Chiral oximes in asymmetric synthesis. Part 2.[1] Addition of butyllithium to benzaldehyde *O*-(1-phenylalkyl)oximes

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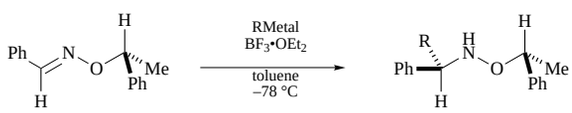
A series of benzaldoxime ethers PhCH=NOCHRPh 5 bearing a chiral auxiliary on oxygen have been prepared to investigate the effect of the auxiliary on the diastereoselectivity of the addition of butyllithium to the oxime C=N bond. By increasing the size of the alkyl group R in the auxiliary, OCHRPh, an increase in de is observed, with the best compromise between ready availability and high levels of asymmetric induction in the product 6 being achieved with the oximes derived from *O*-(1-phenylbutyl)hydroxylamine.

Stereoselective addition reactions to C=N bonds continue to attract the attention of synthetic chemists.[2–15] We have recently reported that addition of organolithium and Grignard reagents to *O*-(1-phenylethyl) aldoximes in the presence of boron trifluoride–diethyl ether gives secondary hydroxylamines in good yield and with varying levels of diastereoselectivity (Scheme 1).[1] Although diastereomeric excesses of 95% could be



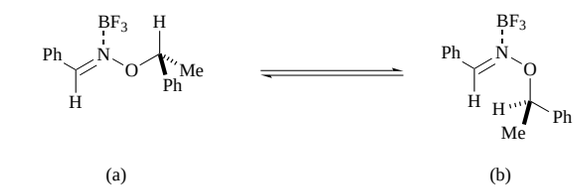
Scheme 1

obtained using the *O*-(1-phenylethyl) oximes, more routinely the de was in the range 60–80%, and therefore a more effective auxiliary was desirable. We report the details of our efforts to improve the levels of 1,4-induction in such additions which have resulted in the development of (***R***)- and (***S***)-***O***-(1-**p**henylbutyl)**hy**droxylamines (ROPHy and SOPHy) as excellent reagents for the preparation of a range of chiral, non-racemic oxime ethers which undergo highly diastereoselective addition reactions.

Results and discussion

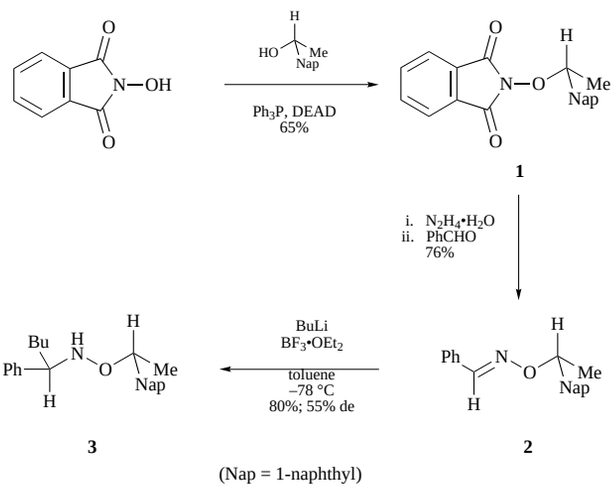
The stereochemical outcome of the addition of organometallic reagents to *O*-(1-phenylethyl) oximes (Scheme 1) was rationalised by assuming the intermediacy of an oxime–boron trifluoride complex [Fig. 1(*a*)].[1] Although the exact conformation of the oxime ethers in solution is unknown we assume that they are effectively planar due to appreciable conjugation of the oxygen lone pair; the almost planar structure of oximes is supported by X-ray studies,[16,17] which also show that the sp^2 carbon and the substituent on oxygen are *trans* about the N–O bond in the solid state. In addition we assume that the boron trifluoride will bind to the nitrogen atom, and that minimum steric interactions will dictate the conformation shown in Fig. 1(*a*), assuming the *trans* arrangement about the N–O bond is maintained in solution. Alternatively, if *cis* conformations about the N–O bond are allowed, then the oxime ethers may adopt the conformation shown in Fig. 1(*b*), although this is likely to be higher in energy.

Therefore in order to improve the levels of diastereoselectivity of the addition reactions, a series of oxime ethers containing different chiral auxiliaries was prepared. Initially it was thought on the basis of Fig. 1(*a*) that if the size of the aromatic group was increased then the diastereoselectivity would similarly increase, and therefore the α-methylnaphthyl oxime ether **2** was prepared as shown in Scheme 2. The Mitsunobu reaction of *N*-



(a) (b)

Fig. 1



1 **2** **3**

(Nap = 1-naphthyl)

Scheme 2

hydroxyphthalimide with racemic 1-(1-naphthyl)ethanol using triphenylphosphine and diethyl azodicarboxylate (DEAD) gave the alkoxyphthalimide **1** as a colourless solid in good yield. Subsequent cleavage of the phthaloyl group and condensation of the hydroxylamine *in situ* with benzaldehyde provided the oxime ether **2** in excellent yield as the *E* isomer. The *in situ* cleavage and condensation was chosen as a convenient one-pot procedure and obviated the need to isolate the *O*-substituted hydroxylamine.

The addition of *n*-butyllithium to the oxime ether **2** in the presence of boron trifluoride–diethyl ether at −78 °C in toluene

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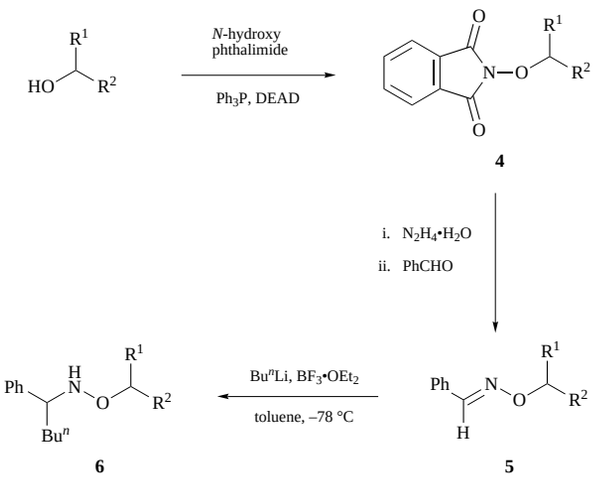
Table 1 Preparation of chiral oxime ethers **5** and their reaction with butyllithium

R^1	R^2	Phthalimide	Yield (%)	Oxime	Yield (%)	Hydroxylamine	Yield (%)	de (%)
Et	Ph	**4a**	65	**5a**	87	**6a**	91	93
Pr^n	Ph	**4b**	80	**5b**	91	**6b**	87	90
Pr^i	Ph	**4c**	32	**5c**	91	**6c**	74	>95
Bu^n	Ph	**4d**	36	**5d**	93	**6d**	80	90
Me	Et	**4e**	95	**5e**	90	**6e**	70	10

gave a good yield of the corresponding hydroxylamine **3** (Scheme 2). However, the diastereoselectivity of the reaction was markedly less for the naphthyl auxiliary (55% de) than that found earlier for the corresponding phenyl auxiliary (71% de).[1] From this result it would appear that the size of the aromatic group in the chiral directing group does not directly influence the stereoselectivity of the reaction, suggesting that it may indeed be oriented away from the C=N bond as shown in Fig. 1(*b*), and therefore that increasing the size of the alkyl group may have the desired effect. In order to investigate this hypothesis a series of auxiliaries was synthesised in which the methyl group of the auxiliary was homologated and the phenyl group was retained as the aryl portion. The chiral alcohols which constitute the chiral directing moiety were either commercially available or prepared in racemic form in almost quantitative yield by reduction of the corresponding ketones with sodium borohydride.

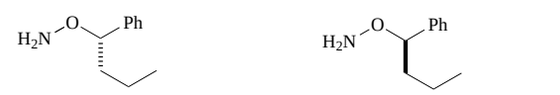
The Mitsunobu reaction of *N*-hydroxyphthalimide with the racemic secondary alcohols produced the alkoxyphthalimides **4a**–**e** in moderate to good yields under optimised conditions (Scheme 3). The Mitsunobu conditions were optimised by the use of two equivalents of *N*-hydroxyphthalimide, triphenylphosphine and DEAD. The resulting THF solution was heated at 50 °C for three days, and in most cases the yields were higher than for the unoptimised conditions. The yields vary in accordance with the relative bulk of the alkyl substituents; for example the Mitsunobu reaction with 1-phenylbutanol gave alkoxyphthalimide **4b** in 87% yield but the isomeric 2-methyl-1-phenylpropanol gave only 32% of **4c** under optimised conditions and 7% under unoptimised conditions. Not surprisingly the severely hindered alcohol 2,2-dimethyl-1-phenylpropanol did not undergo the Mitsunobu reaction with *N*-hydroxyphthalimide. The results are summarised in Table 1. The alkoxyphthalimides **4a**–**e** were cleaved with hydrazine hydrate in ethanol at 50 °C and the resulting hydroxylamines were condensed with benzaldehyde at room temperature *in situ* to produce the corresponding oxime ethers **5a**–**e** solely as their *E* isomers which were isolated by column chromatography as colourless oils (Scheme 3, Table 1).

The efficacy of the auxiliaries in the benzaldoxime ethers **5** was studied by the addition of 3 equiv. of *n*-butyllithium to the oxime ethers at −78 °C in the presence of 3 equiv. of boron trifluoride–diethyl ether in toluene. This reaction produced the corresponding substituted hydroxylamines **6a**–**e** (Scheme 3, Table 1). The diastereoselectivity of the reactions could be readily determined by integration of the benzylic protons in the proton NMR spectra. The results showed that increasing the size of the alkyl group on the auxiliary did indeed increase the diastereoselectivity of the addition reactions. Thus increasing the size of the alkyl group from methyl to ethyl afforded a dramatic increase in selectivity from 71% de for the former to 93% de for the latter. The auxiliary derived from butan-2-ol afforded a very poor de (10%). Addition to the isopropyl oxime ether **5c** gave the best result in which the other diastereomer was barely visible in the proton NMR. Unfortunately the alcohol required for this auxiliary, 2-methyl-1-phenylpropanol, is not commercially available in enantiomerically pure form. However only a slight decrease in diastereoselectivity (*ca.* 5% de) was observed when changing from an isopropyl to an *n*-propyl group, and the alcohol required for the synthesis of the *n*-propyl auxiliary, 1-phenylbutanol, is commercially available



Scheme 3

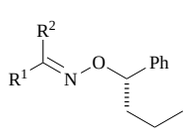
in both enantiomeric forms. Therefore the auxiliaries derived from 1-phenylbutanol, (***S***)-*O*-(1-**p**henylbutyl)**hy**droxylamine (SOPHy) (*S*)-**7** and its enantimer ROPHy (*R*)-**7** were therefore chosen for further study.



(***S***)-***O***-(1-**P**henylbutyl)**hy**droxylamine SOPHy, (*S*)-**7**

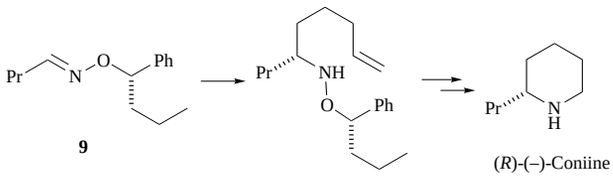
(***R***)-***O***-(1-**P**henylbutyl)**hy**droxylamine ROPHy, (*R*)-**7**

The optically active 1-(phenylbutoxy)phthalimides, (*S*)-(−)-**4b** and (*R*)-(+)-**4b**, were readily prepared from the corresponding (*R*)- and (*S*)-alcohols; the enantiomeric purity of the phthalimides was determined as >96% by ^{1}H NMR spectroscopy in the presence of 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE). Although the non-racemic alkoxyphthalimides could be cleaved and converted into oxime ethers using the one-pot procedure described above, the hydroxylamines themselves were readily isolated; thus SOPHy (*S*)-**7** and ROPHy (*R*)-**7** were isolated as colourless oils in 78 and 84% yield, respectively. The enantiomeric purity of the hydroxylamines was checked by ^{1}H NMR spectroscopy in the presence of TFAE and found to be >96%. SOPHy and ROPHy are readily converted into chiral, non-racemic oxime ethers as exemplified by the preparation of (*S*)-**8a**, **-8b** and **-8c** in good yield from the (*S*)-hydroxylamine.



8a R^1 = Ph, R^2 = Me
8b R^1 = 4-MeO-C_6H_4, R^2 = H
8c R^1 = Bu^t, R^2 = H

Such oxime ethers have considerable potential in asymmetric synthesis, and we have recently reported an asymmetric synthesis of the piperidine alkaloid (*R*)-(−)-coniine from the SOPHy oxime of butyraldehyde **9** (Scheme 4);[18] further applications of SOPHy and ROPHy oximes are under active investigation and will be reported in due course.



Scheme 4

Experimental

For general points, see ref. 1. In the NMR spectra of diastereomeric mixtures, the signals due to the major diastereomer are given along with the signals of the minor isomer that are clearly visible. The integration values in the ^{1}H NMR data are consistent within each isomer; the isomer ratio is stated separately. *J* Values are given in Hz. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Light petroleum refers to the fraction with bp 40–60 °C.

General method for preparation of *N*-(alkoxy)phthalimides

Diethyl azodicarboxylate (6.4 ml, 40.4 mmol) was added to a solution of triphenylphosphine (9.63 g, 37 mmol), *N*-hydroxyphthalimide (6 g, 37 mmol) and the racemic benzyl alcohol (18.5 mmol) in THF (200 ml) at 0 °C. The resulting solution was warmed to 50 °C and stirred for 3 days. The THF was removed under reduced pressure, and diethyl ether (200 ml) and saturated aqueous sodium carbonate (200 ml) were added. The diethyl ether layer was washed with further portions of aqueous sodium carbonate (2 × 100 ml) which were combined and back extracted with diethyl ether (2 × 100 ml). The combined diethyl ether extracts were evaporated, and the residue purified by flash chromatography on silica gel (eluent: diethyl ether–light petroleum).

***N*-[1-(1-Naphthyl)ethoxy]phthalimide 1.** Obtained from the Mitsunobu reaction of 1-(1-naphthyl)ethanol with *N*-hydroxyphthalimide as a crystalline solid (65%), mp 118–120 °C (Found: C, 75.6; H, 4.6; N, 4.4. $C_{20}H_{15}NO_3$ requires C, 75.7; H, 4.8; N, 4.4%) (Found: M$^+$, 317.1052. $C_{20}H_{15}NO_3$ requires *M*, 317.1052); ν_{max}(Nujol)/cm^{-1} 2924, 1790, 1737, 702; δ_H(250 MHz; $CDCl_3$) 8.40 (1H, d, *J* 9.1, ArH), 7.86–7.86 (10H, m, ArH), 6.36 (1H, q, *J* 6.5, OCH), 1.85 (3H, d, *J* 6.5, Me); δ_C(62.9 MHz; $CDCl_3$) 164.2, 135.2, 134.3, 133.9, 131.7, 129.2, 128.9, 128.7, 126.4, 125.6, 125.3, 124.9, 123.3, 81.4, 20.2; 1 ArC not observed; *m/z* (EI) 317 (M$^+$, 5%), 155 (100), 127 (13), 76 (14).

***N*-(1-Phenylpropoxy)phthalimide 4a.** Obtained from the Mitsunobu reaction of 1-phenylpropanol with *N*-hydroxyphthalimide as a crystalline solid (65%), mp 110–111 °C (Found: C, 72.2; H, 5.1; N, 4.9. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%) (Found: M$^+$, 281.1052. $C_{17}H_{15}NO_3$ requires *M*, 281.1052); ν_{max}(Nujol)/cm^{-1} 2925, 1787, 1731, 1465, 1455, 703; δ_H(250 MHz; $CDCl_3$) 7.67 (4H, m, ArH), 7.46 (2H, m, ArH), 7.32 (3H, m, ArH), 5.26 (1H, t, *J* 6.9, OCH), 2.21 (1H, m, C*H*$_2$Me), 1.96 (1H, m, C*H*$_2$Me), 0.97 (3H, t, *J* 7.4, Me); δ_C(62.9 MHz; $CDCl_3$) 163.8, 137.9, 134.1, 128.8, 128.8, 128.2, 128.0, 123.2, 90.5, 27.7, 10.0; *m/z* (EI) 282 (MH$^+$, 21%), 254 (10), 164 (33), 119 (100), 91 (95), 77 (27).

***N*-(1-Phenylbutoxy)phthalimide 4b.**[18] Obtained from the Mitsunobu reaction of 1-phenylbutanol with *N*-hydroxyphthalimide as a crystalline solid (80%), mp 80–81 °C (Found; C, 72.85; H, 5.6; N, 4.7. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%) (Found: M$^+$, 295.1211. $C_{18}H_{17}NO_3$ requires *M*, 295.1208); ν_{max}(Nujol)/cm^{-1} 2922, 1789, 1727, 698; δ_H(250 MHz; $CDCl_3$) 7.70 (4H, m, ArH), 7.45 (2H, m, ArH), 7.29 (3H, m, ArH), 5.34 (1H, t, *J* 7.0, OCH), 2.16 (1 H, m, CHC*H*$_2$), 1.91 (1H, m, CHC*H*$_2$), 1.47 (2H, m, C*H*$_2$Me), 0.97 (3H, t, *J* 7.4, Me); δ_C(62.9 MHz; $CDCl_3$) 163.8, 137.9, 134.1, 128.8, 128.8, 128.2, 128.0, 123.2, 89.0, 36.8, 18.9, 13.8; *m/z* (EI) 163 (3%), 133 (52), 117 (8), 104 (9), 91 (100), 76 (11).

***(S)*-(−)-*N*-(1-Phenylbutoxy)phthalimide (*S*)-4b.** Obtained from (*R*)-(+)-1-phenylbutanol, >96% ee by NMR in the presence of (−)-TFAE, $[\alpha]_D^{19}$ −185.1 (*c* 2, CH_2Cl_2); other data as racemic sample.

***(R)*-(+)-*N*-(1-Phenylbutoxy)phthalimide (*R*)-4b.** Obtained from (*S*)-(−)-1-phenylbutanol, $[\alpha]_D^{19}$ +183.4 (*c* 2, CH_2Cl_2); other data as racemic sample.

***N*-(2-Methyl-1-phenylpropoxy)phthalimide 4c.** Obtained from the Mitsunobu reaction of 2-methyl-1-phenylpropanol with *N*-hydroxyphthalimide as a crystalline solid (32%), mp 120–122 °C (Found: MH$^+$, 296.1287. $C_{18}H_{17}NO_3$ + H requires *M*, 296.1287); ν_{max}(Nujol)/cm^{-1} 2959, 1786, 1729, 1465, 703; δ_H(250 MHz; $CDCl_3$) 7.66 (4H, m, ArH), 7.41 (2H, m, ArH), 7.30 (3H, m, ArH), 5.04 (1H, d, *J* 8.6, OCH), 2.32 (1H, septet, *J* 6.7, C*H*Me$_2$), 1.28 (3H, d, *J* 6.6, Me), 0.79 (3H, d, *J* 6.6, Me); δ_C(62.9 MHz; $CDCl_3$) 164.0, 137.7, 134.5, 129.3, 129.1, 129.0, 128.3, 123.6, 94.8, 33.4, 19.9, 19.4; *m/z* (EI) 133 (13%), 104 (40), 91 (100), 76 (38), 41 (25).

***N*-(1-Phenylpentoxy)phthalimide 4d.** Obtained from the Mitsunobu reaction of 1-phenylpentanol with *N*-hydroxyphthalimide as a crystalline solid (36%), mp 72–75 °C (Found: C, 73.8; H, 6.05; N, 4.5. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%) (Found: M$^+$, 309.1351. $C_{19}H_{19}NO_3$ requires *M*, 309.1365); ν_{max}(Nujol)/cm^{-1} 2923, 1790, 1731, 696; δ_H(250 MHz; $CDCl_3$) 7.67 (4H, m, ArH), 7.46 (2H, m, ArH), 7.31 (3H, m, ArH), 5.33 (1H, t, *J* 7.1, OCH), 2.18 (1H, m, CHC*H*$_2$), 1.91 (1H, m, CHC*H*$_2$), 1.41 (4H, m, C*H*$_2$C*H*$_2$Me), 0.89 (3H, t, *J* 6.7, Me); δ_C(62.9 MHz; $CDCl_3$) 164.0, 138.2, 134.1, 128.8, 128.8, 128.2, 128.0, 123.2, 89.2, 34.4, 27.7, 22.4, 13.9; *m/z* (EI) 310 (MH$^+$, 9%), 254 (11), 164 (20), 147 (97), 117 (31), 104 (43), 91 (100), 76 (29).

***N*-(*sec*-Butoxy)phthalimide 4e.** Obtained from the Mitsunobu reaction of butan-2-ol with *N*-hydroxyphthalimide as a crystalline solid (95%), mp 48–50 °C (Found: C, 65.3; H, 5.7; N, 6.3. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%) (Found: M$^+$, 219.0895. $C_{12}H_{13}NO_3$ requires *M*, 219.0895); ν_{max}(Nujol)/cm^{-1} 2923, 1785, 1739, 1465; δ_H(250 MHz; $CDCl_3$) 7.80 (4H, m, ArH), 4.32 (1H, m, OCH), 1.78 (1H, m, C*H*$_2$Me), 1.63 (1H, m, C*H*$_2$Me), 1.33 (3H, d, *J* 6.2, CH*Me*), 1.02 (3H, t, *J* 7.5, CH$_2$*Me*); δ_C(62.9 MHz; $CDCl_3$) 165.6, 135.4, 130.3, 124.7, 86.9, 29.0, 19.5, 10.8; *m/z* (EI) 220 (MH$^+$, 10%), 163 (100), 146 (10), 133 (24), 104 (38), 90 (22), 76 (36).

General method for the preparation of benzaldehyde *O*-(alkyl)-oximes

A suspension of the *N*-(alkoxy)phthalimide (3.31 mmol) in ethanol (10 ml) was heated until the phthalimide dissolved. Hydrazine hydrate (0.18 ml, 3.64 mmol) was added at this elevated temperature and after a few minutes the solution was allowed to cool to room temperature. Benzaldehyde (0.37 g, 3.5 mmol) was added and the mixture stirred overnight. The solvent was evaporated, and carbon tetrachloride (30 ml) and magnesium sulfate were added to the residue. The resulting suspension was filtered and the filtrate evaporated; the residue was purified by flash chromatography on silica gel (eluent: dichloromethane–light petroleum, 1:2).

Benzaldehyde *O*-[1-(1-naphthyl)ethyl]oxime 2. Obtained from the cleavage of *N*-[1-(1-naphthyl)ethoxy]phthalimide **1** and subsequent condensation of the hydroxylamine with benzaldehyde as a colourless oil (76%) (Found: M$^+$, 275.1307. $C_{19}H_{17}NO$ requires *M*, 275.1310); ν_{max}(film)/cm^{-1} 2979, 1597, 1511, 1447; δ_H(250 MHz; $CDCl_3$) 8.26 (1H, s, CH=N), 8.24 (1H, d, *J* 6.6, ArH), 7.94 (1H, d, *J* 6.6, ArH), 7.85 (1H, d, *J* 6.6, ArH), 7.61 (6H, m, ArH), 7.35 (3H, m, ArH), 6.19 (1H, q, *J* 6.6, OCH), 1.86 (3H, d, *J* 6.6, Me); δ_C(62.9 MHz; $CDCl_3$) 148.8, 138.5, 134.2, 132.2, 130.8, 129.7, 128.8, 128.6, 128.0, 127.0, 126.0, 125.4, 125.4, 123.6, 123.6, 78.5, 21.2; *m/z* (EI) 275 (M$^+$, 5%), 155 (100), 141 (7), 128 (7), 115 (4), 103 (5), 77 (8).

Benzaldehyde *O*-(1-phenylpropyl)oxime 5a. Obtained from the cleavage of *N*-(1-phenylpropoxy)phthalimide **4a** and subsequent condensation of the hydroxylamine with benzaldehyde as a colourless oil (87%) (Found: M$^+$, 239.1309. $C_{16}H_{17}NO$

requires *M*, 239.1310); ν_{max}(film)/cm^{-1} 2968, 2935, 1494, 1448; δ_H(250 MHz; $CDCl_3$) 8.15 (1H, s, HC=N), 7.54 (2H, m, ArH), 7.33 (8H, m, ArH), 5.12 (1H, t, *J* 6.8, OCH), 2.04 (1H, m, CH_2), 1.90 (1H, m, CH_2), 0.96 (3H, t, *J* 7.4, Me); δ_C(62.9 MHz; $CDCl_3$) 148.6, 142.0, 132.5, 129.6, 128.8, 128.6, 128.2, 127.2, 127.0, 86.9, 29.0, 10.0; *m/z* (EI) 239 (M^+, 12%), 119 (100), 91 (95), 77 (44), 65 (15).

Benzaldehyde *O*-(1-phenylbutyl)oxime 5b. Obtained from the cleavage of *N*-(1-phenylbutoxy)phthalimide **4b** and subsequent condensation of the hydroxylamine with benzaldehyde as a colourless oil (91%) (Found: M^+, 253.1470. $C_{17}H_{19}NO$ requires *M*, 253.1467); ν_{max}(film)/cm^{-1} 2959, 2933, 1493, 1448; δ_H(250 MHz; $CDCl_3$) 8.17 (1H, s, HC=N), 7.56 (2H, m, ArH), 7.36 (8H, m, ArH), 5.23 (1H, t, *J* 6.8, OCH), 2.03 (1H, m, CHC*H*$_2$), 1.82 (1H, m, CHC*H*$_2$), 1.48 (2H, m, C*H*$_2$Me), 0.99 (3H, t, *J* 7.3, Me); δ_C(62.9 MHz; $CDCl_3$) 148.5, 142.4, 132.5, 129.6, 128.7, 128.2, 127.4, 127.0, 126.8, 85.5, 38.3, 18.9, 14.0; *m/z* (EI) 253 (M^+, 7%), 212 (5), 133 (92), 117 (7), 104 (22), 91 (100), 77 (35).

Benzaldehyde *O*-(2-methyl-1-phenylpropyl)oxime 5c. Obtained from the cleavage of *N*-(2-methyl-1-phenylpropoxy)-phthalimide **4c** and subsequent condensation of the hydroxylamine with benzaldehyde as a colourless oil (91%) (Found: M^+, 253.1465. $C_{17}H_{19}NO$ requires *M*, 253.1467); ν_{max}(film)/cm^{-1} 2961, 1493, 1448; δ_H(250 MHz; $CDCl_3$) 8.16 (1H, s, HC=N), 7.52 (2H, m, ArH), 7.32 (8H, m, ArH), 4.92 (1H, t, *J* 7.1, OCH), 2.19 (1H, septet, *J* 6.8, C*H*Me$_2$), 1.06 (3H, d, *J* 6.8, Me), 0.86 (3H, d, *J* 6.8, Me); δ_C(62.9 MHz; $CDCl_3$) 148.4, 141.3, 132.5, 129.5, 128.5, 128.3, 127.7, 127.4, 127.0, 90.8, 33.3, 18.8, 18.8; *m/z* (EI) 253 (M^+, 5%), 133 (100), 117 (12), 104 (51), 91 (87), 77 (44).

Benzaldehyde *O*-(1-phenylpentyl)oxime 5d. Obtained from the cleavage of *N*-(1-phenylpentoxy)phthalimide **4d** and subsequent condensation of the hydroxylamine with benzaldehyde as a colourless oil (93%) (Found: M^+, 267.1623. $C_{18}H_{21}NO$ requires *M*, 267.1623); ν_{max}(film)/cm^{-1} 2956, 2933, 1493, 1448; δ_H(250 MHz; $CDCl_3$) 8.22 (1H, s, HC=N), 7.60 (2H, m, ArH), 7.41 (8H, m, ArH), 5.27 (1H, t, *J* 6.8, OCH), 2.11 (1H, m, CHC*H*$_2$), 1.92 (1H, m, CHC*H*$_2$), 1.49 (4H, m, C*H*$_2$C*H*$_2$Me), 0.99 (3H, t, *J* 6.9, Me); δ_C(62.9 MHz; $CDCl_3$) 148.5, 142.5, 132.6, 129.6, 128.5, 128.2, 127.4, 127.0, 126.6, 85.7, 35.9, 27.6, 22.7, 14.0; *m/z* (EI) 267 (M^+, 4%), 147 (62), 104 (14), 91 (100), 77 (22), 69 (47).

Benzaldehyde *O*-(*sec*-butyl)oxime 5e. Obtained from the cleavage of *N*-(*sec*-butoxy)phthalimide **4e** and subsequent condensation of the hydroxylamine with benzaldehyde as a colourless oil (90%) (Found: M^+, 177.1154. $C_{11}H_{15}NO$ requires *M*, 177.1154); ν_{max}(film)/cm^{-1} 2970, 1447, 1374, 1333; δ_H(250 MHz; $CDCl_3$) 8.12 (1H, s, HC=N), 7.62 (2H, m, ArH), 7.40 (3H, m, ArH), 4.30 (1H, m, OCH), 1.78 (1H, m, CHC*H*$_2$), 1.64 (1H, m, CHC*H*$_2$), 1.34 (3H, d, *J* 6.4, CH*Me*), 1.02 (3H, t, *J* 7.5, CH$_2$*Me*); δ_C(62.9 MHz; $CDCl_3$) 147.7, 132.8, 129.4, 128.6, 126.8, 80.7, 28.4, 19.2, 9.7; *m/z* (EI) 177 (M^+, 44%), 121 (100), 104 (68), 77 (77), 57 (78).

General method for the addition of *n*-butyllithium to benzaldehyde *O*-(alkyl)oximes

To a round bottomed flask fitted with a nitrogen inlet was added the benzaldehyde *O*-(alkyl)oxime (1 mmol) and toluene (5 ml). The resulting solution was cooled to −78 °C and boron trifluoride–diethyl ether (0.37 ml, 3 mmol) was added, the solution was stirred for 15 min. *n*-Butyllithium (1.6 M in hexanes; 1.9 ml, 3 mmol) was added dropwise over 15 min. After addition the solution was stirred at −78 °C for 1 h. The reaction mixture was quenched at −78 °C by the addition of water (1 ml), and then allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (20 ml) and water (20 ml). The layers were separated and the aqueous layer was washed with further portions of dichloromethane (2 × 20 ml). The combined organic extracts were washed with brine and then dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on silica gel (dichloromethane–light petroleum, 1:2) gave the hydroxylamine.

1-Phenyl-*N*-[1-(1-naphthyl)ethoxy]pentylamine 3. Obtained by the addition of *n*-butyllithium to oxime ether **2** as a colourless oil (80%, 55% de) (Found: M^+, 333.2094. $C_{23}H_{27}NO$ requires *M*, 333.2093); ν_{max}(film)/cm^{-1} 2956, 2930, 1454, 778; δ_H(250 MHz; $CDCl_3$) major diastereomer 7.83 (1H, d, *J* 7.4, ArH), 7.74 (1H, d, *J* 7.4, ArH), 7.64 (1H, d, *J* 7.4, ArH), 7.33 (4H, m, ArH), 7.18 (5H, m, ArH), 5.46 (1H, br s, NH), 5.36 (1H, q, *J* 6.5, OCH), 3.91 (1H, dd, *J* 6.0 and 8.4, NCH), 1.83 (1H, m, CH_2), 1.56 (3H, d, *J* 6.6, Me), 1.52 (1H, m, CH_2), 1.17 (4H, m, CH_2CH_2), 0.78 (3H, t, *J* 7.4, Me); minor diastereomer 7.98 (1H, d, *J* 7.4, ArH), 7.78 (1H, d, *J* 7.4, ArH), 7.67 (1H, d, *J* 7.4, ArH), 5.16 (1H, q, *J* 6.5, OCH), 3.89 (1H, dd, *J* 6.0 and 8.4, NCH), 1.25 (3H, d, *J* 6.6, Me), 0.77 (3H, t, *J* 7.4, Me); δ_C(100 MHz; $CDCl_3$) major diastereomer 141.6, 138.9, 133.5, 130.6, 128.3, 127.9, 127.8, 127.4, 127.0, 125.4, 125.0, 125.0, 123.2, 122.8, 77.9, 65.6, 33.4, 28.0, 22.4, 20.8, 13.5; minor diastereomer 142.0, 139.5, 133.7, 130.9, 78.4, 65.7, 33.1, 28.7, 22.3, 21.2, 13.6; *m/z* (EI) 334 (MH^+, 10%), 155 (100), 128 (13), 104 (14), 91 (33), 77 (9).

1-Phenyl-*N*-(1-phenylpropoxy)pentylamine 6a. Obtained by the addition of *n*-butyllithium to oxime ether **5a** as a colourless oil (91%, 93% de) (Found: M^+, 297.2095. $C_{20}H_{27}NO$ requires *M*, 297.2093); ν_{max}(film)/cm^{-1} 2959, 2933, 1494, 1454, 699; δ_H(250 MHz; $CDCl_3$) 7.22 (10H, m, ArH), 5.25 (1H, br s, NH), 4.45 (1H, t, *J* 6.8, OCH), 3.93 (1H, dd, *J* 5.1 and 8.8, NCH), 1.86 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.24 (4H, m, CH_2CH_2), 0.87 (3H, t, *J* 7.5, Me), 0.84 (3H, t, *J* 7.2, Me); δ_C(62.9 MHz; $CDCl_3$) 142.9, 141.6, 128.1, 127.7, 127.2, 127.2, 126.7, 86.8, 65.7, 33.4, 29.0, 28.2, 22.7, 13.9, 10.4; 1 ArC not observed; *m/z* (EI) 298 (MH^+, 9%), 179 (40), 147 (22), 119 (71), 91 (100), 77 (16).

1-Phenyl-*N*-(1-phenylbutoxy)pentylamine 6b. Obtained by the addition of *n*-butyllithium to oxime ether **5b** as a colourless oil (87%, 90% de) (Found: M^+, 311.2249. $C_{21}H_{29}NO$ requires *M*, 311.2249); ν_{max}(film)/cm^{-1} 2957, 2932, 1494, 1455, 699; δ_H(250 MHz; $CDCl_3$) major diastereomer 7.29 (10H, m, ArH), 5.33 (1H, br s, NH), 4.57 (1H, t, *J* 7.3, OCH), 3.95 (1H, dd, *J* 5.1 and 8.8, NCH), 2.00–1.16 (10H, m, 5 × CH_2), 0.92 (3H, t, *J* 7.3, Me), 0.90 (3H, t, *J* 7.3, Me); minor diastereomer 4.35 (1H, dd, *J* 5.1 and 8.8, NCH); δ_C(62.9 MHz; $CDCl_3$) 143.4, 141.7, 128.1, 127.7, 127.2, 127.2, 126.6, 85.1, 65.7, 38.4, 33.4, 28.2, 22.7, 19.1, 14.0, 13.9; 1 ArC not observed; *m/z* (EI) 179 (23%), 147 (15), 133 (31), 104 (12), 91 (100), 77 (12).

1-Phenyl-*N*-(2-methyl-1-phenylpropoxy)pentylamine 6c. Obtained by the addition of *n*-butyllithium to oxime ether **5c** as a colourless oil (74%, >95% de) (Found: M^+, 311.2247. $C_{21}H_{29}NO$ requires *M*, 311.2249); ν_{max}(film)/cm^{-1} 2957, 2931, 1494, 1455, 700; δ_H(250 MHz; $CDCl_3$) 7.23 (10H, m, ArH), 5.20 (1H, br s, NH), 4.25 (1H, d, *J* 7.8, OCH), 3.93 (1H, dd, *J* 5.0 and 8.8, NCH), 1.94–1.02 (7H, m, 3 × CH_2 and Me$_2$C*H*), 1.01 (3H, d, *J* 6.7, Me), 0.84 (3H, t, *J* 6.9, Me), 0.70 (3H, d, *J* 6.8, Me); δ_C(62.9 MHz; $CDCl_3$) 141.8, 141.6, 128.1, 127.9, 127.7, 127.3, 127.2, 127.0, 90.7, 65.5, 33.5, 33.3, 28.2, 22.7, 19.3, 19.1, 13.9; *m/z* (EI) 179 (23%), 147 (20), 133 (60), 91 (100), 77 (19).

1-Phenyl-*N*-(1-phenylpentoxy)pentylamine 6d. Obtained by the addition of *n*-butyllithium to oxime ether **5d** as a colourless oil (80%, 90% de) (Found: M^+, 325.2407. $C_{22}H_{31}NO$ requires *M*, 325.2406); ν_{max}(film)/cm^{-1} 2956, 2931, 1494, 1455, 699; δ_H(400 MHz; $CDCl_3$) major diastereomer 7.15 (10H, m, ArH), 5.25 (1H, br s, NH), 4.45 (1H, t, *J* 7.3, OCH), 3.84 (1H, dd, *J* 5.1 and 8.8, NCH), 1.84 (1H, m, CH_2), 1.71 (1 H, m, CH_2), 1.50 (2H, m, CH_2), 1.19 (8H, m, 4 × CH_2), 0.78 (3H, t, *J* 7.3, Me), 0.77 (3H, t, *J* 7.3, Me); minor diastereomer 4.30 (1H, dd, *J* 5.1 and 8.8, NCH); δ_C(100 MHz; $CDCl_3$) major diastereomer 143.4, 142.1, 128.6, 128.2, 127.6, 127.1, 85.8, 66.2, 36.4, 33.9, 28.7, 28.5, 23.1, 23.1, 14.3 (2 × Me); 2 ArC not observed; minor diastereomer 86.0, 66.3, 36.6, 34.0; *m/z* (EI) 179 (47%), 147 (70), 122 (55), 104 (52), 91 (100).

1-Phenyl-*N*-(*sec*-butoxy)pentylamine 6e. Obtained by the addition of *n*-butyllithium to oxime ether **5e** as a colourless oil (70%, 10% de) (Found: M^+, 235.1936. $C_{15}H_{25}NO$ requires *M*, 235.1936); ν_{max}(film)/cm^{-1} 2961, 2931, 1455, 1371, 699; δ_H(250 MHz; $CDCl_3$) major diastereomer 7.18 (5H, m, ArH), 5.29 (1H, br s, NH), 3.84 (1H, dd, *J* 5.1 and 10.4, NCH), 3.42 (1H, m, OCH), 1.77–1.03 (8H, m, 4 × CH_2), 0.90 (3H, d, *J* 6.2, OCH*Me*), 0.80 (3H, t, *J* 7.3, Me), 0.78 (3H, t, *J* 7.3, Me); minor diastereomer 3.82 (1H, dd, *J* 5.1 and 10.4, NCH), 3.40 (1H, m, OCH), 1.02 (3H, d, *J* 6.2, OCH*Me*), 0.79 (3H, t, *J* 7.4, Me), 0.59 (3H, t, *J* 7.4, Me); δ_C(62.9 MHz; $CDCl_3$) major diastereomer 142.1, 128.0, 127.7, 127.1, 80.2, 66.0, 33.3, 28.3, 28.0, 22.7, 18.5, 13.9, 9.8; minor diastereomer 142.2, 80.1, 33.5, 28.0, 18.7, 9.5; *m/z* (EI) 235 (M^+, 10%), 178 (35), 147 (38), 122 (100), 104 (14), 91 (85), 77 (10).

Procedure for the preparation of *O*-(1-phenylbutyl)hydroxylamines 7

The *N*-(1-phenylbutoxy)phthalimide **4b** (3 g, 10 mmol) was suspended in ethanol (30 ml) and heated to 50 °C, and the solution was treated with hydrazine hydrate (1.25 ml, 20 mmol). The mixture was heated under reflux for 1 h, allowed to cool to room temperature, filtered, the solids washed with ethanol (15 ml) and the combined filtrate evaporated to leave a yellow residue. The residue was taken up in dichloromethane (30 ml) and the solution was dried over anhydrous magnesium sulfate. The mixture was filtered and evaporated to a yellow oil, which was purified by flash chromatography on silica gel (eluent: dichloromethane–light petroleum, 3:1).

(*S*)-(−)-*O*-(1-Phenylbutyl)hydroxylamine (*S*)-7. Obtained from the reaction of (*S*)-(−)-*N*-(1-phenylbutoxy)phthalimide with hydrazine hydrate as a colourless oil (78%, ee >96%), $[\alpha]_D^{22}$ −93.3 (*c* 0.9, CH_2Cl_2) (Found: M^+, 165.1154. $C_{10}H_{15}NO$ requires *M*, 165.1153); ν_{max}(CH_2Cl_2)/cm^{-1} 2963, 1581, 1453, 1181, 964; δ_H(300 MHz; $CDCl_3$) 7.32 (5H, m, ArH), 5.15 (2H, br s, NH_2), 4.47 (1H, t, *J* 6.8, OCH), 1.81 (1H, m, CHCH_2), 1.55 (1H, m, CHCH_2), 1.34 (2H, m, CH_2Me), 0.89 (3H, t, *J* 7.3, Me); δ_C(75 MHz; $CDCl_3$) 142.1, 128.4, 127.6, 126.7, 87.3, 38.2, 19.0, 13.9; *m/z* (EI) 165 (M^+, 0.1%), 134 (20), 133 (70), 91 (100), 77 (46).

(*R*)-(+)-*O*-(1-Phenylbutyl)hydroxylamine (*R*)-7. Obtained from the reaction of (*R*)-(+)-*N*-(1-phenylbutoxy)phthalimide with hydrazine hydrate as a colourless oil (84%, ee >96%), $[\alpha]_D^{22}$ +92.9 (*c* 0.99, CH_2Cl_2) (Found: M^+, 165.1154. $C_{10}H_{15}NO$ requires *M*, 165.1153); ν_{max}(CH_2Cl_2)/cm^{-1} 2963, 1581, 1453, 1181, 964; δ_H(300 MHz; $CDCl_3$) 7.32 (5H, m, ArH), 5.15 (2H, br s, NH_2), 4.47 (1H, t, *J* 6.8, OCH), 1.81 (1H, m, CHCH_2), 1.55 (1H, m, CHCH_2), 1.34 (2H, m, CH_2Me), 0.89 (3H, t, *J* 7.3, Me); δ_C(75 MHz; $CDCl_3$) 142.1, 128.4, 127.6, 127.6, 87.3, 38.2, 19.0, 13.9; *m/z* (EI) 165 (M^+, 1%), 134 (1), 133 (10), 91 (100), 77 (8).

(*S*)-(−)-Acetophenone *O*-(1-phenylbutyl)oxime (*S*)-8a

Acetophenone (0.23 ml, 2.02 mmol) was added under nitrogen to a solution of the hydroxylamine (*S*)-**7** (167 mg, 1.01 mmol) in pyridine (2 ml) and the mixture was stirred for 24 h. The pyridine was evaporated and the residue taken up in dichloromethane (15 ml) and dried over anhydrous magnesium sulfate. The mixture was filtered, the filtrate evaporated and the residue was purified by flash chromatography on silica gel (eluent: dichloromethane–light petroleum, 1:2) furnishing the oxime (126 mg, 47%) as a colourless oil, $[\alpha]_D^{22}$ −74.2 (*c* 0.96, CH_2Cl_2) (Found: M^+, 267.1623. $C_{18}H_{21}NO$ requires *M*, 267.1623); ν_{max}(CH_2Cl_2)/cm^{-1} 2963, 1495, 1463, 997, 932; δ_H(300 MHz; $CDCl_3$) 7.56 (2H, m, ArH), 7.32 (8H, m, ArH), 5.23 (1H, t, *J* 6.8, OCH), 2.29 (3H, s, Me), 2.03 (1H, m, CHCH_2), 1.79 (1H, m, CHCH_2), 1.39 (2H, m, CH_2Me), 0.95 (3H, t, *J* 7.2, Me); δ_C(75 MHz; $CDCl_3$) 154.3, 143.0, 136.9, 128.8, 128.3, 128.2, 127.2, 126.7, 126.1, 85.3, 38.6, 18.9, 14.5, 12.9; *m/z* (EI) 267 (M^+, 1%), 133 (34), 106 (2), 91 (100), 77 (17).

(*S*)-(−)-Anisaldehyde *O*-(1-phenylbutyl)oxime (*S*)-8b

Prepared from *p*-anisaldehyde (0.73 ml, 6 mmol) and the hydroxylamine (*S*)-**7** (500 mg, 3 mmol) in pyridine (5 ml) as described above. The crude product was purified by flash chromatography on silica gel (eluent: dichloromethane–light petroleum, 1:2) furnishing the oxime (641 mg, 75%) as a colourless oil, $[\alpha]_D^{23}$ −88.7 (*c* 0.9, CH_2Cl_2) (Found: M^+, 283.1572. $C_{18}H_{21}NO_2$ requires *M*, 283.1572); ν_{max}(CH_2Cl_2)/cm^{-1} 2965, 1607, 1514, 1171, 1028, 944, 832; δ_H(300 MHz; $CDCl_3$) 8.08 (1H, s, HC=N), 7.45 (2H, d, *J* 7.8, ArH), 7.35 (5H, m, ArH), 6.86 (2H, d, *J* 7.8, ArH), 5.16 (1H, t, *J* 6.8, OCH), 3.80 (3H, s, OMe), 2.00 (1H, m, CHCH_2), 1.78 (1H, m, CHCH_2), 139 (2H, m, CH_2Me), 0.95 (3H, t, *J* 7.3, Me); δ_C(75 MHz; $CDCl_3$) 160.79, 148.1, 142.6, 128.4, 128.1, 127.2, 126.7, 125.2, 114.0, 85.2, 55.2, 38.3, 18.4, 14.0; *m/z* (EI) 283 (M^+, 4%), 151 (5), 133 (34), 107 (3), 91 (100), 77 (12).

(*S*)-(−)-Trimethylacetaldehyde *O*-(1-phenylbutoxy)oxime (*S*)-8c

Prepared from trimethylacetaldehyde (0.65 ml, 6 mmol) and the hydroxylamine (*S*)-**7** (500 mg, 3 mmol) in pyridine (5 ml) exactly as described above. The crude product was purified by flash chromatography on silica gel (eluent: dichloromethane–light petroleum, 1:4) furnishing the oxime (587 mg, 84%) as a colourless oil, $[\alpha]_D^{23}$ −116.9 (*c* 1, CH_2Cl_2) (Found: M^+, 233.1780. $C_{15}H_{23}NO$ requires *M*, 233.1780); ν_{max}(CH_2Cl_2)/cm^{-1} 2966, 1477, 1453, 1365, 1025, 917; δ_H(300 MHz; $CDCl_3$) 7.29 (6H, m, ArH and HC=N), 5.03 (1H, t, *J* 6.8, OCH), 1.92 (1H, m, CHCH_2), 1.71 (1H, m, CHCH_2), 1.34 (2H, m, CH_2Me), 1.03 (9H, s, Me_3C), 0.92 (3H, m, Me); δ_C(75 MHz; $CDCl_3$) 158.3, 142.5, 128.0, 127.1, 126.8, 84.3, 38.1, 33.5, 27.6, 18.79, 14.0; *m/z* (EI) 233 (M^+, 0.1%), 190 (3), 133 (96), 100 (2), 91 (100), 84 (8), 77 (54), 70 (11), 57 (74).

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