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Asymmetric synthesis of β-amino alcohols by the transfer hydrogenation of α-keto imines

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Dedicated to Professor Bohumil Štibr, on the occasion of his 70th birthday

ABSTRACT

The asymmetric transfer hydrogenation of representative aryl and benzofuranyl 2-*tert*-butylaminoethanones with formic acid–triethylamine, catalyzed by RhCl[(*R*,*R*)-TsDPEN](C$_5$Me$_5$), produced the corresponding β-*tert*-butylamino alcohols in 97–99% ee. A short asymmetric synthesis of (*R*)-bufuralol, a potent β-adrenergic receptor antagonist, is described. This approach to β-amino alcohols from ketones circumvents the halogenation–reduction–amination sequence.

1. Introduction

Chiral β-amino alcohols are widely used as auxiliaries and ligands,[1–4] precursors of oxazaborolidines,[5,6] and are important physiologically active compounds.[7–9] Various asymmetric syntheses of these compounds, for example, by the aminohydroxylation of olefins,[10] the reduction–amination of α-halo and α-tosyloxy ketones,[5,6,11,12] and by other approaches,[13–17] have been developed. The resolution of racemic β-amino alcohols, enzymatic reduction and catalytic reduction of α-amino ketones has been applied on an industrial scale.[9] An attractive alternative to the aforementioned reductive methods is the asymmetric transfer hydrogenation of α-functionalized ketones, which avoids the use of dihydrogen under pressure, and employs phosphine-free catalysts.[1,2,18–25] Very recently, imidazole-substituted acetophenones were reduced in this way with high selectivity,[26] and we reduced α-dialkylamino ketones to the corresponding β-dialkylamino alcohols in >95% ee.[27]

This study is focused on the asymmetric transfer hydrogenation of aryl and heteroaryl *N*-alkyl α-keto imines, readily available from the corresponding glyoxals. The approach makes an access to β-amino alcohols from ketones possibly circumventing the halogenation–reduction–amination or halogenation–amination–reduction sequences. Earlier, α-keto imines were reduced with borane/oxazaborolidines (10–20 mol %) producing β-amino alcohols, 89–95% ee.[28] However, the catalyst loading in the transfer hydrogenation is much lower, below 1 mol %, and the reducing agent is an inexpensive formic acid. Recently, we prepared (*R*)-2-*tert*-butylamino-1-(7-ethylbenzofuran-2-yl)ethanol [(*R*)-bufuralol], a potent non-selective β-adrenergic receptor antagonist, via the transfer hydrogenation of 1-(7-ethylbenzofuran-2-yl)-2-chloroethanone achieving 96% ee.[25] The asymmetric synthesis of this important compound by the transfer hydrogenation of 2-*tert*-butylimino-1-(7-ethylbenzofuran-2-yl)ethanone could be a convenient alternative.

2. Results and discussion

Ring-substituted phenylglyoxals and (benzofuran-2-yl)glyoxals **8**–**14** were readily prepared by oxidation of the corresponding acetophenones **1**–**5** and (benzoburan-2-yl)ethanones **6**–**7** with selenium dioxide, and isolated as hydrates following a standard general procedure.[29] The glyoxals were reacted with amines at room temperature[30] to produce α-keto imines **15**–**24** in excellent yields (Scheme 1).

α-Keto imines **15**–**19** and **22**–**24**, derived from acetophenones, were obtained in 71–98% yields when the reaction was carried out in toluene at room temperature, whereas in 1,4-dioxane the products could not be obtained. Benzofuran derivatives **20** and **21** were prepared either in benzene at room temperature or in 1,4-dioxane at reflux. The stability of **15**–**24** decreased in the order tertiary > secondary > primary alkyl derivatives. The *N*-*tert*-butyl α-keto imines were stable at room temperature, whereas the liquid primary *N*-propyl derivative **24** readily formed a glassy solid.

The transfer hydrogenation of **15**–**21** was carried out with formic acid–triethylamine 5:2, catalyzed by RhCl[(*R*,*R*)-TsDPEN](C$_5$Me$_5$), in DMF or ethyl acetate at room temperature. The conversion and enantioselectivities were higher for the reactions in DMF, 30–95% and 97–99% ee, than in ethyl acetate 10–85% and 80–97% ee. In the aryl series, **15**–**17** reacted readily, the conversion of methoxy-substituted **18** was lower and the nitro-substituted **19** was unreactive (Table 1).

Both the keto and imino groups were reduced and the configuration of the product β-amino alcohols **25**–**27** was (*S*), as determined

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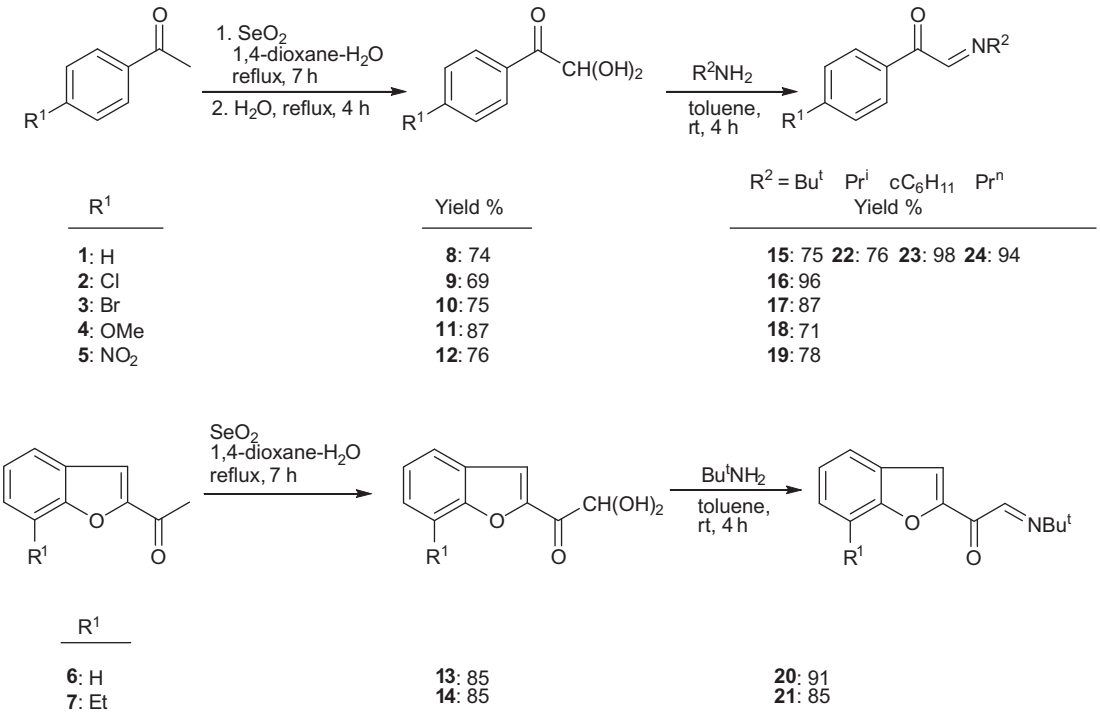
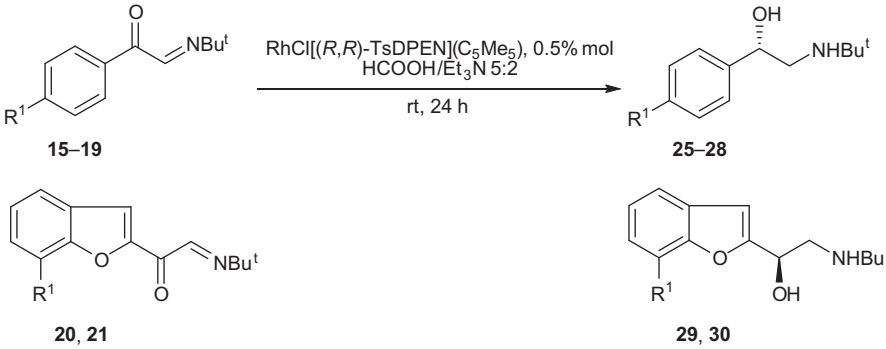


Scheme 1. Synthesis of *N*-alkyl α-imino ketones.

Table 1
Transfer hydrogenation of **15**–**19** and **20** and **21** with formic acid–triethylamine, 5:2, catalyzed by RhCl[(*R*,*R*)-TsDPEN](C$_5$Me$_5$)



	R^1	Solvent	Conv. %		Yield[a] (%)	ee[b] (%)	Conf.
15	H	DMF	85	**25**	31	99	(*S*)[c]
		AcOEt	35			80	
16	Cl	DMF	90	**26**	46	97	(*S*)[d]
		AcOEt	85			97	
17	Br	DMF	90	**27**	48	98	(*S*)[d]
		AcOEt	50			95	
18	OMe	DMF	30	**28**		97	
		AcOEt	10			87	
19	NO$_2$	DMF	n.r.				
		AcOEt	n.r.				
20	H	DMF		**29**	57	98	(*R*)[e]
		AcOEt			56	95	
21	Et	DMF		**30**	73	98	(*R*)[f]
		AcOEt			47	95	

[a] Isolated.
[b] By HPLC analysis, on a β-DEX 325 chiral column, see Section 4.
[c] By comparison with a commercial sample (Aldrich).
[d] X-ray crystal structure.
[e] By comparison of the sign of rotation with the reported data.[31]
[f] X-ray crystal structure of the hydrochloride.

by comparison with a commercial sample for **25** and by X-ray analysis for **26** and **27** (Figs. 1 and 2).

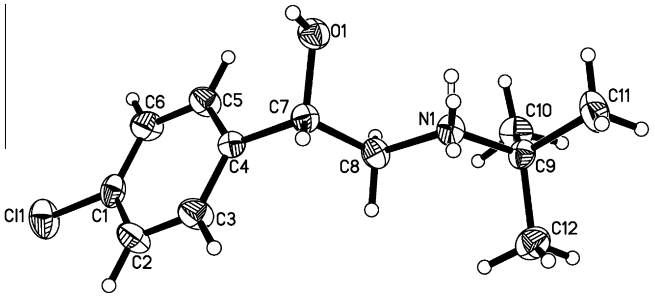


Figure 1. The X-ray structure of (*S*)-2-*tert*-butylamino-1-(4-chlorophenyl)ethanol.

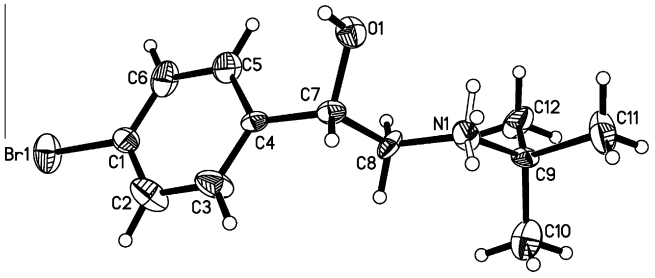


Figure 2. The X-ray structure of (*S*)-1-(4-bromophenyl)-2-(*tert*-butylamino) ethanol.

Benzofuranyl keto imines **20** and **21** undergo reduction in DMF and ethyl acetate with high enantioselectivity. The isolated yield and selectivity achieved for (*R*)-bufuralol **30**, 73% and 98% ee, makes its synthesis by this approach the most selective and convenient. The X-ray structure of its hydrochloride is shown in Figure 3. *sec*-Alkyl-substituted α-keto imines **22** and **23** are not stable for prolonged periods at room temperature, and attempts to reduce them, under the same conditions as the *tert*-butyl derivatives, were unsuccessful.

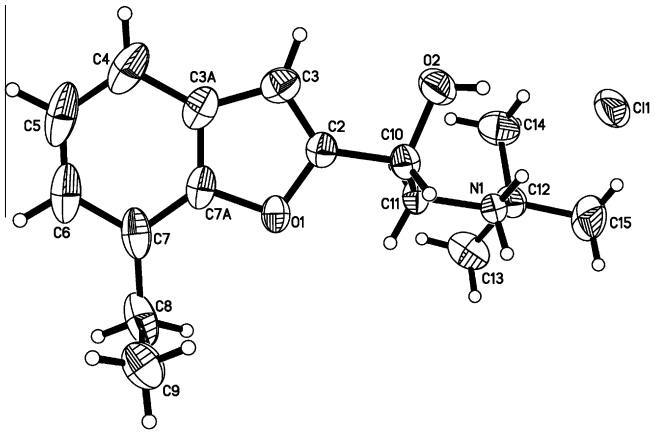
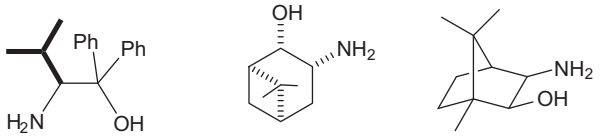


Figure 3. The X-ray structure of (*R*)-2-*tert*-butylamino-1-(7-ethylbenzofuran-2-yl)ethanol hydrochloride.

For the sake of comparison, the reduction of chloro-substituted α-keto imine **16** with borane/oxazaborolidines, generated from (*S*)-1,1-diphenylvalinol **31**,[32] and two terpene β-amino alcohols **32**[33] and **33**,[34] was also examined (Fig. 4).

The reduction of **16** was carried out in toluene with borane/THF/oxazaborolidine in the molar ratio 1:1:1 at 0 °C. After 1 h, 1 equiv of borane/THF was added for reduction of the imino group.



31 **32** **33**

Figure 4. Precursors of the oxazaborolidines.

The yields of the product amino alcohols obtained in the presence of oxazaborolidines generated from **31**–**33** were high, 93–98%, however, the selectivities of the reduction, 35%, 36% and 65% ee, respectively, were much lower as compared to those achieved by transfer hydrogenation.

3. Conclusion

In conclusion, the asymmetric transfer hydrogenation of *N*-*tert*-butyl α-keto imines, catalyzed with RhCl[(*R*,*R*)-TsDPEN](C$_5$Me$_5$), is a convenient highly selective key transformation in the asymmetric synthesis of *N*-*tert*-butyl β-amino alcohols from aryl and benzofuranyl methyl ketones, which circumvents the halogenation–reduction–amination and halogenation–amination–reduction sequences. In this way a short convenient synthesis of (*R*)-bufuralol, 98%ee, has been achieved. A further search for the conditions and catalysts enabling the reduction of the less stable *N*-*sec*-alkyl α-keto imines is in progress.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 and Bruker AMX 300 spectrometers. IR spectra were recorded on a Perkin–Elmer Spectrum RX I instrument using sodium chloride plates. Optical rotations were measured on an Optical Activity PolAAr 3000 automatic polarimeter. GC analyses were performed on a Perkin–Elmer Auto System XL chromatograph and HPLC analyses on a Shimadzu LC-10AT chromatograph. Melting points were determined in open glass capillaries and are uncorrected. X-ray diffraction data were measured using Oxford Sapphire CCD diffractometer with MoKα radiation, $\lambda = 0.71073$ Å at 293(2) K. The numerical absorption correction was applied, based on the crystal shape.[35] For all crystals, the absolute structure was determined by the Flack method.[36] The structures were solved by direct methods and refined with the full-matrix least-squares on F^2 with the use of SHELX-97 program package.[37] Elemental analyses were performed by the Microanalysis Laboratory, Faculty of Chemistry, Nicolaus Copernicus University.

4.2. Materials

Silica Gel 60, Merck 230–400, was used for preparative column chromatography. Macherey-Nagel Polygram Sil G/UV 254 0.2 mm plates were used for analytical TLC. RhCl[(*R*,*R*)-TsDPEN](C$_5$Me$_5$) was prepared from (*R*,*R*)-1,2-diphenylethylenediamine (Aldrich) and pentamethylcyclopentadienylrhodium(III) chloride dimer (Aldrich), according to the literature.[38]

4.3. 2-*tert*-Butylimino-1-phenylethanone 15

tert-Butylamine (0.69 mL, 6.5 mmol) was added to a solution of **8**[29,30] (1.00 g, 6.5 mmol) in toluene (40 mL) and the mixture was stirred for 3 h at room temperature, washed with water (3 × 10 mL) and

dried with anhydrous magnesium sulfate. The solvent was removed and a pale yellow liquid product was obtained, 0.92 g, 75% yield. Lit.[30] 69%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.33 (s, 9H, CH_3), 7.42–7.53 (m, 2H, CH), 7.58 (tt, J = 7.2, 1.5 Hz, 1H, CH), 8.01 (s, 1H, CH), 8.20 (dm, J = 7.2 Hz, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 29.0 (3 × CH_3), 59.1 (C), 128.1 (2 × CH), 130.6 (2 × CH), 133.2 (CH), 135.2 (C), 154.2 (CH), 191.5 (CO).

4.4. (*S*)-(+)-2-*tert*-Butylamino-1-phenylethanol 25

To a solution of **15** (0.50 g, 2.6 mmol) in DMF (10 mL) was added RhCl[(*R*,*R*)-TsDPEN](C_5Me_5) (8.25 mg, 0.012 mmol), formic acid–triethylamine 5:2 (0.8 mL), and the mixture was stirred under nitrogen for 24 h at room temperature. The volatiles were removed under reduced pressure, and the product was isolated by column chromatography on silica gel, petroleum ether/ethyl acetate/methanol/triethylamine 3:2:1:0.1, 0.16 g, 31%, mp 111–112 °C, $[\alpha]_D^{20} = +80.5$ (*c* 0.75, $CHCl_3$). A commercial sample (Aldrich) (*R*), $[\alpha]_D^{20} = -80$ (*c* 1, $CHCl_3$). GC analysis, β-DEX 325 column, 30 m, 0.25 mm, 130 °C, (*S*) 44.71 min, 99.39%, (*R*) 46.91 min, 0.61%, 98.8% ee. The racemate was also analyzed.

4.5. 2-*tert*-Butylimino-1-(4-chlorophenyl)ethanone 16

Prepared from **9**,[39] according to the procedure described in Section 4.3, 96%, mp 55–57 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.32 (s, 9H, CH_3), 7.42 (AA′ spin system, 2H, CH), 7.96 (s, 1H, CH), 8.18 (BB′ spin system, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 29.0 (3 × CH_3), 59.3 (C), 128.5 (2 × CH), 132.2 (2 × CH), 133.6 (C), 135.9 (C), 154.4 (CH), 190.2 (CO). IR, HCB, (cm^{-1}): 2967, 1659, 1586, 1482, 1399, 1358, 1285, 1228, 1088, 1010, 735. Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.52; H, 6.35; N, 6.20.

4.6. (*S*)-(+)-2-*tert*-Butylamino-1-(4-chlorophenyl)ethanol 26

Prepared from **16** (0.25 g, 1.1 mmol) according to the procedure described in Section 4.4. The product was isolated by column chromatography, *n*-hexane/ethyl acetate/methanol 6:2:1. A pale brown solid obtained was dissolved in diethyl ether (10 mL) and the solution was washed with 2 M aqueous sodium hydroxide (4 mL) and dried over anhydrous magnesium sulfate. The solvent was removed and a pale grey solid was obtained, 0.12 g, 46%, mp 158–161 °C, $[\alpha]_D^{20} = +66.6$ (*c* 2.06, $CHCl_3$), 97% ee, determined by GC analysis, chiral column β-DEX 325, 30 m, 0.25 mm, 150 °C, (*S*) 47.73 min, 98.62%, (*R*) 49.54 min, 1.38%. The racemate prepared by the reduction of **16** with sodium tetrahydroborate was also analyzed, mp 136–138 °C. Lit.[40] mp 135–136 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.10 (s, 9H, CH_3), 2.51 (dd, J = 12.0, 8.6 Hz, 1H, CH_2), 2.90 (dd, J = 12.0, 3.8 Hz, 1H, CH_3), 4.57 (dd, J = 8.6, 3.8 Hz, 1H, CH), 7.25–7.32 (m, 4H, CH). ^{13}C NMR (50 MHZ, $CDCl_3$) δ (ppm): 28.8 (3 × CH_3), 50.0 (CH_2), 51.1 (C), 71.1 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 133.1 (C), 141.2 (C). IR, HBC, (cm^{-1}): 3355, 3082, 2967, 1591, 1487, 1399, 1368, 1223, 1088, 1015. X-ray crystal structure: $C_{12}H_{18}ClNO$, M_r = 227.73. Colourless 0.25 × 0.12 × 0.08 mm crystal obtained from the petroleum ether/ethyl acetate solution, monoclinic space group C2. Cell parameters: a = 21.351(4), b = 5.7170(10), c = 11.422(2) Å, β = 116.11(3)°, V = 1251.9(4) Å^3, D_{calc} = 1.208 mg/m^3, Z = 4, $F(000)$ = 488, μ = 0.281 mm^{-1}. The maximum and minimum transmissions of 0.9772 and 0.9325. R_1 = 0.0576, wR_2 = 0.1048 for reflections $I > 2\sigma(I)$. The absolute structure Flack parameter x = −0.06(11). The structural data have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 780731). Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.20; H, 7.90; N, 6.19.

4.7. 1-(4-Bromophenyl)-2-(*tert*-butylimino)ethanone 17

Prepared from **10**[41] by the procedure described in Section 4.3, 87%, mp 71–72 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.32 (s, 9H, CH_3), 6.90–7.00 (AA′ spin system, 2H, CH), 7.96 (s, 1H, CH), 8.16–8.21 (BB′ spin system, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 29.0 (3 × CH_3), 59.3 (C), 128.5 (2 × CH), 132.2 (2 × CH), 133.6 (C), 135.9 (C), 154.4 (CH), 190.3 (CO). IR, HCB, (cm^{-1}): 2967, 1659, 1581, 1477, 1389, 1358, 1285, 1217, 1062, 1010, 896, 756, 725. Anal. Calcd for $C_{12}H_{14}BrNO$: C, 53.75; H, 5.26; N, 5.22. Found: C, 53.45; H, 5.17; N, 5.25.

4.8. (*S*)-(+)-1-(4-Bromophenyl)-2-(*tert*-butylamino)ethanol 27

Prepared from **17** (0.25 g, 0.9 mmol) by transfer hydrogenation following the procedure described in Section 4.4, 0.12 g, 48% yield, pale grey solid, mp 164–166 °C, $[\alpha]_D^{20} = +65.9$ (*c* 2.05, $CHCl_3$), 98% ee determined by GC analysis, β-DEX 325 column 30 m, 0.25 mm, (*S*) 78.86 min, 99.10%, (*R*) 81.35 min, 0.90%. The racemate was also analyzed. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.10 (s, 9H, CH_3), 2.51 (dd, J = 12.0, 8.6 Hz, 1H, CH_2), 2.90 (dd, J = 12.0, 3.8 Hz, 1H, CH_2), 4.57 (dd, J = 8.6, 3.8 Hz, 1H, CH), 6.85–6.98 (AA′ spin system, 2H, CH), 7.25–7.32 (BB′ spin system, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 28.8 (3 × CH_3), 50.0 (CH_2), 51.1 (C), 71.1 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 133.1 (C), 141.2 (C). IR, HCB, (cm^{-1}): 3360, 3092, 2967, 1477, 1394, 1368, 1332, 1254, 1223, 1072, 1010. X-ray crystal structure: $C_{12}H_{18}BrNO$, M_r = 272.18. Colourless 0.23 × 0.10 × 0.06 mm crystal obtained from the petroleum ether/ethyl acetate solution, monoclinic space group C2. Cell parameters: a = 21.437(4), b = 5.7370(10), c = 11.561(2) Å, β = 115.91(3)°, V = 1278.9(4) Å^3, D_{calc} = 1.414 mg/m^3, Z = 4, $F(000)$ = 560, μ = 3.191 mm^{-1}. The maximum and minimum transmissions of 0.8287 and 0.5229. R_1 = 0.0808, wR_2 = 0.1852 for reflections $I > 2\sigma(I)$. The absolute structure Flack parameter x = 0.09(4). The structural data have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 780732). Anal. Calcd for $C_{12}H_{18}BrNO$: C, 52.95; H, 6.67; N, 5.15. Found: C, 53.01; H, 6.61; N, 5.10.

4.9. 1-(Benzofuran-2-yl)-2-(*tert*-butylimino)ethanone 20

To a solution of **13**[42] (1.92 g, 10 mmol) in 1,4-dioxane (65 mL) was added *tert*-butylamine (0.73 g, 10 mmol) and the mixture was stirred for 3 h at room temperature. The solvent was removed and the product was crystallized from *n*-hexane, 2.09 g, 91%, mp 112–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.36 (s, 9H, CH_3), 7.30 (ddd, J = 7.8, 6.9, 0.9 Hz, 1H, CH), 7.48 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, CH), 7.61 (ddd, J = 8.4, 1.8, 0.9 Hz, 1H, CH), 7.74 (ddd, J = 7.8, 1.2, 0.9 Hz, 1H, CH), 7.97 (s, 1H, CH), 8.18 (d, J = 0, 9 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.9 (3 × CH_3), 59.3 (C), 112.4 (CH), 119.4 (CH), 123.7 (CH), 123.8 (CH), 127.2 (C), 128.7 (CH), 150.1 (C), 153.8 (CH), 155.8 (C), 180.5 (CO). IR, KBr (cm^{-1}): 3381, 2985, 1653, 1565, 1166, 986, 829, 785, 655. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.40; H, 6.45; N, 6.09.

4.10. (*R*)-(+)-1-(Benzofuran-2-yl)-2-(*tert*-butylamino)ethanol 29

Prepared from **20** (0.60 g, 2.6 mmol) following the procedure described in Section 4.4. The product was isolated by column chromatography on silica gel, *n*-hexane/ethyl acetate/diethyl ether/methanol/triethylamine 6:4:1:0.5:0.2, 0.35 g, 57%, mp 150–152 °C, $[\alpha]_D^{23} = +37.6$ (*c* 2.10, THF), 98% ee, determined by HPLC analysis, Daicel Chiracel OD-H column 250 × 4.6 mm, 5 μm, *n*-hexane/isopropanol 99:1, flow 0.7 mL/min, (*R*) 24.22 min, 99.32%, (*S*) 33.96 min, 0.68%. Identified by comparison with (*S*)-**29** prepared earlier.[31] The racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$)

δ (ppm): 1.12 (s, 9H, CH_3), 2.99 (dd, J = 12.0, 6.6 Hz, 1H, CH_2), 3.05 (dd, J = 12.0, 4.5 Hz, 1H, CH_2), 4.78 (ddd, J = 6.6, 4.5, 0.9 Hz, 1H, CH), 6.67 (t, J = 0.9 Hz, 1H, CH), 7.21 (td, J = 7.2, 1.2 Hz, 1H, CH), 7.26 (td, J = 7.2, 1.5 Hz, 1H, CH), 7.46 (ddd, J = 7.5, 1.5, 0.6 Hz, 1H, CH), 7.54 (ddd, J = 7.5, 2.1, 0.6 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 29.1 (3 × CH_3), 46.2 (CH_2), 50.6 (C), 66.4 (CH), 103.1 (CH), 111.2 (CH), 120.9 (CH), 122.7 (CH), 123.9 (CH), 128.2 (C), 154.8 (C), 158.5 (C). IR, KBr (cm^{-1}): 3086, 2964, 2921, 1454, 1224, 1090, 961, 808, 755.

4.11. 2-*tert*-Butylimino-1-(7-ethylbenzofuran-2-yl)ethanone 21

Prepared from **14** following the procedure described in Section 4.9, 85%, mp 67–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.36 (s, 9H, CH_3), 1.362 (t, J = 7.5 Hz, 3H, CH_3), 3.02 (q, J = 7.5 Hz, 2H, CH_2), 7.24 (t, J = 7.5 Hz, 1H, CH), 7.32 (dm, J = 7.5 Hz, 1H, CH), 7.57 (dd, J = 7.5, 1.5 Hz, 1H, CH), 7.98 (s, 1H, CH), 8.15 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 14.0 (CH_3), 22.6 (CH_2), 29.0 (3 × CH_3), 59.3 (C), 119.8 (CH), 121.1 (CH), 124.0 (CH), 126.9 (C), 127.6 (CH), 129.0 (C), 150.0 (C), 154.0 (C), 154.6 (C), 180.6 (CO). IR, KBr (cm^{-1}): 3424, 2968, 1686, 1656, 1554, 1168, 1001, 848, 745. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.57; H, 7.36; N, 5.38.

4.12. (*R*)-(+)-*tert*-Butylamino-1-(7-ethylbenzofuran-2-yl)ethanol 30

Prepared by transfer hydrogenation of **21** following the procedure described in Section 4.4, 73%, mp 56–58 °C, $[\alpha]_D^{20} = +27.2$ (c 1.93, EtOH), 98% ee determined by HPLC analysis, Daicel Chiracel OD-H column 250 × 4.6 mm, 5 μm, *n*-hexane/isopropanol 95:5, flow 0.7 mL/min, (*R*) 8.99 min, 99.09%, (*S*) 14.39 min, 0.91%. Identified by comparison with (*R*)-**30** prepared earlier.[25] The racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.12 (s, 9H, CH_3), 1.34 (t, J = 7.5 Hz, 3H, CH_3), 2.93 (q, J = 7.5 Hz, 2H, CH_2), 3.00 (dd, J = 12.0, 6.3 Hz, 1H, CH_2N), 3.05 (dd, J = 12.0, 4.5 Hz, 1H, CH_2N), 4.81 (ddd, J = 6.3, 4.5, 0.9 Hz, 1H, CH), 6.66 (d, J = 0.9 Hz, 1H, CH), 7.08 (ddd, J = 7.2, 1.5, 0.6 Hz, 1H, CH), 7.15 (t, J = 7.5 Hz, 1H, CH), 7.37 (dd, J = 7.5, 1.5 Hz, 1H CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 14.1 (CH_3), 22.8 (CH_2), 29.1 (3 × CH_3), 46.2 (C), 50.3 (CH_2), 66.5 (CH), 103.1 (CH), 118.4 (CH), 122.8 (CH), 123.0 (CH), 127.6 (C), 127.8 (C), 154.3 (C), 158.3 (C). X-ray crystal structure (hydrochloride): $C_{16}H_{24}ClNO_2$, M_r = 297.83. Colourless 0.46 × 0.34 × 0.30 mm crystal from acetone solution, orthorhombic space group $P2_12_12_1$. Cell parameters: a = 7.795(2), b = 10.358(2), c = 21.086(4) Å, V = 1702.5(6) Å^3, D_{calc} = 1.162 mg/m^3, Z = 4, $F(000)$ = 640, μ = 0.226 mm^{-1}. The maximum and minimum transmissions of 0.9360 and 0.9028. R_1 = 0.0528, wR_2 = 0.1489 for reflections $I > 2\sigma(I)$. The absolute structure Flack parameter x = 0.00(8). The structural data have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 780733).

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