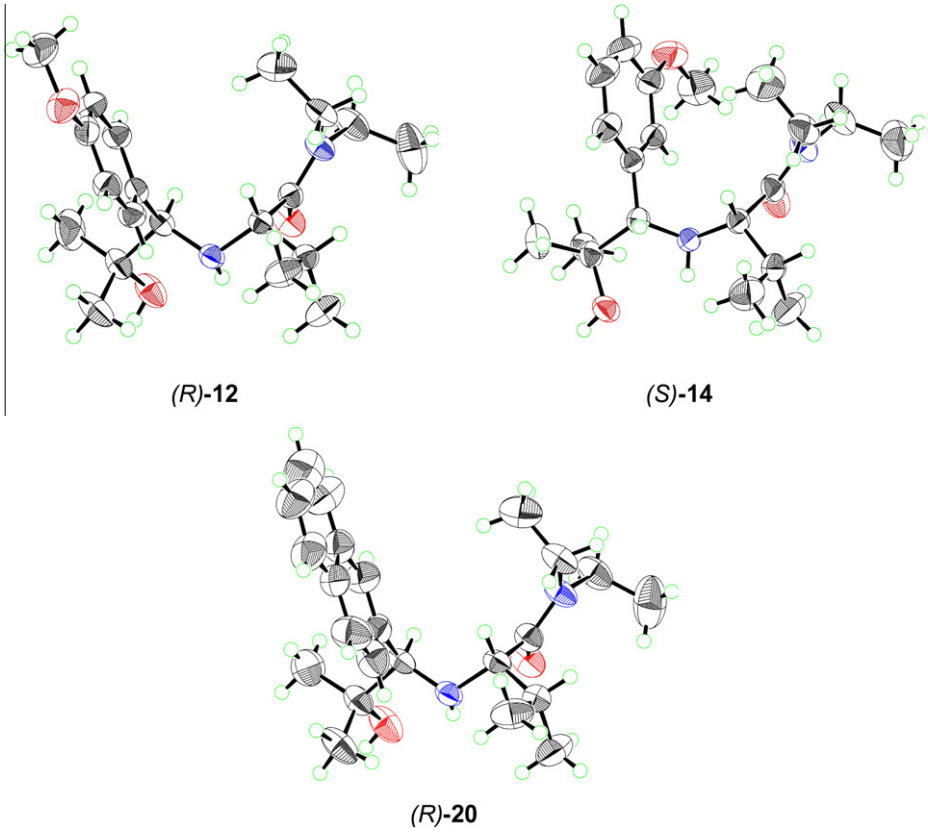
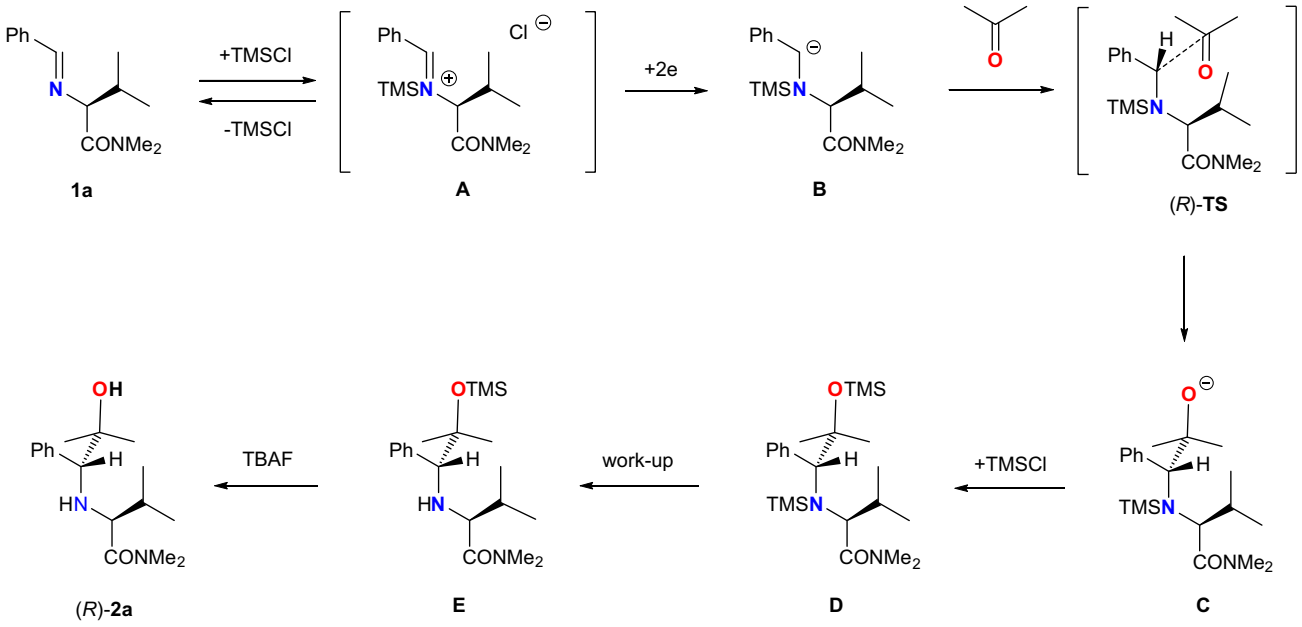


Figure 3. X-ray crystal structures of (*R*)-**12**, (*S*)-**14**, and (*R*)-**20**.



Scheme 1. Reaction mechanism of electroreductive coupling of **1a** with acetone.

addition of **B** to acetone, the energetically lowest transition states leading to the (*R*)- and (*S*)-adducts were optimized by the DFT method at the B3LYP/6-311+G(d,p) level and their energies were calculated using the PCM model for the THF solvent at the same level (Fig. 4). The results of the calculations show that (*R*)-TS is lower in energy than (*S*)-TS (0.81 kcal/mol corresponding to *R*:*S* = 80:20); this is in good agreement with the experimental results [(*R*):(*S*) = 72:28].

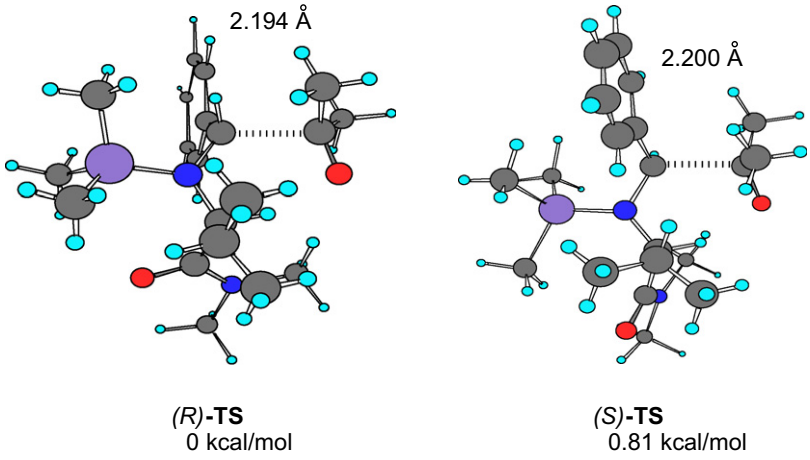


Figure 4. Optimized structures and relative energies at the B3LYP/6-311+G(d,p) level using the IEFPCM model (THF) of transition states (*R*)-**TS** and (*S*)-**TS** for the addition of **B** to acetone.

3. Conclusion

The electroreduction of chiral aromatic (*S*)-α-imino *N*,*N*-dialkylamides derived from (*S*)-α-amino acids with acetone in the presence of TMSCl and TEA led to cross-coupled products, β-amino alcohols has been reported, in moderate to good yields and (*R*)-stereoselectivity. Electron withdrawing group substituted aromatic imines and naphthyl imines afforded β-amino alcohols with relatively high (*R*)-stereoselectivity. The electroreductive coupling with cyclopentanone and cyclohexanone gave the corresponding β-amino alcohols with good to high diastereoselectivity, although the yields decreased.

4. Experimental

4.1. General

All ^{1}H and ^{13}C NMR spectra were measured on a JEOL GMX-500 spectrometer with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu FTIR-8300 infrared spectrometer. Optical rotations were obtained on a Jasco DIP-360 digital polarimeter. Melting points were uncorrected. Column chromatography was performed on silica gel 60. THF was freshly distilled from sodium benzophenone ketyl. TMSCl and TEA were distilled from CaH_2.

4.2. Chiral α-imino *N*,*N*-dialkylamides

Chiral α-imino *N*,*N*-dialkylamides were synthesized by the treatment of (*S*)-α-amino acid *N*,*N*-dialkylamides with aromatic aldehydes in dichloromethane in the presence of magnesium sulfate at room temperature. Solid imines were purified by recrystallization, whereas paste ones were used without purification.

4.2.1. (*S*,*E*)-2-(Benzylideneamino)-*N*,*N*,3-trimethylbutanamide 1a

White solid. R_f 0.3 (hexanes–ethyl acetate, 2:1). Mp 115–117 °C (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{22} = +40.6$ (*c* 1.02, $CHCl_3$). IR (KBr) 1638, 1599, 1578, 845, 824, 764, 746, 700, 652 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3H, *J* = 6.9 Hz), 1.00 (d, 3 H, *J* = 6.9 Hz), 2.36–2.47 (m, 1H), 2.97 (s, 3 H), 3.23 (s, 3 H), 3.93 (d, 1 H, *J* = 9.2 Hz), 7.39–7.46 (m, 3H), 7.76–7.79 (m, 2H), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.4 (q), 19.7 (q), 30.9 (d), 36.0 (q), 37.0 (q), 80.1 (d), 128.3 (d), 128.4 (d), 130.7 (d), 135.8 (s), 161.7 (d), 171.1 (s). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.34; H, 8.73; N, 11.96.

4.2.2. (*S*,*E*)-2-(Benzylideneamino)-*N*,*N*-diethyl-3-methylbutanamide 1b

White solid. R_f 0.5 (hexanes–ethyl acetate, 2:1). Mp 51–52 °C (hexanes–ethyl acetate, 5:1). $[\alpha]_D^{23} = -15.0$ (*c* 1.15, $CHCl_3$). IR (KBr) 1641, 1578, 937, 835, 812, 758, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, *J* = 6.4 Hz), 1.02 (d, 3H, *J* = 6.9 Hz), 1.15 (t, 3H, *J* = 6.9 Hz), 1.19 (t, 3H, *J* = 6.9 Hz), 2.37–2.46 (m, 1H), 3.30–3.39 (m, 1H), 3.41–3.51 (m, 2H), 3.65–3.74 (m, 1H), 3.93 (d, 1H, *J* = 9.6 Hz), 7.40–7.47 (m, 3H), 7.76–7.82 (m, 2H), 8.32 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.8 (q), 14.7 (q), 19.4 (q), 19.8 (q), 31.3 (d), 40.4 (t), 41.3 (t), 79.3 (d), 128.2 (d), 128.4 (d), 130.7 (d), 135.9 (s), 161.5 (d), 170.3 (s). Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.74; H, 9.33; N, 10.57.

4.2.3. (*S*,*E*)-2-(Benzylideneamino)-3-methyl-1-(piperidin-1-yl)butan-1-one 1c

Colorless paste. R_f 0.5 (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{20} = +12.7$ (*c* 1.04, $CHCl_3$). IR (neat) 1630, 1578, 996, 957, 853, 845, 806, 756, 743, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3H, *J* = 6.4 Hz), 1.03 (d, 3H, *J* = 6.9 Hz), 1.47–1.67 (m, 6 H), 2.31–2.42 (m, 1H), 3.47–3.53 (m, 1H), 3.60–3.67 (m, 1H), 3.68–3.75 (m, 1H), 3.86–3.93 (m, 2H), 7.38–7.46 (m, 3H), 7.73–7.78 (m, 2H), 8.27 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7 (q), 19.8 (q), 24.5 (t), 25.7 (t), 26.5 (t), 30.9 (d), 43.5 (t), 46.5 (t), 81.6 (d), 128.2 (d), 128.4 (d), 130.7 (d), 135.9 (s), 161.6 (d), 169.5 (s).

4.2.4. (2*S*,3*S*,*E*)-2-(Benzylideneamino)-*N*,*N*,3-trimethylpentanamide 3a

White solid. R_f 0.25 (hexanes–ethyl acetate, 2:1). Mp 65–67 °C (hexanes–ethyl acetate, 10:1). $[\alpha]_D^{21} = -40.6$ (*c* 1.02, $CHCl_3$). IR (KBr) 1630, 1580, 974, 810, 775, 760, 746, 698, 650 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.6 Hz), 0.96 (d, 3H, *J* = 7.0 Hz), 0.91–1.06 (m, 1H), 1.46–1.58 (m, 1H), 2.15–2.28 (m, 1H), 2.96 (s, 3H), 3.24 (s, 3H), 4.03 (d, 1H, *J* = 9.6 Hz), 7.37–7.47 (m, 3H), 7.73–7.80 (m, 2H), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.7 (q), 15.7 (q), 25.4 (t), 36.1 (q), 36.99 (d), 37.09 (q), 79.0 (d), 128.3 (d), 128.5 (d), 130.8 (d), 135.9 (s), 161.8 (d), 171.3 (s). Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.05; H, 9.11; N, 11.19.

4.2.5. (2*S*,3*S*,*E*)-2-(Benzylideneamino)-*N*,*N*-diethyl-3-methylpentanamide 3b

Colorless paste. R_f 0.55 (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{26} = +7.0$ (*c* 1.08, $CHCl_3$). IR (neat) 1632, 1578, 804, 773, 756, 746, 696 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.6 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 0.98–1.07 (m, 1H), 1.13 (t, 3H, *J* = 7.3 Hz), 1.16 (t, 3H, *J* = 7.3 Hz), 1.49–1.58 (m, 1H), 2.16–2.25 (m, 1H), 3.27–3.35 (m, 1H), 3.40–3.49 (m, 2H), 3.66–3.74 (m, 1H), 4.01 (d, 1H, *J* = 9.8 Hz), 7.38–7.45 (m, 3H), 7.75–7.80 (m, 2H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.6 (q), 12.7 (q), 14.7 (q), 15.7 (q), 25.3 (t), 37.3 (d), 40.3 (t), 41.3 (t), 78.0 (d), 128.2 (d), 128.4 (d), 130.7 (d), 135.9 (s), 161.5 (d), 170.3 (s).

4.2.6. (*S*,*E*)-2-(Benzylideneamino)-*N*,*N*,4-trimethylpentanamide 5

White solid. R_f 0.3 (hexanes–ethyl acetate, 2:1). Mp 85–87 °C (hexanes–ethyl acetate, 10:1). $[\alpha]_D^{20} = -32.2$ (*c* 1.01, $CHCl_3$). IR (KBr) 1630, 1580, 988, 802, 760, 743, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, *J* = 6.9 Hz), 0.95 (d, 3H, *J* = 6.4 Hz), 1.56–1.87 (m, 3H), 2.97 (s, 3H), 3.18 (s, 3H), 4.53 (t, 1H, *J* = 6.9 Hz), 7.38–7.45 (m, 3H), 7.74–7.78 (m, 2H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 22.2 (q), 23.0 (q), 24.8 (d), 36.0 (q), 37.0 (q), 42.0 (t), 68.9 (d), 128.3 (d), 128.5 (d), 130.8 (d),136.0 (s), 161.6 (d), 171.6 (s). Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.94; H, 9.08; N, 11.23.

4.2.7. (*S*,*E*)-2-(Benzylideneamino)-*N*,*N*-dimethyl-3-phenylpropanamide 7

White solid. R_f 0.7 (hexanes–ethyl acetate, 5:1). Mp 117.5–119 °C (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{22} = -183$ (*c* 1.02, $CHCl_3$). IR (KBr) 1634, 1578, 966, 839, 795, 756, 741, 708, 692, 669 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.95 (s, 3H), 2.99 (s, 3H), 3.08 (dd, 1H, *J* = 7.5, 13.6 Hz), 3.35 (dd, 1H, *J* = 6.1, 13.6 Hz), 4.62 (dd, 1H, *J* = 6.1, 7.5 Hz), 7.15–7.27 (m, 5 H), 7.36–7.44 (m, 3H), 7.68–7.72 (m, 2H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 35.9 (q), 36.8 (q), 39.4 (t), 71.5 (d), 126.2 (d), 128.1 (d), 128.2 (d), 128.3 (d), 129.6 (d), 130.8 (d), 135.7 (s), 138.1 (s), 162.3 (d), 170.6 (s). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.08; H, 7.20; N, 9.93.

4.2.8. (*S*,*E*)-Methyl 4-(benzylideneamino)-5-(dimethylamino)-5-oxopentanoate 9

Pale yellow paste. $[\alpha]_D^{22} = -44.3$ (*c* 1.20, $CHCl_3$). IR (neat) 1733, 1699, 1647, 1579, 1497, 758, 696 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.12–2.20 (m, 1H), 2.26–2.34 (m, 1H), 2.38–2.44 (m, 2H), 2.98 (s, 3H), 3.13 (s, 3H), 3.65 (s, 3H), 4.50–4.53 (m, 1H), 7.38–7.47 (m, 3H), 7.73–7.78 (m, 2H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.1 (t), 30.2 (t), 35.8 (q), 36.8 (q), 51.4 (q), 68.8 (d), 128.2 (d), 128.4 (d), 130.9 (d), 135.5 (s), 162.5 (d), 170.5 (s), 173.4 (s).

4.2.9. (*S*,*E*)-*N*,*N*-Diethyl-2-(4-methoxybenzylideneamino)-3-methylbutanamide 11

Colorless paste. R_f 0.6 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{23} = -5.0$ (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.86 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 1.12 (t, 3H, *J* = 7.1Hz), 1.16 (t, 3H, *J* = 7.2 Hz), 2.32–2.43 (m, 1H), 3.28–3.37 (m, 1H), 3.38–3.48 (m, 2H), 3.62–3.72 (m, 1H), 3.84 (s, 3H), 3.86 (d, 1H, *J* = 10.3Hz), 6.90–6.95 (m, 2H), 7.69–7.74 (m, 2H), 8.22 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.7 (q), 14.6 (q), 19.4 (q), 19.7 (q), 31.2 (d), 40.2 (t), 41.2 (t), 55.0 (q), 79.1 (d), 113.7 (d), 128.8 (s), 129.7 (d), 160.6 (d), 161.6 (s), 170.4 (s).

4.2.10. (*S*,*E*)-*N*,*N*-Diethyl-2-(3-methoxybenzylideneamino)-3-methylbutanamide 13

Colorless paste. R_f 0.6 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{20} = -13.4$ (*c* 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.89 (d, 3H, *J* = 6.7 Hz), 1.00 (d, 3H, *J* = 6.5 Hz), 1.13 (t, 3H, *J* = 7.1Hz), 1.17 (t, 3H, *J* = 7.1 Hz), 2.35–2.44 (m, 1H), 3.29–3.37 (m, 1H), 3.38–3.48 (m, 2H), 3.63–3.72 (m, 1H), 3.85 (s, 3H), 3.91 (d, 1H, *J* = 9.5 Hz), 6.96–7.00 (m, 1H), 7.27–7.34 (m, 2H), 7.37–7.39 (m, 1H), 8.27 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.8 (q), 14.8 (q), 19.4 (q), 19.8 (q), 31.3 (d), 40.4 (t), 41.3 (t), 55.2 (q), 79.2 (d), 111.8 (d), 117.3 (d), 121.6 (d), 129.3 (d), 137.4 (s), 159.7 (s), 161.4 (d), 170.3 (s).

4.2.11. (*S*,*E*)-2-(4-Cyanobenzylideneamino)-*N*,*N*-diethyl-3-methylbutanamide 15

Colorless paste. R_f 0.45 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{23} = +3.7$ (*c* 1.08, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.90 (d, 3H, *J* = 6.5 Hz), 1.01 (d, 3H, *J* = 6.6 Hz), 1.14 (t, 3H, *J* = 7.0 Hz), 1.17 (t, 3H, *J* = 7.1Hz), 2.34–2.46 (m, 1H), 3.31–3.51 (m, 3H), 3.56–3.66 (m, 1H), 4.01 (d, 1H, *J* = 9.5 Hz), 7.68–7.73 (m, 2H), 7.85–7.90 (m, 2H), 8.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.7 (q), 14.7 (q), 19.3 (q), 19.7 (q), 31.4 (d), 40.4 (t), 41.4 (t), 78.5 (d), 113.8 (s), 118.2 (s), 128.6 (d), 132.1 (d), 139.6 (s), 159.6 (d), 169.7 (s).

4.2.12. (*S*,*E*)-*N*,*N*-Diethyl-3-methyl-2-(naphthalen-1-ylmethyleneamino)butanamide 17

White solid. R_f 0.4 (hexanes–ethyl acetate, 2:1). Mp 54–56 °C. $[\alpha]_D^{22} = -1.1$ (*c* 1.01, $CHCl_3$). IR (KBr) 1620, 1574, 939, 818, 802, 773, 737, 723 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (d, 3H, *J* = 6.5 Hz), 1.06 (d, 3H, *J* = 6.2Hz), 1.15 (t, 3H, *J* = 7.0 Hz), 1.18 (t, 3H, *J* = 7.0 Hz), 2.44–2.54 (m, 1H), 3.31–3.40 (m, 1H), 3.43–3.57 (m, 2H), 3.68–3.76 (m, 1H), 4.03 (d, 1H, *J* = 9.3Hz), 7.50–7.55 (m, 2H), 7.56–7.60 (m, 1H), 7.87–7.95 (m, 3H), 8.90 (d, 1H, *J* = 8.3Hz), 8.96 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.8 (q), 14.8 (q), 19.6 (q), 20.0 (q), 31.5 (d), 40.4 (t), 41.3 (t), 80.3 (d), 124.2 (d), 125.1 (d), 125.9 (d), 127.1 (d), 128.5 (d), 129.1 (d), 131.1 (d), 131.2 (s), 131.3 (s), 133.7 (s), 161.4 (d), 170.4 (s). Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.42; H, 8.43; N, 8.93.

4.2.13. (*S*,*E*)-*N*,*N*-Diethyl-3-methyl-2-(naphthalen-2-ylmethyleneamino)butanamide 19

Colorless paste. R_f 0.4 (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{22} = -22.4$ (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.93 (d, 3H, *J* = 6.7 Hz), 1.03 (d, 3H, *J* = 6.6 Hz), 1.14 (t, 3H, *J* = 7.0 Hz), 1.19 (t, 3H, *J* = 7.0 Hz), 2.40–2.48 (m, 1H), 3.31–3.39 (m, 1H), 3.41–3.51 (m, 2H), 3.67–3.75 (m, 1H), 3.98 (d, 1H, *J* = 9.6 Hz), 7.48–7.55 (m, 2H), 7.83–7.91 (m, 3H), 8.03–8.05 (m, 1H), 8.06 (br s, 1H), 8.46 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.8 (q), 14.8 (q), 19.5 (q), 19.9 (q), 31.5 (d), 40.4 (t), 41.4 (t), 79.3 (d), 123.8 (d), 126.3 (d), 127.1 (d), 127.7 (d), 128.2 (d), 128.5 (d), 130.3 (d), 132.9 (s), 133.6 (s), 134.7 (s), 161.6 (d), 170.4 (s).

4.3. Typical procedure for electroreductive coupling and desilylation

A 0.3 M solution of Bu_4NClO_4 in THF (15 mL) was placed in the cathodic chamber of a divided cell (40 mL beaker, 3 cm diameter, 6 cm height) equipped with a platinum cathode (5 × 5 cm^2), a platinum anode (2 × 1 cm^2), and a ceramic cylindrical diaphragm (1.5 cm diameter). A 0.3 M solution of Bu_4NClO_4 in DMF (4 mL) was placed in the anodic chamber (inside the diaphragm). Imine **1a** (232 mg, 1 mmol), acetone (348 mg, 5 mmol), TMSCl (0.64 mL, 5 mmol), and triethylamine (0.70 mL, 5 mmol) were added to the cathodic chamber. After 300 C of electricity was passed at a constant current of 100 mA at room temperature, the catholyte was evaporated in vacuo. The residue was diluted with Et_2O (30 mL) and the insoluble Bu_4NClO_4 was filtered off. The filtrate was evaporated in vacuo. The residue was dissolved in THF (10 mL). To the solution was added 1 M TBAF in THF (1.0 mL, 1.0 mmol) in an ice bath, and then the mixture was stirred at this temperature for 15 min. After the addition of acetic acid (60 mg, 1.0 mmol), the

solvent was removed in vacuo. The crude mixture was purified by column chromatography on silica gel to give **2a** in a 68% yield with a (*R*):(*S*) = 72:28 diastereomeric ratio.

4.3.1. (*S*)-2-((*R*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*,3-trimethylbutanamide (*R*)-2a

White solid. R_f 0.25 (hexanes–ethyl acetate, 1:5). Mp 175 °C (hexanes–ethyl acetate, 1:2). $[\alpha]_D^{24} = -76.0$ (*c* 1.05, $CHCl_3$). IR (KBr) 3479, 1634, 1493, 895, 791, 746, 710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.87 (d, 3H, *J* = 6.9 Hz), 1.01 (d, 3 H, *J* = 6.9 Hz), 1.05 (s, 3H), 1.19 (s, 3H), 1.72–1.80 (m, 1H), 2.53 (s, 3H), 2.57 (br s, 1H), 2.68 (br s, 1H), 2.96 (s, 3H), 3.02 (d, 1H, *J* = 6.4 Hz), 3.31 (s, 1H), 7.24–7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.4 (q), 19.6 (q), 23.6 (q), 28.2 (q), 31.6 (d), 35.3 (q), 36.4 (q), 59.9 (d), 70.0 (d), 72.5 (s), 127.1 (d), 127.5 (d), 129.2 (d), 140.1 (s), 175.2 (s). Anal. Calcd for $C_{17}H_{28}N_2O_2$: C, 69.83; H, 9.85; N, 9.58. Found: C, 69.84; H, 9.88; N, 9.51.

4.3.2. (*S*)-2-((*S*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*,3-trimethylbutanamide (*S*)-2a

Colorless paste. R_f 0.5 (hexanes–ethyl acetate, 1:5). $[\alpha]_D^{23} = +44.3$ (*c* 1.40, $CHCl_3$). IR (neat) 3431, 1636, 737, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (d, 3H, *J* = 6.9 Hz), 1.04 (d, 3H, *J* = 6.9 Hz), 1.09 (s, 3H), 1.10 (s, 3H), 1.78–1.85 (m, 1H), 2.49 (s, 3H), 2.53 (s, 3H), 2.77 (br s, 1H), 2.98 (d, 1H, *J* = 7.3Hz), 3.43 (s, 1H), 4.06 (br s, 1H), 7.15–7.29 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.7 (q), 19.3 (q), 23.8 (q), 27.0 (q), 32.8 (d), 35.0 (q), 36.6 (q), 62.6 (d), 72.2 (s), 74.9 (d), 127.2 (d), 127.5 (d), 128.5 (d), 139.6 (s), 175.1 (s). Anal. Calcd for $C_{17}H_{28}N_2O_2$: C, 69.83; H, 9.85; N, 9.58. Found: C, 69.72; H, 9.83; N, 9.46.

4.3.3. (*S*)-*N*,*N*-Diethyl-2-((*R*)-2-hydroxy-2-methyl-1-phenylpropylamino)-3-methylbutanamide (*R*)-2b

White solid. R_f 0.3 (hexanes–ethyl acetate, 1:1). Mp 106–107 °C (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{24} = -84.8$ (*c* 1.09, $CHCl_3$). IR (KBr) 3422, 1620, 880, 772, 741, 704 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, *J* = 6.9 Hz), 0.94 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.9 Hz), 1.07 (s, 3H), 1.12 (t, 3H, *J* = 6.9 Hz), 1.18 (s, 3H), 1.70–1.80 (m, 1H), 2.67 (br s, 1H), 2.78 (br s, 1H), 2.78–2.87 (m, 1H), 2.98 (d, 1H, *J* = 5.5 Hz), 3.01–3.16 (m, 2H), 3.32 (s, 1H), 3.60–3.68 (m, 1H), 7.23–7.31 (m, 3H), 7.34–7.39 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.7 (q), 13.8 (q), 17.5 (q), 20.0 (q), 23.4 (q), 28.0 (q), 31.6 (d), 39.7 (t), 40.7 (t), 59.6 (d), 69.9 (d), 72.4 (s), 126.9 (d), 127.3 (d), 129.2 (d), 140.1 (s), 173.7 (s). Anal. Calcd for $C_{19}H_{32}N_2O_2$: C, 71.21; H, 10.06; N, 8.74. Found: C, 71.25; H, 10.09; N, 8.69.

4.3.4. (*S*)-*N*,*N*-Diethyl-2-((*S*)-2-hydroxy-2-methyl-1-phenylpropylamino)-3-methylbutanamide (*S*)-2b

Colorless paste. R_f 0.55 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{23} = +35.6$ (*c* 1.26, $CHCl_3$). IR (neat) 3437, 1632, 737, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.65 (t, 3H, *J* = 6.9 Hz), 0.87 (t, 3H, *J* = 7.3 Hz), 0.96 (d, 3H, *J* = 6.4 Hz), 0.98 (d, 3H, *J* = 6.9 Hz), 1.09 (s, 3H), 1.10 (s, 3H), 1.72–1.81 (m, 1H), 2.85–3.02 (m, 4 H), 3.07–3.25 (m, 2H), 3.44 (s, 1H), 4.23 (br s, 1H), 7.16–7.25 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 12.6 (q), 13.5 (q), 17.5 (q), 20.0 (q), 23.6 (q), 26.9 (q), 32.8 (d), 40.2 (t), 41.4 (t), 62.0 (d), 72.2 (s), 74.8 (d), 127.5 (d), 128.0 (d), 128.6 (d), 139.6 (s), 173.6 (s). Anal. Calcd for $C_{19}H_{32}N_2O_2$: C, 71.21; H, 10.06; N, 8.74. Found: C, 71.40; H, 10.14; N, 8.58%.

4.3.5. (*S*)-2-((*R*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-3-methyl-1-(piperidin-1-yl)butan-1-one (*R*)-2c

White solid. R_f 0.4 (hexanes–ethyl acetate, 1:2). Mp 154.5–156 °C (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{22} = -73.7$ (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.89 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.9 Hz), 1.05 (s, 3H), 1.18 (s, 3H), 1.22–1.38 (m, 3H), 1.50–1.63 (m, 2H), 1.70–1.78 (m, 1H), 2.63 (br s, 1H), 2.80 (s, 1H), 2.96 (t, 2H, *J* = 5.5 Hz), 3.03 (d, 1H, *J* = 6.4 Hz), 3.33 (s, 1H), 3.45–3.52 (m, 1H), 3.65–3.72 (m, 1H), 7.23–7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.1 (q), 20.1 (q), 24.0 (q), 24.4 (t), 25.9 (t), 26.2 (t), 28.4 (q), 31.7 (d), 42.9 (t), 46.0 (t), 59.8 (d), 70.2 (d), 72.7 (s), 127.2 (d), 127.6 (d), 129.3 (d), 140.2 (s), 173.2 (s). Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.21; H, 9.73; N, 8.40.

4.3.6. (*S*)-2-((*S*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-3-methyl-1-(piperidin-1-yl)butan-1-one (*S*)-2c

White solid. R_f 0.6 (hexanes–ethyl acetate, 1:2). Mp 104.5–106 °C (hexane). $[\alpha]_D^{21} = +57.7$ (*c* 0.92, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.73–0.82 (m, 1H), 0.92 (d, 3H, *J* = 6.9 Hz), 0.98 (d, 3H, *J* = 6.9 Hz), 1.09 (s, 3H), 1.11 (s, 3H), 1.10–1.16 (m, 1H), 1.21–1.44 (m, 4 H), 1.65 (br s, 1H), 1.72–1.80 (m, 1H), 2.89–2.95 (m, 1H), 2.97–3.10 (m, 3H), 3.37–3.44 (m, 2H), 4.19 (br s, 1H), 7.17–7.28 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.1 (q), 19.9 (q), 23.8 (q), 24.3 (t), 25.2 (t), 25.7 (t), 27.1 (q), 32.9 (d), 42.9 (t), 46.4 (t), 61.9 (d), 72.3 (s), 75.3 (d), 127.1 (d), 127.7 (d), 128.8 (d), 139.8 (s), 173.0 (s). Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.26; H, 9.68; N, 8.41.

4.3.7. (2*S*,3*S*)-2-((*R*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*,3-trimethylpentanamide (*R*)-4a

White solid. R_f 0.35 (hexanes–ethyl acetate, 1:2). Mp 148–149 °C (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{23} = -72.0$ (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.81 (d, 3H, *J* = 7.1 Hz), 0.86 (t, 3H, *J* = 7.8 Hz), 1.06 (s, 3H), 1.18 (s, 3H), 1.19–1.28 (m, 1H), 1.49–1.61 (m, 1H), 1.78–1.90 (m, 1H), 2.50 (s, 3H), 2.57 (br s, 1H), 2.87 (br s, 1H), 2.96 (s, 3H), 3.07 (d, 1H, *J* = 7.4 Hz), 3.33 (s, 1H), 7.22–7.38 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 11.0 (q), 15.6 (q), 23.6 (q), 24.6 (t), 28.2 (q), 35.3 (q), 36.5 (q), 38.2 (d), 58.9 (d), 70.0 (d), 72.5 (s), 127.1 (d), 127.5 (d), 129.2 (d), 140.1 (s), 175.4 (s). Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.52; H, 9.87; N, 9.08.

4.3.8. (2*S*,3*S*)-2-((*S*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*,3-trimethylpentanamide (*S*)-4a

Colorless paste. R_f 0.6 (hexanes–ethyl acetate, 1:2). $[\alpha]_D^{23} = -40.4$ (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.80 (d, 3H, *J* = 7.1Hz), 0.90 (t, 3H, *J* = 7.5 Hz), 1.09 (s, 6 H), 1.17–1.30 (m, 1H), 1.56–1.67 (m, 1H), 1.76–1.87 (m, 1H), 2.47 (s, 3H), 2.51 (s, 3H), 3.05 (d, 1H, *J* = 8.1Hz), 3.42 (s, 1H), 4.03 (br s, 1H), 7.15–7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 11.1 (q), 15.2 (q), 23.8 (q), 25.0 (t), 27.0 (q), 35.0 (q), 36.6 (q), 39.3 (d), 61.3 (d), 72.2 (s), 74.8 (d), 127.2 (d), 127.5 (d), 128.5 (d), 139.6 (s), 175.2 (s). Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.66; H, 9.95; N, 9.02.

4.3.9. (2*S*,3*S*)-*N*,*N*-Diethyl-2-((*R*)-2-hydroxy-2-methyl-1-phenylpropylamino)-3-methylpentanamide (*R*)-4b

Colorless paste. R_f 0.55 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{24} = -73.1$ (*c* 1.50, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, *J* = 7.1 Hz), 0.87 (t, 3H, *J* = 7.5 Hz), 0.89 (d, 3H, *J* = 7.1 Hz), 1.06 (s, 3H), 1.12 (t, 3H, *J* = 7.2 Hz), 1.17 (s, 3H), 1.15–1.24 (m, 1H), 1.45–1.54 (m, 1H), 1.74–1.82 (m, 1H), 2.72 (br s, 1H), 2.77–2.85 (m, 1H), 2.99–3.07 (m, 1H), 3.01 (d, 1H, *J* = 6.4 Hz), 3.11–3.19 (m, 1H), 3.31 (s, 1H), 3.58–3.66 (m, 1H), 7.23–7.31 (m, 3H), 7.33–7.38 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 11.4 (q), 12.8 (q), 13.8 (q), 16.2 (q), 23.6 (q), 24.2 (t), 28.2 (q), 38.6 (d), 39.9 (t), 40.9 (t), 59.3 (d), 70.0 (d), 72.6 (s), 127.1 (d), 127.5 (d), 129.3 (d), 140.1 (s), 174.1 (s). Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.93; H, 10.38; N, 8.20.

4.3.10. (2*S*,3*S*)-*N*,*N*-Diethyl-2-((*S*)-2-hydroxy-2-methyl-1-phenylpropylamino)-3-methylpentanamide (*S*)-4b

Colorless paste. R_f 0.7 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{24} = +27.6$ (*c* 1.14, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.67 (t, 3H, *J* = 7.2 Hz), 0.86 (t, 3H, *J* = 7.2 Hz), 0.89 (t, 3H, *J* = 7.5 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 1.07 (s, 3H), 1.09 (s, 3H), 1.20–1.30 (m, 1H), 1.50–1.59 (m, 1H), 1.66–1.75 (m, 1H), 2.87–2.98 (m, 3H), 3.01 (d, 1H, *J* = 6.1 Hz), 3.12–3.20 (m, 1H), 3.44 (s, 1H), 4.23 (br s, 1H), 7.15–7.25 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 11.4 (q), 12.5 (q), 13.6 (q), 16.1 (q), 23.6 (q), 24.3 (t), 26.9 (q), 39.8 (d), 40.1 (t), 41.5 (t), 61.6 (d), 72.3 (s), 74.7 (d), 127.0 (d), 127.5 (d), 128.6 (d), 139.6 (s), 173.8 (s). Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.37. Found: C, 72.02; H, 10.34; N, 8.18.

4.3.11. (*S*)-2-((*R*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*,4-trimethylpentanamide (*R*)-6

White solid. R_f 0.4 (hexanes–ethyl acetate, 1:2). Mp 99.5–101.5 °C (hexane). $[\alpha]_D^{21} = -78.7$ (*c* 1.01, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.74 (d, 3H, *J* = 6.5 Hz), 0.90 (d, 3H, *J* = 6.6 Hz), 1.05 (s, 3H), 1.08–1.15 (m, 1H), 1.19 (s, 3H), 1.40–1.48 (m, 1H), 1.98–2.08 (m, 1H), 2.55 (s, 3H), 2.68 (br s, 2H), 2.94 (s, 3H), 3.27 (dd, 1H, *J* = 3.3, 10.7 Hz), 3.37 (s, 1H), 7.23–7.38 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 23.6 (q), 24.0 (q), 24.4 (d), 28.5 (q), 35.6 (q), 36.1 (q), 42.8 (t), 53.3 (d), 70.1 (d), 72.5 (s), 127.3 (d), 127.7 (d), 129.2 (d), 140.2 (s), 175.8 (s). Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.57; H, 9.90; N, 9.08.

4.3.12. (*S*)-2-((*S*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*,4-trimethylpentanamide (*S*)-6

Colorless paste. R_f 0.45 (hexanes–ethyl acetate, 1:2). $[\alpha]_D^{24} = +21.1$ (*c* 0.90, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.90 (d, 3H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 6.9 Hz), 1.10 (s, 6 H), 1.21–1.28 (m, 1H), 1.51–1.58 (m, 1H), 1.78–1.87 (m, 1H), 2.09 (br s, 1H), 2.55 (s, 3H), 2.57 (s, 3H), 3.36 (dd, 1H, *J* = 4.9, 9.1 Hz), 3.45 (s, 1H), 3.57 (br s, 1H), 7.19–7.29 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 22.1 (q), 23.3 (q), 23.8 (q), 24.5 (d), 27.2 (q), 35.3 (q), 36.5 (q), 43.9 (t), 54.9 (d), 72.2 (s), 74.1 (d), 127.3 (d), 127.6 (d), 128.6 (d), 139.5 (s), 175.6 (s). Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.72; H, 10.04; N, 8.96.

4.3.13. (*S*)-2-((*R*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*-dimethyl-3-phenylpropanamide (*R*)-8

Colorless paste. R_f 0.4 (hexanes–ethyl acetate, 1:5). $[\alpha]_D^{23} = +12.0$ (*c* 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.04 (s, 3H), 1.17 (s, 3H), 2.11 (s, 3H), 2.74–2.87 (m, 2H), 2.84 (s, 3H), 3.03 (br s, 2H), 3.39 (s, 1H), 3.47 (t, 1H, *J* = 7.2 Hz), 7.08–7.25 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 24.0 (q), 28.2 (q), 35.4 (q), 35.9 (q), 40.6 (t), 56.8 (d), 69.9 (d), 72.4 (s), 126.3 (d), 127.2 (d), 127.7 (d), 128.0 (d), 129.0 (d), 129.2 (d), 137.9 (s), 139.7 (s), 174.5 (s). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.18; H, 8.34; N, 8.02.

4.3.14. (*S*)-2-((*S*)-2-Hydroxy-2-methyl-1-phenylpropylamino)-*N*,*N*-dimethyl-3-phenylpropanamide (*S*)-8

White solid. R_f 0.5 (hexanes–ethyl acetate, 1:5). Mp 133–135 °C (hexanes–ethyl acetate, 5:1). $[\alpha]_D^{25} = +109$ (*c* 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.04 (s, 3H), 1.07 (s, 3H), 2.23 (s, 3H), 2.48 (s, 3H), 2.83 (dd, 1H, *J* = 7.9, 13.1 Hz), 2.91 (dd, 1H, *J* = 7.0, 13.1 Hz), 3.38 (s, 1H), 3.52 (dd, 1H, *J* = 7.0, 7.9 Hz), 3.54 (br s, 2H), 7.11–7.28 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 23.9 (q), 27.1 (q), 35.0 (q), 36.2 (q), 41.1 (t), 58.7 (d), 72.0 (s), 73.3 (d), 126.4 (d), 127.2 (d), 127.6 (d), 128.2 (d), 128.5 (d), 129.1 (d), 138.0 (s), 139.4 (s), 174.3 (s). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.07; H, 8.32; N, 8.19.

4.3.15. (*S*)-Methyl 5-(dimethylamino)-4-((*R*)-2-hydroxy-2-methyl-1-phenylpropylamino)-5-oxopentanoate (*R*)-10

Colorless paste. R_f 0.2 (hexanes–ethyl acetate, 1:5). $[\alpha]_D^{23} = +58.7$ (*c* 1.73, $CHCl_3$). IR (neat) 3433, 1734, 1636, 1493, 885, 739, 706 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.15 (s, 3H), 1.56–1.66 (m, 1H), 1.75–1.84 (m, 1H), 2.43–2.50 (m, 1H), 2.67 (s, 3H), 2.68–2.76 (m, 1H), 2.95 (s, 3H), 3.25 (dd, 1H, *J* = 3.7, 11.0 Hz), 3.33 (s, 1H), 3.61 (s, 3H), 3.69 (br s, 2H), 7.21–7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 23.0 (q), 27.6 (t), 28.1 (q), 29.7 (t), 35.5 (q), 36.1 (q), 51.2 (q), 53.7 (d), 70.1 (d), 72.6 (s), 127.1 (d), 127.5 (d), 128.9 (d), 139.8 (s), 173.6 (s), 175.0 (s). Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.37; H, 8.81; N, 7.84.

4.3.16. (*S*)-Methyl 5-(dimethylamino)-4-((*S*)-2-hydroxy-2-methyl-1-phenylpropylamino)-5-oxopentanoate (*S*)-10

Colorless paste. R_f 0.3 (hexanes–ethyl acetate, 1:5). $[\alpha]_D^{23} = +31.4$ (*c* 1.14, $CHCl_3$). IR (neat) 3433, 1734, 1638, 1493, 737, 704 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.11 (s, 3H), 1.73–1.85 (m, 2H), 2.38–2.45 (m, 2H), 2.57 (s, 3H), 2.61 (s, 3H), 3.42 (s, 1H), 3.41–3.45 (m, 1H), 3.69 (s, 3H), 7.17–7.29 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 24.1 (q), 27.2 (q), 29.0 (t), 29.6 (t), 35.2 (q), 36.5 (q), 51.5 (q), 55.4 (d), 72.2 (s), 73.8 (d), 127.2 (d), 127.6 (d), 128.5 (d), 139.4 (s), 174.1 (s), 174.6 (s). Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.39; H, 8.79; N, 7.75.

4.3.17. (*S*)-*N*,*N*-Diethyl-2-((*R*)-2-hydroxy-1-(4-methoxyphenyl)-2-methylpropylamino)-3-methylbutanamide (*R*)-12

White solid. R_f 0.55 (hexanes–ethyl acetate, 1:2). Mp 139–140.5 °C (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{24} = +90.0$ (*c* 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 6.9 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 0.98 (d, 3H, *J* = 6.9 Hz), 1.05 (s, 3H), 1.12 (t, 3H, *J* = 6.9 Hz), 1.16 (s, 3H), 1.71–1.78 (m, 1H), 2.62 (br s, 2H), 2.81–2.90 (m, 1H), 2.97 (d, 1H, *J* = 5.5 Hz), 3.03–3.16 (m, 4 H), 3.25 (s, 1H), 3.61–3.69 (m, 1H), 3.81 (s, 3H), 6.81–6.86 (m, 2H), 7.24–7.30 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.9 (q), 14.1 (q), 17.6 (q), 20.2 (q), 23.9 (q), 28.1 (q), 31.7 (d), 39.9 (t), 40.9 (t), 55.0 (q), 59.9 (d), 69.4 (d), 72.7 (s), 112.9 (d), 130.2 (d), 132.1 (s), 158.7 (s), 173.9 (s). Anal. Calcd for $C_{20}H_{34}N_2O_3$: C, 68.54; H, 9.78; N, 7.99. Found: C, 68.57; H, 9.78; N, 7.91.

4.3.18. (*S*)-*N*,*N*-Diethyl-2-((*S*)-2-hydroxy-1-(4-methoxyphenyl)-2-methylpropylamino)-3-methylbutanamide (*S*)-12

Colorless paste. R_f 0.6 (hexanes–ethyl acetate, 1:2). $[\alpha]_D^{22} = +56.0$ (*c* 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.72 (t, 3H, *J* = 7.3Hz), 0.88 (t, 3H, *J* = 7.3Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.98 (d, 3H, *J* = 6.5 Hz), 1.08 (s, 6 H), 1.74–1.81 (m, 1H), 2.89–3.05 (m, 4 H), 3.14–3.23 (m, 1H), 3.39 (s, 1H), 3.56 (br s, 2H), 6.76–6.80 (m, 2H), 7.07–7.11 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.6 (q), 13.7 (q), 17.6 (q), 20.0 (q), 23.6 (q), 26.9 (q), 32.8 (d), 40.2 (t), 41.5 (t), 55.1 (q), 62.2 (d), 72.4 (s), 74.1 (d), 113.0 (d), 129.6 (d), 131.6 (s), 158.7 (s), 173.8 (s). Anal. Calcd for $C_{20}H_{34}N_2O_3$: C, 68.54; H, 9.78; N, 7.99. Found: C, 68.68; H, 9.87; N, 7.72.

4.3.19. (*S*)-*N*,*N*-Diethyl-2-((*R*)-2-hydroxy-1-(3-methoxyphenyl)-2-methylpropylamino)-3-methylbutanamide (*R*)-14

Colorless paste. R_f 0.2 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{25} = +85.0$ (*c* 1.01, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 6.9 Hz), 0.95 (d, 3H, *J* = 6.9 Hz), 1.00 (d, 3H, *J* = 6.6 Hz), 1.09 (s, 3H), 1.12 (t, 3H, *J* = 7.0 Hz), 1.18 (s, 3H), 1.72–1.80 (m, 1H), 2.55 (br s, 2H), 2.82–2.90 (m, 1H), 3.00 (d, 1H, *J* = 5.5 Hz), 3.04–3.16 (m, 2H), 3.29 (s, 1H), 3.61–3.69 (m, 1H), 3.79 (s, 3H), 6.78–6.83 (m, 1H), 6.90 (brd, 1H, *J* = 7.3 Hz), 7.00 (br s, 1H), 7.18 (t, 1H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 12.7 (q), 13.8 (q), 17.7 (q), 20.1 (q), 23.5 (q), 28.2 (q), 31.7 (d), 39.9 (t), 41.0 (t), 54.8 (q), 59.8 (d), 69.9 (d), 72.6 (s), 112.8 (d), 114.2 (d),

122.0 (d), 128.3 (d), 141.9 (s), 159.0 (s), 174.0 (s). Anal. Calcd for $C_{20}H_{34}N_2O_3$: C, 68.54; H, 9.78; N, 7.99. Found: C, 68.72; H, 9.90; N, 7.75.

4.3.20. (*S*)-*N*,*N*-Diethyl-2-((*S*)-2-hydroxy-1-(3-methoxyphenyl)-2-methylpropylamino)-3-methylbutanamide (*S*)-14

White solid. R_f 0.5 (hexanes–ethyl acetate, 1:1). Mp 94–96 °C. $[\alpha]_D^{19} = +49.6$ (*c* 1.02, $CHCl_3$). IR (KBr) 3364, 1632, 1601, 1593, 945, 899, 833, 797, 777, 762, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.69 (t, 3H, *J* = 7.3 Hz), 0.88 (t, 3H, *J* = 7.0 Hz), 0.95 (d, 3H, *J* = 6.9 Hz), 0.98 (d, 3H, *J* = 6.9 Hz), 1.11 (s, 3H), 1.12 (s, 3H), 1.74–1.81 (m, 1H), 2.89–3.04 (m, 4 H), 3.18–3.27 (m, 1H), 3.43 (s, 1H), 3.78 (s, 3H), 4.11 (br s, 2H), 6.71–6.78 (m, 3H), 7.11–7.16 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 12.6 (q), 13.6 (q), 17.7 (q), 20.1 (q), 23.9 (q), 27.0 (q), 32.9 (d), 40.2 (t), 41.6 (t), 55.1 (q), 62.2 (d), 72.5 (s), 74.8 (d), 112.9 (d), 113.9 (d), 121.3 (d), 128.6 (d), 141.3 (s), 159.1 (s), 173.9 (s). Anal. Calcd for $C_{20}H_{34}N_2O_3$: C, 68.54; H, 9.78; N, 7.99. Found: C, 68.59; H, 9.82; N, 7.88.

4.3.21. (*S*)-2-((*R*)-1-(4-Cyanophenyl)-2-hydroxy-2-methylpropylamino)-*N*,*N*-diethyl-3-methylbutanamide (*R*)-16

Colorless paste. R_f 0.3 (hexanes–ethyl acetate, 1:2). $[\alpha]_D^{23} = -92.3$ (*c* 1.11, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, *J* = 7.3 Hz), 0.95 (d, 3H, *J* = 6.9 Hz), 0.97 (d, 3H, *J* = 6.9 Hz), 1.05 (s, 3H), 1.12 (t, 3H, *J* = 7.1 Hz), 1.17 (s, 3H), 1.72–1.80 (m, 1H), 2.77–3.18 (m, 6 H), 3.36 (s, 1H), 3.65–3.73 (m, 1H), 7.50–7.55 (m, 2H), 7.58–7.62 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.8 (q), 14.0 (q), 17.4 (q), 20.1 (q), 23.6 (q), 27.9 (q), 31.6 (d), 40.0 (t), 40.9 (t), 60.1 (d), 70.0 (d), 72.4 (s), 110.8 (s), 118.6 (s), 130.0 (d), 131.2 (d), 146.5 (s), 173.4 (s). Anal. Calcd for $C_{20}H_{31}N_3O_2$: C, 69.53; H, 9.04; N, 12.16. Found: C, 69.74; H, 9.18; N, 12.03.

4.3.22. (*S*)-2-((*S*)-1-(4-Cyanophenyl)-2-hydroxy-2-methylpropylamino)-*N*,*N*-diethyl-3-methylbutanamide (*S*)-16

Colorless paste. R_f 0.65 (hexanes–ethyl acetate, 1:2). $[\alpha]_D^{21} = +42.0$ (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.73 (t, 3H, *J* = 7.6 Hz), 0.88 (t, 3H, *J* = 7.3 Hz), 0.96 (d, 3H, *J* = 6.7 Hz), 0.97 (d, 3H, *J* = 6.8 Hz), 1.06 (s, 3H), 1.12 (s, 3H), 1.73–1.82 (m, 1H), 2.90–3.25 (m, 7 H), 3.47 (s, 1H), 7.32–7.37 (m, 2H), 7.53–7.58 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.6 (q), 13.9 (q), 17.4 (q), 20.1 (q), 24.1 (q), 27.0 (q), 32.8 (d), 40.3 (t), 41.5 (t), 62.4 (d), 72.3 (s), 74.4 (d), 110.9 (s), 118.6 (s), 129.5 (d), 131.3 (d), 146.0 (s), 173.2 (s). Anal. Calcd for $C_{20}H_{31}N_3O_2$: C, 69.53; H, 9.04; N, 12.16. Found: C, 69.68; H, 9.22; N, 11.96.

4.3.23. (*S*)-*N*,*N*-Diethyl-2-((*R*)-2-hydroxy-2-methyl-1-(naphthalen-1-yl)propylamino)-3-methylbutanamide (*R*)-18

White solid. R_f 0.25 (hexanes–ethyl acetate, 1:1). Mp 76.5–78.5 °C. $[\alpha]_D^{23} = -7.4$ (*c* 1.12, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.31 (t, 3H, *J* = 7.1 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 1.01 (d, 3H, *J* = 6.8 Hz), 1.09 (t, 3H, *J* = 7.3Hz), 1.10 (s, 3H), 1.24 (s, 3H), 1.67–1.78 (m, 1H), 2.48–2.65 (m, 2H), 2.89 (d, 1H, *J* = 5.5 Hz), 3.07–3.16 (m, 1H), 3.45–3.54 (m, 1H), 4.42 (s, 1H), 7.34–7.44 (m, 2H), 7.52 (t, 1H, *J* = 7.7 Hz), 7.77 (br s, 1H, *J* = 8.1 Hz), 7.82–7.85 (m, 1H), 7.92–7.95 (m, 1H), 8.06–8.10 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 12.9 (q), 13.0 (q), 17.8 (q), 20.2 (q), 24.2 (q), 28.6 (q), 31.8 (d), 40.0 (t), 40.7 (t), 59.8 (d), 61.9 (d), 73.7 (s), 123.5 (d), 124.8 (d), 125.1 (d), 125.4 (d), 126.6 (d), 127.4 (d), 128.7 (d), 133.4 (s), 133.5 (s), 135.9 (s), 174.1 (s). Anal. Calcd for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; N, 7.56. Found: C, 74.50; H, 9.26; N, 7.58.

4.3.24. (*S*)-*N*,*N*-Diethyl-2-((*S*)-2-hydroxy-2-methyl-1-(naphthalen-1-yl)propylamino)-3-methylbutanamide (*S*)-18

Colorless paste. R_f 0.45 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{23} = -22.0$ (*c* 0.95, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.28 (t, 3H, *J* = 7.1 Hz), 0.68 (t, 3H, *J* = 7.1 Hz), 0.97 (d, 3H, *J* = 6.9 Hz), 1.02 (d, 3H, *J* = 6.8 Hz), 1.09 (s, 3H), 1.20 (s, 3H), 1.70–1.80 (m, 1H), 2.54–2.64 (m, 1H), 2.67–2.86 (m, 2H), 2.94 (d, 1H, *J* = 5.5 Hz), 2.94–3.03 (m, 1H), 4.51 (s, 1H), 7.39–7.56 (m, 4 H), 7.71 (br s, 1H, *J* = 8.1 Hz), 7.80–7.84 (m, 1H), 8.16 (brd, 1H, *J* = 8.6 Hz). ^{13}C NMR ($CDCl_3$) δ 12.5 (q), 13.2 (q), 17.8 (q), 20.1 (q), 24.3 (q), 27.2 (q), 32.9 (d), 40.0 (t), 41.1 (t), 62.5 (d), 66.8 (d), 73.5 (s), 123.1 (d), 125.0 (d), 125.76 (d), 125.80 (d), 127.5 (d), 128.9 (d), 132.9 (s), 133.5 (s), 136.1 (s), 173.5 (s). Anal. Calcd for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; N, 7.56. Found: C, 74.66; H, 9.32; N, 7.38.

4.3.25. (*S*)-*N*,*N*-Diethyl-2-((*R*)-2-hydroxy-2-methyl-1-(naphthalen-2-yl)propylamino)-3-methylbutanamide (*R*)-20

White solid. R_f 0.3 (hexanes–ethyl acetate, 1:1). Mp 109.5–110 °C (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{22} = +95.8$ (*c* 1.10, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.75 (t, 3H, *J* = 7.3Hz), 0.94 (d, 3H, *J* = 6.8 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 1.12 (s, 3H), 1.13 (t, 3H, *J* = 7.0 Hz), 1.22 (s, 3H), 1.72–1.80 (m, 1H), 2.34–2.82 (m, 1H), 2.93–3.17 (m, 5 H), 3.48 (s, 1H), 3.62–3.70 (m, 1H), 7.44–7.49 (m, 2H), 7.55–7.61 (m, 1H), 7.76–7.85 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 12.9 (q), 13.9 (q), 17.7 (q), 20.2 (q), 23.8 (q), 28.3 (q), 31.8 (d), 39.9 (t), 40.9 (t), 60.1 (d), 70.3 (d), 72.9 (s), 125.5 (d), 125.7 (d), 127.0 (d), 127.4 (d), 127.6 (d), 128.4 (d), 132.9 (s), 138.1 (s), 174.1 (s). Anal. Calcd for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; N, 7.56. Found: C, 74.54; H, 9.28; N, 7.52.

4.3.26. (*S*)-*N*,*N*-Diethyl-2-((*S*)-2-hydroxy-2-methyl-1-(naphthalen-2-yl)propylamino)-3-methylbutanamide (*S*)-20

Colorless paste. R_f 0.45 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{24} = +57.6$ (*c* 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.50 (t, 3H, *J* = 6.9 Hz), 0.64 (t, 3H, *J* = 6.9 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 1.01 (d, 3H, *J* = 6.8 Hz), 1.15 (s, 6 H), 1.76–1.84 (m, 1H), 2.09 (s, 1H), 2.74–2.89 (m, 3H), 2.98–3.06 (m, 2H), 3.62 (s, 1H), 4.31 (br s, 1H), 7.32–7.37 (m, 1H), 7.40–7.47 (m, 2H), 7.63 (br s, 1H), 7.72 (brd, 1H, *J* = 8.8 Hz), 7.75–7.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.4 (q), 13.5 (q), 17.9 (q), 20.0 (q), 23.9 (q), 27.1 (q), 32.9 (d), 40.2 (t), 41.5 (t), 62.4 (d), 72.7 (s), 74.9 (d), 125.6 (d), 125.9 (d), 126.6 (d), 127.2 (d), 127.4 (d), 127.6 (d), 127.7 (d), 132.7 (s), 132.8 (s), 137.3 (s), 173.8 (s). Anal. Calcd for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; N, 7.56. Found: C, 74.67; H, 9.38; N, 7.41.

4.3.27. (*S*)-2-((*R*)-(1-Hydroxycyclopentyl)(phenyl)methylamino)-*N*,*N*,3-trimethylbutanamide (*R*)-21a

White solid. R_f 0.45 (hexanes–ethyl acetate, 1:2). Mp 104–105 °C (hexanes–ethyl acetate, 2:1). $[\alpha]_D^{24} = -54.4$ (*c* 1.04, $CHCl_3$). IR (KBr) 3454, 1632, 856, 760, 706 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (d, 3H, *J* = 6.9 Hz), 1.01 (d, 3H, *J* = 6.9 Hz), 1.12–1.18 (m, 1H), 1.39–1.87 (m, 8 H), 2.48 (s, 3H), 2.91 (br s, 1H), 2.95 (s, 3H), 3.02 (d, 1H, *J* = 6.9 Hz), 3.40 (s, 1H), 7.20–7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.5 (q), 19.6 (q), 23.5 (t), 23.7 (t), 31.8 (d), 35.4 (q), 36.4 (q), 36.5 (t), 38.8 (t), 59.7 (d), 68.6 (d), 83.9 (s), 127.3 (d), 127.8 (d), 129.1 (d), 139.9 (s), 174.8 (s). Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.70; H, 9.53; N, 8.75.

4.3.28. (*S*)-2-((*S*)-(1-Hydroxycyclopentyl)(phenyl)methylamino)-*N*,*N*,3-trimethylbutanamide (*S*)-21a

Colorless paste. R_f 0.5 (hexanes–ethyl acetate, 1:2). IR (neat) 3422, 1628, 1493, 731, 704 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.87 (d, 3H, *J* = 6.9 Hz), 1.02 (d, 3H, *J* = 6.9 Hz), 1.35–1.65 (m, 4 H), 1.67–1.86 (m, 5 H), 2.50 (s, 3H), 2.61 (s, 3H), 3.04 (d, 1H, *J* = 7.3 Hz), 3.60 (s, 1H), 7.19–7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.6 (q), 19.4 (q), 23.2 (t), 23.3 (t), 32.8 (q), 35.1 (t), 36.7 (q), 37.3 (t), 62.3 (d), 72.2 (d), 83.9 (s), 127.2 (d), 127.6 (d), 128.8 (d), 140.3 (s), 175.2 (s).

4.3.29. *N,N*-Diethyl-2-((1-hydroxycyclopentyl)(phenyl)-methylamino)-3-methylbutanamide 21b (9:1 diastereomeric mixture)

Pale yellow paste. R_f 0.4 (hexanes–ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$) δ 0.67 (t, 0.3H, J = 7.3 Hz), 0.77 (t, 2.7 H, J = 7.3 Hz), 0.87–1.21 (m, 9 H), 1.33–1.89 (m, 9 H), 2.70–3.05 (m, 4 H), 3.07–3.17 (m, 0.9 H), 3.21–3.30 (m, 0.1H), 3.41 (s, 0.9 H), 3.56–3.66 (m, 1.1H), 7.13–7.45 (m, 5 H). ^{13}C NMR ($CDCl_3$) major: δ 12.8 (q), 13.8 (q), 17.5 (q), 20.2 (q), 23.5 (t), 23.6 (t), 31.7 (d), 36.3 (t), 38.4 (t), 39.8 (t), 40.8 (t), 59.4 (d), 68.4 (d), 83.9 (s), 127.58 (d), 127.60 (d), 129.1 (d), 139.9 (s), 173.4 (s); minor: δ 12.6 (q), 13.5 (q), 17.4 (q), 20.0 (q), 23.0 (t), 23.1 (t), 32.7 (d), 34.7 (t), 36.9 (t), 40.1 (t), 41.4 (t), 61.7 (d), 72.1 (d), 83.8 (s), 126.9 (d), 127.2 (d), 128.8 (d), 140.2 (s), 173.6 (s).

4.3.30. (*S*)-2-((*R*)-(1-Hydroxycyclohexyl)(phenyl)methylamino)-*N,N*,3-trimethylbutanamide (*R*)-22a

White solid. R_f 0.55 (hexanes–ethyl acetate, 1:1). Mp 103–105 °C. $[\alpha]_D^{22} = +35.1$ (c 1.15, $CHCl_3$). IR (KBr) 3383, 1630, 1559, 974, 883, 797, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J = 7.1 Hz), 1.00 (d, 3H, J = 6.8 Hz), 1.02–1.12 (m, 2H), 1.32–1.79 (m, 9 H), 2.47 (s, 3H), 2.87 (br s, 2H), 2.94 (s, 3H), 3.00 (d, 1H, J = 6.8 Hz), 3.32 (s, 1H), 7.23–7.34 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.5 (q), 19.6 (q), 21.5 (t), 21.7 (t), 25.8 (t), 31.8 (d), 32.9 (t), 35.4 (q), 36.0 (t), 36.5 (q), 59.9 (d), 69.7 (d), 72.8 (s), 127.2 (d), 127.7 (d), 129.6 (d), 139.5 (s), 175.1 (s). Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.35; H, 9.77; N, 8.38.

4.3.31. (*S*)-2-((*S*)-(1-Hydroxycyclohexyl)(phenyl)methylamino)-*N,N*,3-trimethylbutanamide (*S*)-22a

Colorless paste. R_f 0.6 (hexanes–ethyl acetate, 1:1). $[\alpha]_D^{23} = +15.8$ (c 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.85 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.7 Hz), 0.89–1.85 (m, 11H), 2.48 (S, 3H), 2.52 (s, 3H), 2.84 (br s, 2H), 2.97 (d, 1H, J = 7.5 Hz), 3.36 (s, 1H), 7.14–7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 18.8 (q), 19.4 (q), 21.5 (t), 21.9 (t), 25.8 (t), 31.7 (t), 32.9 (d), 35.1 (q), 35.3 (t), 36.7 (q), 62.8 (d), 73.0 (s), 75.1 (d), 127.1 (d), 127.5 (d), 128.9 (d), 139.6 (s), 175.2 (s). Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.44; H, 9.80; N, 8.21.

4.3.32. (*S*)-*N,N*-Diethyl-2-((*R*)-(1-hydroxycyclohexyl)(phenyl)-methylamino)-3-methylbutanamide (*R*)-22b

Pale yellow paste. R_f 0.3 (hexanes–ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$) δ 0.79 (t, 3H, J = 7.1 Hz), 0.82–1.83 (m, 20 H), 2.62–2.84 (m, 2H), 2.91–3.04 (m, 2H), 3.31 (s, 1H), 3.55–3.65 (m, 1H), 7.19–7.40 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 12.9 (q), 13.9 (q), 17.6 (q), 20.2 (q), 21.5 (t), 21.7 (t), 25.8 (t), 31.8 (d), 33.0 (t), 35.9 (t), 39.9 (t), 40.9 (t), 59.7 (d), 69.6 (d), 72.8 (s), 127.2 (d), 127.5 (d), 129.6 (d), 139.5 (s), 173.6 (s).

4.3.33. (2*S*)-*N,N*-Diethyl-2-(2-hydroxy-1-phenylpentylamino)-3-methylbutanamide 23 (ca. 1:1:1:1 diastereomeric mixture)

Colorless paste. R_f 0.35 (hexanes–ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$) δ 0.74–1.34 (m, 18 H), 1.42–1.56 (m, 1H), 1.70–1.87 (m, 1H), 2.77–3.38 (m, 5 H), 3.43–3.82 (m, 2H), 4.17 (br s, 2H), 7.12–7.38 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 12.5 (q), 12.65 (q), 12.70 (q), 12.72 (q), 13.66 (q), 13.69 (q), 13.75 (q), 13.80 (q), 13.84 (q), 13.9 (q), 14.0 (q), 17.3 (q), 17.5 (q), 17.6 (q), 17.7 (q), 18.6 (t), 18.7 (t), 19.0 (t), 19.2 (t), 19.7 (q), 19.9 (q), 20.0 (q) 21.5 (q), 31.4 (d), 31.7 (d), 32.1 (d), 32.3 (d), 34.1 (t), 34.6 (t), 35.1 (t), 35.8 (t), 39.95 (t), 40.04(t), 40.1 (t), 40.96 (t), 41.03 (t), 41.3 (t), 41.4 (t), 59.5 (d), 59.8 (d), 60.6 (d), 61.6 (d), 65.4 (d), 66.9 (d), 67.1 (d), 71.1 (d), 71.7 (d), 74.2 (d), 74.5 (d), 74.7 (d), 127.10 (d), 127.14 (d), 127.3 (d), 127.5 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.16 (d), 128.22 (d), 128.4 (d), 128.7 (d), 139.0 (s), 139.8 (s), 140.0 (s), 140.2 (s), 172.7 (s), 172.8 (s), 173.3 (s), 173.8 (s).

4.4. X-ray crystallographic analysis

All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR-97 and refined with SHELXL-97. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. All calculations were performed using the Yadokari-XG software package. CCDC 846727–846734 contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

4.4.1. Crystal data for (*R*)-2a (CCDC 846729)

$C_{17}H_{28}N_2O_2$, FW = 292.41, mp 175 °C, orthorhombic, $P2(1)2(1)2(1)$ (no. 19), colorless block, a = 9.3264(11) Å, b = 11.7753(14) Å, c = 15.943(2) Å, V = 1750.9(4) Å^3, T = 223 K, Z = 4, D_{calcd} = 1.109 g/cm^3, μ = 0.72 cm^{-1}, GOF = 1.031.

4.4.2. Crystal data for (*R*)-2c (CCDC 846730)

$C_{20}H_{32}N_2O_2$, FW = 332.48, mp 154.5–156 °C, monoclinic, $C2$ (no. 5), colorless block, a = 23.771(4) Å, b = 8.4539(14) Å, c = 9.9533 (15) Å, β = 95.403(9), V = 1991.3(5) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.109 g/cm^3, μ = 0.71 cm^{-1}, GOF = 1.023.

4.4.3. Crystal data for (*S*)-2c (CCDC 846734)

$C_{20}H_{32}N_2O_2$, FW = 332.48, mp 104.5–106 °C, orthorhombic, $P2(1)2(1)2(1)$ (no. 19), colorless block, a = 9.094(3) Å, b = 11.307 (3) Å, c = 19.527(6) Å, V = 2008.1(10) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.100 g/cm^3, μ = 0.71 cm^{-1}, GOF = 1.037.

4.4.4. Crystal data for (*R*)-4a (CCDC 846731)

$C_{18}H_{30}N_2O_2$, FW = 306.44, mp 148–149 °C, orthorhombic, $P2(1)2(1)2(1)$ (no 19), colorless block, a = 9.2602(8) Å, b = 12.6526(9) Å, c = 15.8514(9) Å, V = 1857.2(2) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.096 g/cm^3, μ = 0.71 cm^{-1}, GOF = 1.016.

4.4.5. Crystal data for (*R*)-6 (CCDC 846732)

$C_{18}H_{30}N_2O_2$, FW = 306.44, mp 99.5–101.5 °C, orthorhombic, $P2(1)2(1)2(1)$ (no 19), colorless block, a = 8.9519(8) Å, b = 12.5092(9) Å, c = 16.8022(14) Å, V = 1881.5(3) Å^3, T = 203 K, Z = 4, D_{calcd} = 1.082 g/cm^3, μ = 0.70 cm^{-1}, GOF = 1.030.

4.4.6. Crystal data for (*R*)-12 (CCDC 846727)

$C_{20}H_{34}N_2O_3$, FW = 350.49, mp 139–140.5 °C, orthorhombic, $P2(1)2(1)2(1)$ (no 19), colorless block, a = 9.6712(11) Å, b = 11.6120(10) Å, c = 18.4141(19) Å, V = 2067.9(4) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.126 g/cm^3, μ = 0.75 cm^{-1}, GOF = 1.033.

4.4.7. Crystal data for (*S*)-14 (CCDC 846728)

$C_{20}H_{34}N_2O_3$, FW = 350.49, mp 94–96 °C, monoclinic, $P2_1$ (no 4), colorless block, a = 9.533(3) Å, b = 9.3432(18) Å, c = 12.252(4) Å, β = 109.943(11), V = 1025.8(5) Å^3, T = 298 K, Z = 2, D_{calcd} = 1.135 g/cm^3, μ = 0.76 cm^{-1}, GOF = 1.016.

4.4.8. Crystal data for (*R*)-20 (CCDC 846733)

$C_{23}H_{34}N_2O_2$, FW = 370.52, mp 109.5–110 °C, orthorhombic, $P2(1)2(1)2(1)$ (no 19), colorless block, a = 9.9694(19) Å, b = 11.601(2) Å, c = 19.281(3) Å, V = 2229.8(7) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.104 g/cm^3, μ = 0.70 cm^{-1}, GOF = 1.005.

4.5. Computational methodology

All calculations were carried out with the Gaussian 03 program.[9] Geometry optimization was performed at the B3LYP/6-311+G(d,p) level throughout (in gas phase at 298 K). All optimized

geometries were verified by the vibrational analysis. As for the transition states, it was confirmed that these structures had only one imaginary frequency. The imaginary frequency was ascertained to be consistent with the addition of **B** to acetone by displaying the vibrational mode using the Gauss View program. Single point calculations were carried out for the optimized transition states using the IEFPCM model for the THF solvent at the same level as the geometry optimization to take the solvent effect into consideration.

References

1. Roskamp, E. J.; Pederswn, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551.
2. Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469.
3. Guijarro, D.; Yus, M. *Tetrahedron* **1993**, *49*, 7761.
4. Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1995**, *36*, 5955.
5. (a) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141; (b) Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315; (c) Taniguchi, N.; Uemura, M. *J. Am. Chem. Soc.* **2000**, *122*, 8301; (d) Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2002**, *4*, 835; (e) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956; (f) Lin, X.; Bentley, P. A.; Xie, H. *Tetrahedron Lett.* **2005**, *46*, 7849.
6. Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191.
7. For reviews, see: (a) Ager, D. J.; Prakash, L.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
8. (a) Kise, N.; Ozaki, H.; Moriyama, N.; Kitagishi, Y.; Ueda, N. *J. Am. Chem. Soc.* **2003**, *125*, 11591; (b) Kise, N.; Ohya, K.; Arimoto, K.; Yamashita, Y.; Hirano, Y.; Ono, T.; Ueda, N. *J. Org. Chem.* **2004**, *69*, 7710; (c) Kise, N.; Hirano, Y.; Tanaka, Y. *Org. Lett.* **2006**, *8*, 1323.
9. The calculations were carried out using the Gaussian 03 program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 2003.