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Chiral Oximes in Asymmetric Synthesis. Addition of Organometallic Reagents to *O*-(1-Phenylethyl) Aldoximes

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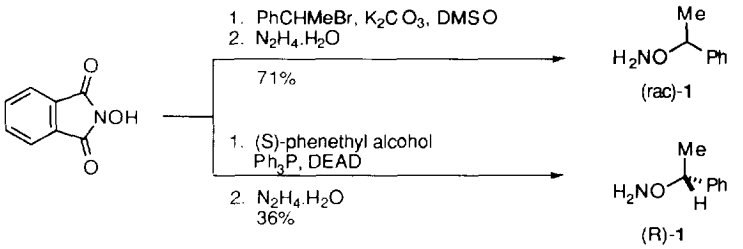
Abstract: Addition of Grignard and organolithium reagents to *O*-(1-phenylethyl) aldoximes in the presence of boron trifluoride etherate gives secondary hydroxylamines in 21-84% yield with up to 95% diastereomeric excess.

The chemistry of alkenes and carbonyl compounds is fundamental to much of organic synthesis, and with the recent emphasis on asymmetric synthesis, it is not surprising that 'chiral versions' of the well known addition reactions to C=C and C=O bonds have been extensively studied. In contrast, asymmetric additions to C=N bonds have only recently begun to attract attention. Asymmetric addition reactions to chiral imines,[1-3] to chiral hydrazones,[4-6] as well as additions to achiral derivatives in the presence of chiral mediators[7] have all been reported. In the case of oximes, nucleophilic additions to chiral derivatives have also been investigated,[8-13] although the use of chiral oxime ethers, RCH=NOR*, is rare.[8,9,13] In view of this, and in connection with our studies on the cycloaddition reactions of oxime ethers,[14] we were interested in developing further the asymmetric addition reactions to simple oxime ethers as a route to homochiral hydroxylamines and amines.[15]

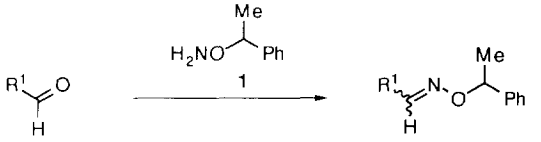
RESULTS AND DISCUSSION

The derivatives chosen for study were the simple *O*-(1-phenylethyl) aldoximes **2**, and the carboxylic acid derivatives, **4**. The starting material for the aldoximes **2** was *O*-(1-phenylethyl) hydroxylamine **1**. This was initially prepared in racemic form by alkylation of *N*-hydroxyphthalimide with (1-phenylethyl)bromide followed by cleavage of the phthaloyl group with hydrazine hydrate.[16] The (+)-(R)-hydroxylamine **1** was prepared by Mitsunobu inversion of (S)-(−)-1-phenethyl alcohol as shown in Scheme 1.[17] The resulting alkoxyphthalimide derivative was analysed by 1-H NMR spectroscopy employing the chiral shift reagent Eu(hfc)$_3$, and shown to be formed in >95% enantiomeric excess. Subsequent cleavage with hydrazine gave (+)-(R)-hydroxylamine **1**.

Reaction of the hydroxylamine **1** with the appropriate aldehyde in pyridine or ethanol gave the aldoximes **2** in good yield (Scheme 2, Table 1). The benzaldoxime **2a** and the pivaldoxime **2b** were both formed exclusively as their *E*-isomers (assigned on the basis of the chemical shift of the RC***H***=NOR* proton in their 1-H NMR spectra), whereas oximes **2c** and **2d** were formed as *E*/*Z*-mixtures (Table 1).



Scheme 1

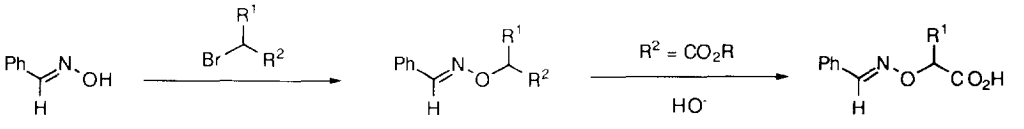


Scheme 2

Table 1. Preparation of *O*-(1-phenylethyl) aldoximes **2**

R[1]	*Product*	*E*:*Z*	*Yield*/%
Ph	**2a**	100:0	70
t-Bu	**2b**	100:0	83
i-Pr	**2c**	76:24	97
Me	**2d**	46:54	98

The benzaldoxime **2a** was also prepared (84%) by alkylation of benzaldoxime with (1-bromoethyl)benzene (Scheme 3). This method was also used to prepare the oximes **3**, by alkylation with the appropriate α-bromoester (58-76%). The oximes **3** were formed as single geometric isomers, and the *E*-stereochemistry of **3c** was confirmed by *X*-ray crystallography (Figure 1). Hydrolysis of the ester groups in oximes **3** gave the corresponding acids **4** (52-98%) Scheme 3).



Scheme 3

Both **4c** and **4a** formed crystals suitable for *X*-ray crystallography. Oxime acid **4a** crystallises as the carboxylic acid dimer (Figure 3), whereas **4c** crystallises as the monomer (Figure 2). The crystal structures of **3c** and **4c** show that although the different groups on the chiral auxiliary obviously render the two faces of the C=N bond inequivalent, in the solid state at least, the auxiliary is quite a distance away from the electrophilic carbon of the oxime C=N bond.†

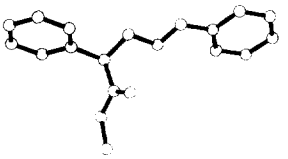


Figure 1. *X*-ray crystal structure of *O*-(1-methoxycarbonylbenzyl) benzaldoxime **3c**.

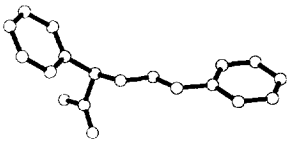


Figure 2. *X*-ray crystal structure of *O*-(1-carboxybenzyl) benzaldoxime **4c**.

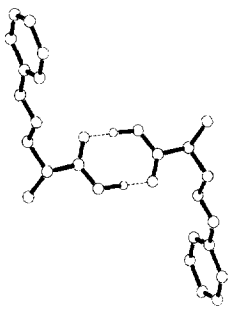


Figure 3. *X*-ray crystal structure of *O*-(carboxyethyl)benzaldoxime **4a** (as carboxylic acid dimer).

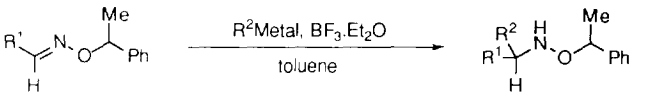
The addition of organometallics to the oxime ethers **2** was carried out in the presence of boron trifluoride etherate in toluene at -78°C.[9,18,19,20] Three equivalents of both the organometallic reagent and boron trifluoride etherate were required for complete consumption of the starting oxime. Allylmagnesium bromide, *n*-butyllithium and *t*-butyllithium added cleanly to oxime ethers **2** to give the corresponding hydroxylamines **5** in reasonable yield (Table 2). Other organometallic reagents, *e.g.* isopropylmagnesium chloride, and phenyllithium gave poorer results (Table 2), and t-butylmagnesium bromide and diethylzinc did not add at all. Several other Lewis acids were also tried. Of these, only zinc chloride gave any desired product in the addition

† *The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.*

of butyllithium to **2a** but the yield (13%) and d.e. (<10%) were both low. No reaction occurred with titanium tetra-isopropoxide, and use of aluminium chloride, iron(III) chloride, tin(IV) chloride or titanium tetrachloride resulted in decomposition of the starting oxime ether. Addition of *n*-butyllithium to **2a** at 0°C resulted in a poorer yield (30%) and d.e. (30%) of **5a**.

The diastereomeric ratio could be readily determined from the 1-H NMR spectrum of the mixture of hydroxylamines **5**. Only the acetaldoxime **2d** gave poor results, presumably a consequence of the fact that it is a *ca.* 1:1 mixture of *syn*/*anti* isomers. As expected addition of *t*-butyllithium to the oxime **2a** resulted in the formation of a major diastereomer opposite to that obtained in the addition of phenyllithium to **2b**. Attempted addition of *n*-butyllithium to the oximes **4a** and **4c** resulted only in attack on the carboxylic acid group.

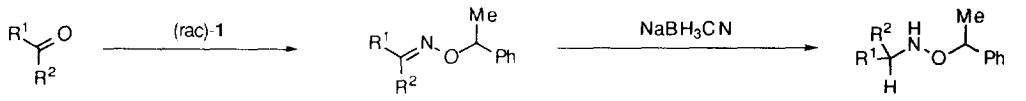
Table 2. Addition of organometallic reagents to oxime ethers **2**



2 **5**

Oxime ether	R^1	R^2*Metal*	*Product*	*Yield*/%	*d.e.*/%
2a	Ph	*n*-BuLi	**5a**	64	71
2a	Ph	*t*-BuLi	**5b**	54	38
2a	Ph	H_2C=$CHCH_2MgBr$	**5c**	70	69
2a	Ph	*i*-PrMgCl	**5d**	30	74
2b	*t*-Bu	*n*-BuLi	**5e**	84	74
2b	*t*-Bu	H_2C=$CHCH_2MgBr$	**5f**	62	44
2b	*t*-Bu	PhLi	**5b**	21	95
2c	*i*-Pr	*n*-BuLi	**5g**	83	77
2c	*i*-Pr	H_2C=$CHCH_2MgBr$	**5h**	70	59
2d	Me	*n*-BuLi	**5i**	70	5
2d	Me	H_2C=$CHCH_2MgBr$	**5j**	58	14

In order to confirm our NMR assignments of the diastereomerically enriched mixtures of hydroxylamines **5**, the secondary hydroxylamines **5** were also prepared as *ca.* 1:1 mixtures of diastereomers by reduction of the corresponding ketoximes **6** (Scheme 4). The ketoximes **6** were prepared by reaction of the corresponding ketones with (racemic)-hydroxylamine **1** in good yield (Table 3). The reduction of oximes can be carried out under a variety of conditions,[21] but sodium cyanoborohydride is often the reagent of choice when hydroxylamines are the required products.[22] Reduction of the ketoximes **6a**-**6g** with sodium cyanoborohydride under acidic conditions gave the expected hydroxylamines **5** (Scheme 4 and Table 3) in reasonable yield. In most cases, the diastereomeric excess in the reduction step was negligible.[23]



6 **5**

Scheme 4

Table 3 Preparation and reduction of ketoximes **6**.

R^1	R^2	*Ketoxime*	*E : Z*	*Yield/%*	*Reduction*	*Product Yield*	*d.e./%*
Ph	Bu	**6a**	100 : 0	96	**5a**	53	19
Ph	allyl	**6b**	100 : 0	89	**5c**	45	12
t-Bu	Bu	**6c**	100 : 0	50	**5e**	60	<5
t-Bu	allyl	**6d**	100 : 0	97	**5f**	65	<5
i-Pr	Bu	**6e**	76 : 24	99	**5g**	61	<5
i-Pr	allyl	**6f**	79 :21	79	**5h**	53	<5
Me	Bu	**6g**	60 :40	86	**5i**	58	<5

The stereochemical outcome of the reaction was proved in two ways. Firstly, the hydrochloride salt of the major diastereomer of hydroxylamine **5c** formed crystals suitable for *X*-ray analysis. The structure is shown in Figure 4, and confirms that both stereocentres have the same configuration.

Secondly, the reaction sequence was repeated using the optically pure (R)-hydroxylamine **1**. Addition of *n*-butyllithium to the oxime ether (+)-**2a**, gave the substituted hydroxylamine **5a**, cleavage of which with zinc/acetic acid/ultrasound[24] gave 1-phenylpentylamine **8** in 84% yield (Scheme 5), with $[\alpha]_D$ = +8.7° (c=20.1, $CDCl_3$). Comparison with the literature values for material with 85% e.e.,[4] $[\alpha]_D$= +14.1° (neat), and with 92% e.e.,[25] $[\alpha]_D$= +11.7° (c=1, $CHCl_3$), strongly suggests that the stereochemistry of the hydroxylamine **5a** was (R,R). In the reductive cleavage of the N-O bond, the chiral auxiliary was recovered as 1-phenylethyl alcohol in 87% yield, and shown to possess a positive rotation, $[\alpha]_D$ = +42° (c=0.83, MeOH), confirming it to be the (R)-enantiomer [authentic (R)-1-phenylethyl alcohol has $[\alpha]_D$ = +45° (c=0.87, MeOH)].

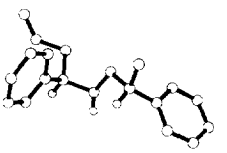
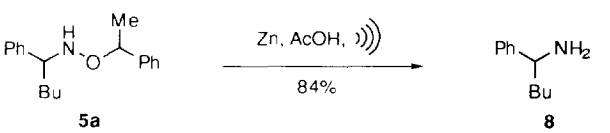


Figure 4. *X*-ray crystal structure of hydroxylamine **5c**.HCl.

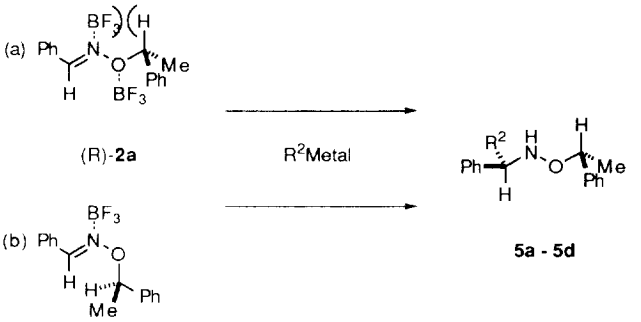


5a **8**

Scheme 5

Although the exact conformation of the oxime ethers in solution are unknown in order to rationalise our results we assume that, due to the appreciable conjugation of the oxygen lone pair, they are effectively planar. The almost planar structure of oximes is supported by *X*-ray studies,[26] which also show that the oxime sp^2-carbon and the substituent on oxygen are *trans* about the N-O bond. On this basis, we propose two possible

models for the BF_3 complexed oxime (Scheme 6). In the first, two BF_3 are complexed, whereas in the second only one BF_3 is complexed (to nitrogen). Assuming minimum steric interactions in the complexed oxime ether, and attack on the C=N bond from the least hindered side, leads to the prediction (for both models) that the newly formed sp^3-centre will have the same configuration as the chiral auxiliary attached to the oxime oxygen.



Scheme 6

Further applications of this methodology for the conversion of aldehydes into chiral amines using the readily available (1-phenylethyl) chiral auxiliary are being investigated.

EXPERIMENTAL

'Light petroleum' refers to the fraction boiling between 40°C and 60°C, and ether refers to diethyl ether; solvents were dried using standard methods. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with Ehrlich's reagent or phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60; samples were applied pre-adsorbed on silica or as a saturated solution in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded neat or as Nujol mulls. ^1H and ^{13}C NMR spectra were recorded using a Bruker AC-250 instrument in deuteriochloroform as solvent. In reporting the NMR data for mixtures of diastereomers, signals arising from the major and minor isomers are reported separately if possible; the integration of signals is consistent within each isomer, *e.g.* a methyl group is reported as 3H for both isomers even though the peaks are unequal in area when the ratio of isomers is >1:1. High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (SERC Mass Spectrometry Service Swansea). Compounds characterised by high resolution mass spectrometry were chromatographically homogeneous.

(±)-N-*(1-Phenylethoxy)phthalimide*

N-Hydroxyphthalimide (2.7 g, 1.6 mmol), (1-bromoethyl)benzene (9.18 g, 50 mmol), anhydrous potassium carbonate (6.8 g, 49 mmol) and DMSO (27 mL) were stirred together at 80°C. After 30 min, the mixture was poured into water (100 mL) and the solid filtered. The solid was dried at reduced pressure and recrystallised (ethanol) yielding the *phthalimide* (3.2 g, 73%) as a crystalline solid, m.p. 93-94°C, (Found: C, 71.88; H, 4.72; N, 5.23. $C_{16}H_{13}NO_3$ requires C, 71.90; H, 4.90; N, 5.24%); υ_{max}(Nujol)/cm^{-1} 2923, 1739, 1468, 1377; δ_H (250 MHz; $CDCl_3$) 7.72 (4H, m, ArH), 7.49 (2H, m, ArH), 7.33 (3H, m, ArH), 5.50 (1H, q, *J*=6.5 Hz,

OCH), 1.72 (3H, d, J=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 163.6, 138.8, 134.3, 128.9, 128.8, 128.3, 127.6, 123.3, 85.1, 20.4; *m/z* (EI) 268 (MH^+, 36%), 267 (M^+, 3), 240 (9), 222 (5), 209 (5), 195 (4), 181 (13), 163 (100).

(R)-(+)-N-*(1-Phenylethoxy)phthalimide*
Diethyl azodicarboxylate (0.38 g, 2.2 mmol) was added to a solution of *N*-hydroxyphthalimide (0.33 g, 2 mmol), triphenylphosphine (0.52 g, 2 mmol) and (S)-(–)-1-phenylethyl alcohol (0.24 g, 2 mmol) in THF (20 mL) at room temperature. The resulting solution was allowed to stand for 24 h. The solution was evaporated to dryness and the residue chromatographed on silica gel (dichloromethane-light petroleum 1:1) to give the *phthalimide*, (0.26 g, 49%, e.e. >95%); $[\alpha]_D$ +222° (*c*=1, MeOH).

(R)-(+)-O-*(1-Phenylethyl) hydroxylamine* **1**
Hydrazine hydrate (0.15 g, 4.6 mmol) was added to a solution of (+)-*N*-(1-phenylethoxy)phthalimide (0.91 g, 3.4 mmol) in absolute ethanol (5 mL) at room temperature and the mixture was heated under reflux. After 10 min, the cooled mixture was filtered and the filtrate evaporated under reduced pressure yielding the *hydroxylamine* **1** (0.34 g, 73%) as a colourless oil, b.p. 80°C/1 mbar, (Found: M^+, 137.0839. $C_8H_{11}NO$ requires M, 137.0841); $[\alpha]_D$ +105° (*c*=1, MeOH); υ_{max}(film)/cm^{-1} 3317, 2976, 1585, 1495, 1452, 1074; δ_H (250 MHz; $CDCl_3$) 7.33 (5H, m, ArH), 5.17 (2H, broad s, NH_2), 4.65 (1H, q, J=6.5 Hz, OCH), 1.43 (3H, d, J=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 143.0, 128.6, 127.7, 126.3, 82.9, 21.9; *m/z* (EI) 105 (M^+ -ONH_2, 100%), 77 (18), 51 (9).

Preparation of O-*(1-Phenylethyl) Oxime Ethers from Aldehydes*

(R)-(+)-O-*(1-Phenylethyl) benzaldoxime* **2a**
O-(1-Phenylethyl) hydroxylamine **1** (0.137 g, 1 mmol) and dry pyridine (10 mL) were added to a dry round bottomed flask at room temperature. Benzaldehyde (0.106 g, 1 mmol) was added to it in a dropwise manner. The reaction mixture was stirred for 2 h. Water (20 mL) and dichloromethane (20 mL) were added and the layers separated. The aqueous layer was washed with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL) and HCl (2M; 20 mL), dried ($MgSO_4$) and filtered. Evaporation of the solvent *in vacuo* afforded the *title compound* **2a** (0.19 g, 85%, E:Z 100:0) as a clear oil, b.p. 130°C/1 mbar, (Found: C 80.01; H, 6.77; N, 6.20. $C_{15}H_{15}NO$ requires C, 79.96; H, 6.72; N, 6.22%); $[\alpha]_D$ +100° (*c*=1, MeOH); υ_{max}(film)/cm^{-1} 2978, 1575, 1448, 1083, 1072, 958; δ_H (250 MHz; $CDCl_3$) 8.12 (1H, s, CH=N), 7.23 (10H, m, ArH), 5.35 (1H, q, J=6.6 Hz, OCH), 1.61 (3H, d, J=6.6 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.6, 143.1, 132.5, 129.6, 128.6, 128.3, 127.5, 127.0, 126.4, 81.3, 21.9; *m/z* (EI) 226 (MH^+, 28%), 225 (M^+, 17), 122 (20), 105 (100).

Similarly prepared were the following:-

(R)-(+)-O-*(1-Phenylethyl) trimethylacetaldehyde oxime* **2b**
(83%, E:Z 100:0) as a clear oil, b.p. 130°C, (Found: MH^+, 206.1545. $C_{13}H_{19}NO$ requires MH, 206.1545); $[\alpha]_D$ +10° (*c*=1, MeOH); υ_{max}(film)/cm^{-1} 2968, 1601, 1454, 1366, 1084; δ_H (250 MHz; $CDCl_3$) 7.35 (6H, m, ArH, CH=N), 5.19 (1H, q, J=6.6 Hz, OCH), 1.54 (3H, d, J=6.6 Hz, Me), 1.06 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 158.3, 143.7, 128.1, 127.2, 126.4, 80.2, 33.5, 27.5, 21.6; *m/z* (CI) 206 (MH^+, 100%), 192 (10).

O-*(1-Phenylethyl) isobutyraldehyde oxime* **2c**
(97%, E:Z 73:27) as a clear oil, b.p. 80°C/1 mbar, (Found: MH^+, 192.1388. $C_{12}H_{17}NO$ requires MH, 192.1388); υ_{max}(film)/cm^{-1} 2968, 1445, 1082; (E isomer) δ_H (250 MHz; $CDCl_3$) 7.31 (6H, m, ArH, CH=N),

5.20 (1H, q, *J*=6.6 Hz, OCH), 2.46 (1H, septet, *J*=6.7 Hz, C*H*Me$_2$), 1.54 (3H, d, *J*=6.6 Hz, Me), 1.07 (3H, d, *J*=6.7 Hz, CH*Me*Me), 1.04 (3H, d, *J*=6.7 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 156.1, 143.2, 128.2, 127.3, 126.3, 80.3, 29.3, 21.9, 20.14, 20.11; (Z isomer) δ_H (250 MHz; $CDCl_3$) 6.80 (1H, d, *J*=7.1 Hz, CH=N), 5.21 (1H, q, *J*=6.6 Hz, OCH), 3.25 (1H, septet, *J*=6.7 Hz, C*H*Me$_2$), 1.07 (3H, d, *J*=6.7 Hz, CH*Me*Me), 1.05 (3H, d, *J*=6.7 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 157.3, 143.6, 128.3, 126.0, 80.6, 25.1, 22.2, 19.72, 19.69; *m/z* (CI) 192 (MH^+, 100%), 164 (7), 122 (4).

O-*(1-Phenylethyl) acetaldoxime* **2d**
(98%, E:Z 46:54) as a clear oil, b.p. 60°C/2 mbar, (Found: MH^+, 164.1075. $C_{10}H_{13}NO$ requires MH, 164.1075); υ_{max}(film)/cm^{-1} 2978, 1645; (E isomer) δ_H (250 MHz; $CDCl_3$) 7.49 (1H, q, *J*=5.9 Hz, CH=N), 7.30 (5H, m, ArH), 5.20 (1H, q, *J*=6.5 Hz, OCH), 1.82 (3H, d, *J*=5.9 Hz, MeCH=N), 1.54 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.8, 146.8, 128.2, 127.2, 126.2, 80.3, 21.9, 12.0; (Z isomer) δ_H (250 MHz; $CDCl_3$) 6.77 (1H, q, *J*=5.5 Hz, CH=N), 5.25 (1H, q, *J*=6.6 Hz, OCH), 1.91 (3H, d, *J*=5.5 Hz, MeCH=N), 1.56 (3H, d, *J*=6.6 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 143.6, 126.0, 80.6, 22.1, 15.2; *m/z* (EI) 105 (100%), 77 (24), 51 (15), 39 (5).

Preparation of O*-Alkyl Benzaldoximes by Alkylation of* syn*-Benzaldoxime*

(±)-O-*(1-Phenylethyl) benzaldoxime oxime* **2a**
To a stirred solution of *syn*-benzaldoxime (1.25 g, 10 mmol) and anhydrous potassium carbonate (2.07 g, 15 mmol) in DMSO (50 mL) was added dropwise (1-bromoethyl)benzene (2.3 g, 12 mmol). The mixture was stirred overnight at room temperature. Excess solvent was removed *in vacuo*. The residue was extracted with dichloromethane (20 mL) and washed with water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography on silica gel using dichloromethane-light petroleum (1:2) as eluent yielding the *oxime ether* **2a** (1.95 g, 84%, E:Z 100:0) with identical spectroscopic properties to the (+)-(R)-enantiomer prepared above.

O-*(1-Ethoxycarbonylethyl) benzaldoxime* **3a**
To a stirred solution of *syn*-benzaldoxime (0.12 g, 1 mmol) and potassium *t*-butoxide (0.13 g, 1.2 mmol) in *t*-butanol (10 mL) was added dropwise ethyl 2-bromopropionate (0.18 g, 1 mmol). The mixture was stirred overnight at room temperature. Excess solvent was removed under reduced pressure. The residue was extracted with ether (20 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the the crude ester which was purified by column chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60°C) (1:2) as eluent to furnish the *title compound* **3a** (1.6 g, 76%) as a yellow oil, (Found: M^+, 221.1051. $C_{12}H_{15}NO_3$ requires M, 221.1052); υ_{max}(film)/cm^{-1} 2932, 1750; δ_H (250 MHz; $CDCl_3$) 8.17 (1H, s, CH=N), 7.56 (2H, m, ArH), 7.36 (3H, m, ArH), 4.81 (1H, q, *J*=7.0 Hz, OCH), 4.42 (2H, q, *J*=7.2 Hz, C*H*$_2$Me), 1.53 (3H, d, *J*=7.0 Hz, Me), 1.29 (3H, t, *J*=7.2 Hz, CH$_2$*Me*); δ_C (62.9 MHz; $CDCl_3$) 175.1, 149.8, 132.6, 130.0, 128.7, 127.3, 77.8, 60.9, 17.0, 14.2; *m/z* (EI) 211 (M^+, 11%), 148 (9), 104 (100).

Similarly prepared were the following:-

O-*(1-Ethoxycarbonyl-2-methylpropyl) benzaldoxime* **3b**
Obtained from the alkylation of benzaldoxime with ethyl 2-bromo-3-methylbutanoate, (60%) as a colourless oil, (Found: C, 67.40; H, 7.70; N, 5.54. $C_{14}H_{19}NO_3$ requires C, 67.43; H, 7.69; N, 5.62%); υ_{max}(film)/cm^{-1} 2970, 2935, 1751; δ_H (250 MHz; $CDCl_3$) 8.20 (1H, s, CH=N), 7.56 (2H, m, ArH), 7.33 (3H, m, ArH), 4.50 (1H, d, *J*=6.1 Hz, OCH), 4.24 (2H, m, C*H*$_2$Me), 2.21 (1H, septet, *J*=6.8 Hz, C*H*Me$_2$) 1.28 (3H, t, *J*=7.1

Hz, CH_2Me), 1.05 (6H, 2d, J=6.8 Hz, $CHMe_2$); δ_C (62.9 MHz; $CDCl_3$) 171.8, 149.8, 131.9, 130.0, 128.6, 127.2, 86.9, 60.6, 30.4, 17.0, 18.6, 18.1, 14.3; *m/z* (EI) 249 (M^+, 6%), 176 (18), 104 (100).

O-*(1-Methoxycarbonylbenzyl) benzaldoxime* **3c**
Obtained from the alkylation of benzaldoxime with methyl 2-bromo-2-phenylacetate, (58%) as a colourless solid, m.p. 50-60°C, (Found: C, 71.74; H, 5.90; N, 5.19. $C_{14}H_{19}NO_3$ requires C, 71.35; H, 5.62; N, 5.20%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3030, 2956, 1752; δ_H (250 MHz; $CDCl_3$) 8.27 (1H, s, CH=N), 7.55 (4H, m, ArH), 7.39 (6H, m, ArH), 5.73 (1H, s, OCH), 3.76 (3H, s, CO_2Me); δ_C (62.9 MHz; $CDCl_3$) 170.9, 150.5, 134.5, 131.4, 130.1, 129.0, 128.6, 128.5, 127.6, 127.2, 83.6, 52.2; *m/z* (EI) 270 (MH^+, 4%), 269 (M^+, 12), 230 (8), 228 (8), 210 (100).

Hydrolysis of Oxime Esters **3**

O-*(1-Carboxyethyl) benzaldoxime* **4a**
A solution of **3a** (0.22 g, 1 mmol), lithium hydroxide (0.12 g, 5 mmol), water (5 mL) and THF (5 mL) was stirred for 2 h at room temperature. The mixture was acidified with HCl (6 M) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to give a white solid, recrystallization (petroleum ether/ether) furnished the *title compound* **4a** (0.10 g, 52%) as colourless crystals, m.p. 114-115°C, (Found: C, 62.13; H, 5.74; N, 7.14. $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3403, 3025, 2990, 1730; δ_H (250 MHz; $CDCl_3$) 8.19 (1H, s, CH=N), 7.51 (2H, m, ArH), 7.37 (3H, m, ArH), 4.86 (1H, q, J=7.1 Hz, OCH), 1.58 (3H, d, J=7.1 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 178.8, 150.3, 131.6, 130.2, 128.7, 128.6, 127.4, 77.3, 16.9; *m/z* (EI) 122 (MH^+, 75%), 105 (100), 77 (79).

O-*(1-Carboxy-2-methylpropyl) benzaldoxime* **4b**
Obtained from the hydrolysis of the *oxime ester* **3b** (98%) as colourless crystals, m.p. 64-66°C, (Found: M^+, 221.1056. $C_{12}H_{15}NO_3$ requires M, 221.1052); υ_{max}(Nujol)/cm^{-1} 3420, 3164, 2969, 1726; δ_H (250 MHz; $CDCl_3$) 9.70 (1H, broad s, CO_2H), 8.20 (1H, s, CH=N), 7.70 (2H, m, ArH), 7.36 (3H, m, ArH), 4.59 (1H, d, J=5.7 Hz, OCH), 2.25 (1H, septet, J=5.7 Hz, $CHMe_2$) 1.05 (6H, 2d, J=6.8 Hz, $CHMe_2$); δ_C (62.9 MHz; $CDCl_3$) 191.0, 163.5, 145.0, 143.5, 142.0, 140.7, 99.6, 43.8, 32.1, 31.1; *m/z* (EI) 222 (MH^+, 23%), 221 (M^+, 10), 176 (13), 138 (24), 104 (100).

O-*(1-Carboxybenzyl) benzaldoxime* **4c**
Obtained from the hydrolysis of the *oxime ester* **3c** (68%) as colourless crystals, m.p. 99-100°C, (Found: C, 70.32; H, 5.14; N, 5.36. $C_{15}H_{13}NO_3$ requires C, 70.56; H, 5.14; N, 5.49%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3068, 3014, 1724; δ_H (250 MHz; $CDCl_3$) 8.25 (1H, s, CH=N), 7.45 (11H, m, ArH, CO_2H) 5.73 (1H, s, OCH); δ_C (62.9 MHz; $CDCl_3$) 176.5, 151.0, 134.1, 131.3, 130.3, 129.27, 128.8, 128.7, 127.7, 127.4, 83.3; *m/z* (EI) 256 (MH^+, 100%), 255 (M^+, 17).

Addition of Organometallics to O-*(1-Phenylethyl) Aldoxime*

1-Phenyl-N-*(1-phenylethoxy)-1-pentylamine* **5a**
To a round bottomed flask fitted with a nitrogen inlet was added (+)-(R)-**2a** (0.225 g, 1 mmol) and toluene (5 mL). The resulting solution was cooled to -78°C and boron trifluoride etherate (0.37 mL, 3 mmol) was added, the solution was stirred for 10 min. *n*-Butyllithium (1.6 M, 1.9 mL, 3 mmol) was added dropwise over 10 min. After addition the solution was stirred at -78°C until all the starting material had been consumed, monitored by TLC (usually 1-12 h). The reaction was quenched at -78°C by the addition of water (1 mL), and then allowed to warm up 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 portion was washed with further portions of dichloromethane (2 x 20 mL). The combined organic extracts were washed with brine (10 mL) and then dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel using dichloromethane-light petroleum (1:2) as eluent to give the *title compound* **5a** (0.18 g, 64%, d.e. 71%) as a colourless oil, b.p. 100°C/1 mbar, (Found: M^+, 283.1945. $C_{19}H_{25}NO$ requires M, 283.1936); $[\alpha]_D$ +60° (*c*=1, MeOH); υ_{max}(film)/cm^{-1} 3270, 2957, 1604, 1454; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.26 (10H, m, ArH), 5.40 (1H, broad s, NH), 4.67 (1H, q, *J*=6.6 Hz, OCH), 3.95 (1H, dd, *J*=5.2 and 8.7 Hz, CHN, 1.90 (1H, m, CH_2CHN), 1.65 (1H, m, CH_2CHN), 1.43 (3H, d, *J*=6.6 Hz, *Me*CHPh) 1.27 (4H, m, CH_2), 0.87 (3H, t, *J*=6.9 Hz, $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 143.5, 141.7, 128.3, 128.1, 127.8, 127.26, 126.33, 126.28, 80.9, 65.9, 33.5, 28.3, 22.7, 21.5, 14.0; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.51 (1H, q, *J*=6.6 Hz, OCH); δ_C (62.9 MHz; $CDCl_3$) 144.0, 142.7, 127.24, 81.0, 33.4, 29.8, 22.6, 21.7; *m/z* (EI) 284 (MH^+, 2%), 179 (22), 147 (16), 122 (41), 105 (100), 91 (53), 78 (30), 60 (11), 51 (15), 41 (20), 27 (15).

Similarly prepared were the following:-

2,2-Dimethyl-1-phenyl-N-*(1-phenylethoxy) propylamine* **5b**
Obtained by the addition of *tert*-butyllithium to (±)-**2a** (54%, d.e. 38%) as a colourless oil, (Found: M^+, 283.1926. $C_{19}H_{25}NO$ requires M, 283.1936); υ_{max}(film)/cm^{-1} 2973, 1454, 1365, 700; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.22 (10H, m, ArH), 5.68 (1H, broad s, NH), 4.65 (1H, q, *J*=6.6 Hz, OCH), 3.79 (1H, s, CHN), 1.41 (3H, d, *J*=6.6 Hz, Me), 0.90 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 142.4, 140.3, 128.8, 128.1, 127.33, 127.25, 126.7, 126.5, 79.9, 74.0, 27.4, 20.7; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.58 (1H, q, *J*=6.6 Hz, OCH), 3.75 (1H, s, CHN), 1.11 (3H, d, *J*=6.6Hz, Me) 0.82 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 143.8, 140.6, 128.9, 128.2, 127.19, 127.14, 126.6, 126.2, 81.0, 74.4, 27.2, 21.8; *m/z* (EI) 226 (14%), 122 (77), 105 (100), 91 (23), 77 (45), 57 (48), 41 (66), 27 (38).

2,2-Dimethyl-1-phenyl-N-*(1-phenylethoxy) propylamine* **5b**
Obtained by the addition of phenyllithium to (±)-**2b** (21%, d.e. >95%) as a colourless oil, (Found: M^+, 283.1900. $C_{19}H_{25}NO$ requires M, 283.1936); υ_{max}(film)/cm^{-1} 2973, 1454, 1365, 700; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.33 (10H, m, ArH), 5.74 (1H, bs, NH), 4.52 (1H, q, *J*=6.6 Hz, OCH), 3.74 (1H, s, CHN), 1.11 (3H, d, *J*=6.6 Hz, Me) 0.82 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 143.8, 140.6, 128.9, 128.2, 127.2, 127.1, 126.6, 126.3, 81.0, 74.4, 33.7, 27.2, 21.8; *m/z* (EI) 284 (MH^+, 24%), 226 (47), 147 (29), 122 (83), 105 (100), 91 (45), 77 (60), 57 (52), 41 (55), 27 (38).

1-Phenyl-N-*(1-phenylethoxy) but-3-enylamine* **5c**
Obtained by the addition of allylmagnesium bromide to (±)-**2a** (70%, d.e. 69%) as a colourless oil, (Found: M^+, 267.1637. $C_{18}H_{21}NO$ requires M, 267.1623); υ_{max}(film)/cm^{-1} 2973, 1650, 1451; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.26 (10H, m, ArH), 5.72 (1H, m, CH=), 5.51 (1H, broad s, NH), 5.00 (2H, m, $=CH_2$), 4.65 (1H, q, *J*=6.5 Hz, OCH), 4.03 (1H, t, *J*=6.9 Hz, CHN), 2.66 (1H, m, $CH_2CH=CH_2$), 2.48 (1H, m, $CH_2CH=CH_2$), 1.43 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 143.2, 141.5, 135.0, 128.2, 128.13, 127.8, 127.3, 127.2, 126.3, 117.2, 80.9, 65.0, 38.4, 21.3; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.51 (1H, q, *J*=6.5 Hz, OCH), 1.22 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 144.0, 142.2, 134.7, 128.3, 128.17, 127.7, 126.2, 117.5, 81.1, 64.9, 38.3, 21.7; *m/z* (EI) 268 (MH^+, 75%), 131 (62), 122 (80), 105 (100), 91 (61), 77 (67), 65 (16), 51 (47), 39 (54), 27 (27).

2-Methyl-1-phenyl-N-*(1-phenylethoxy) propylamine* **5d**
Obtained by the addition of isopropylmagnesium chloride to (±)-**2a** (30%, d.e. 74%) as a colourless oil, (Found: M^+, 269.1765. $C_{18}H_{23}NO$ requires M, 269.1776); υ_{max}(film)/cm^{-1} 3200, 2974, 1453, 700; (major

diastereomer) δ_H (250 MHz; $CDCl_3$) 7.25 (10H, m, ArH), 5.68 (1H, broad s, NH), 4.65 (1H, q, J=6.5 Hz, OCH), 3.74 (1H, d, J=7.0 Hz, CHN), 2.08 (1H, septet, J=6.8 Hz, C*H*Me$_2$), 1.41 (3H, d, J=6.5 Hz, Me), 0.98 (3H, d, J=6.8 Hz, CH*Me*Me), 0.77 (3H, d, J=6.8 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 144.4, 141.6, 128.3, 128.2, 127.8, 127.2, 127.0, 126.3, 81.6, 72.4, 31.6, 22.7, 21.0, 19.7; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.53 (1H, q, J=6.5 Hz, OCH), 3.65 (1H, d, J=7.0 Hz, CHN), 1.90 (1H, septet, J=6.8 Hz, C*H*Me$_2$), 1.17 (3H, d, J=6.5 Hz, Me), 0.91 (3H, d, J=6.8 Hz, CH*Me*Me), 0.68 (3H, d, J=6.8 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 145.3, 142.7, 127.1, 82.0, 72.8, 31.8, 22.3, 20.9, 20.1; *m/z* (EI) 270 (MH^+, 2), 165 (12), 133 (11), 226 (5), 165 (12), 133 (11), 122 (65), 105 (100), 91 (45), 77 (40), 65 (7), 51 (25), 27 (23).

*2,2-Dimethyl-*N*-(1-phenylethoxy)-3-heptylamine* **5e**

Obtained by the addition of *n*-butyllithium to (+)-**2b** (84%, d.e. 74%) as a colourless oil, (Found: MH^+, 264.2327. $C_{17}H_{29}NO$ requires MH, 264.2327); $[\alpha]_D$ +69° (*c*=0.51, MeOH); υ_{max}(film)/cm^{-1} 3392, 2957, 1452, 1365; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.30 (5H, m, ArH), 4.74 (1H, q, J=6.6 Hz, OCH), 2.40 (1H, dd, J=3.0 and 7.8 Hz, CHN), 1.37 (3H, d, J=6.6 Hz, Me), 1.35 (6H, m, $(CH_2)_3$), 0.92 (3H, t, J=6.9 Hz, $(CH_2)_3$*Me*), 0.90 (9H, s, CMe$_3$); δ_C (62.9 MHz; $CDCl_3$) 144.6, 128.2, 127.2, 126.2, 80.6, 69.6, 34.8, 30.4, 28.2, 27.4, 23.0, 22.1, 14.10; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.73 (1H, q, J=6.6 Hz, OCH); δ_C (62.9) MHz; $CDCl_3$) 144.2, 128.3, 127.1, 126.0, 80.3, 69.3, 34.4, 30.3, 27.9, 27.2, 22.8, 22.3, 14.05; *m/z* (CI) 264 (MH^+, 100%), 206 (44), 144 (10), 122 (10).

*2,2-Dimethyl-*N*-(1-phenylethoxy)-3-hex-5-enylamine* **5f**

Obtained by the addition of allylmagnesium bromide to (±)-**2b** (62%, d.e. 44%) as a colourless oil, (Found: M^+, 247.1923. $C_{16}H_{25}NO$ requires M, 247.1936); υ_{max}(film)/cm^{-1} 2979, 1650, 1451, 1365; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.20 (5H, m, ArH), 5.87 (1H, m, CH=), 5.4 (1H, broad s, NH), 5.01 (2H, m, =CH_2), 4.74 (1H, q, J=6.6 Hz, OCH), 2.52 (1H, dd, J=5.0 and 7.6 Hz, CHN), 2.34 (2H, m, C*H*$_2$CH=CH_2), 1.43 (3H, d, J=6.6 Hz, Me), 0.96 (9H, s, CMe$_3$); δ_C (62.9 MHz; $CDCl_3$) 144.0, 137.7, 128.2, 127.20, 126.2, 116.1, 80.14, 66.6, 34.5, 32.52, 27.6, 22.0; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 2.62 (1H, dd, J=5.0 and 7.6 Hz, CHN), 1.41 (3H, d, J=6.6 Hz, Me), 0.99 (9H, s, CMe$_3$); δ_C (62.9 MHz; $CDCl_3$) 144.2, 137.5, 128.3, 127.16, 126.0, 116.9, 68.3, 34.7, 27.3, 22.4; *m/z* (EI) 248 (MH^+, 12%), 190 (20), 105 (100), 86 (77), 77 (23), 69 (11), 57 (25), 51 (11), 41 (49), 29 (21).

*2-Methyl-*N*-(1-phenylethoxy)-3-heptylamine* **5g**

Obtained by the addition of *n*-butyllithium to **2c** (83%, d.e. 77%) as a colourless oil, b.p. 120°C/4 mbar, (Found: MH^+, 250.2171. $C_{16}H_{27}NO$ requires MH, 250.2171); υ_{max}(film)/cm^{-1} 2959, 1455; δ_H (250 MHz; $CDCl_3$) 7.30 (5H, m, ArH), 5.29 (1H, broad s, NH), 4.71 (1H, q, J=6.5 Hz, OCH), 2.64 (1H, m, CHN), 1.92 (1H, septet, J=6.7 Hz, C*H*Me$_2$), 1.43 (3H, d, J=6.6 Hz, Me) 1.34 (6H, m, $(CH_2)_3$), 0.96 (3H, t, J=6.9 Hz, $(CH_2)_3$*Me*), 0.91 (3H, d, J=6.7 Hz, CH*Me*Me), 0.84 (3H, d, J=6.7 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) (major diastereomer) 143.9, 128.2, 127.2, 126.3, 80.5, 65.6, 29.0, 28.6, 27.68, 22.93, 21.8, 18.9, 17.8, 14.0; (minor diastereomer) δ_C (62.9 MHz; $CDCl_3$) 126.2, 80.8, 65.7, 29.1, 28.7, 22.85, 22.0, 17.7, 13.9; *m/z* (CI) 250 (MH^+, 26%), 234 (4), 130 (100), 86 (8).

*2-Methyl-*N*-(1-phenylethoxy)-3-hex-5-enylamine* **5h**

Obtained by the addition of allylmagnesium bromide to **2c** (70%, d.e. 59%) as a colourless oil, (Found: MH^+, 234.1858. $C_{15}H_{23}NO$ requires MH, 234.1858); υ_{max}(film)/cm^{-1} 2975, 1650, 1454; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.18 (5H, m, ArH), 5.71 (1H, m, CH=), 5.1 (1H, broad s, NH), 4.97 (2H, m, =CH_2), 4.60 (1H, q, J=6.6 Hz, OCH), 2.56 (1H, m, CHN), 2.11 (2H, m, C*H*$_2$CH=CH_2), 1.76 (1H, septet, J=5.5 Hz, C*H*Me$_2$), 1.34 (3H, d, J=6.6 Hz, Me), 0.82 (3H, d, J=6.6 Hz, CH*Me*Me), 0.75 (3H, d, J=6.6 Hz,

CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 143.8, 136.3, 128.25, 127.3, 126.4, 116.7, 80.7, 65.1, 32.7, 28.5, 21.8, 19.1, 18.2; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 2.59 (1H, m, CHN), 1.32 (3H, d, J=6.6 Hz, Me), 0.83 (3H, d, J=6.6 Hz, CH*Me*Me), 0.76 (3H, d, J=6.6 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 143.9, 136.1, 128.31, 127.2, 126.1, 117.0, 80.8, 65.0, 32.0, 28.6, 21.0, 17.7; *m/z* (EI) 234 (MH^+, 100%), 192 (3), 122 (15), 114 (10).

N-*(1-Phenylethoxy)-2-hexylamine* **5i**

Obtained by the addition of *n*-butyllithium to **2d** (70 %, d.e. <5%) as a colourless oil, b.p. 105°C/1 mbar, (Found: MH^+, 222.1858. $C_{14}H_{23}NO$ requires MH, 222.1858); υ_{max}(film)/cm^{-1} 2959, 1453, 1370; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.30 (5H, m, ArH), 4.71 (1H, q, J=6.6 Hz, OCH), 2.96 (1H, m, CHN), 1.43 (3H, d, J=6.6 Hz, Me) 1.24 (6H, m, $(CH_2)_3$), 1.01 (3H, d, J=6.2 Hz, *Me*CHN), 0.91 (3H, t, J=6.9 Hz, $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 144.0, 128.4, 127.3, 126.3, 81.2, 56.13, 33.9, 28.2, 22.9, 22.01, 18.5, 14.1; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 1.09 (3H, d, J=6.2 Hz, *Me*CHN), 0.87 (3H, t, J=6.9 Hz, $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 143.9, 126.2, 81.1, 56.10, 33.6, 21.95, 18.0, 14.0; *m/z* (EI) 222 (MH^+, 41%), 105 (100), 60 (58), 43 (49).

N-*(1-Phenylethoxy)-2-pent-4-enylamine* **5j**

Obtained by the addition of allylmagnesium bromide to **2d** (58%, d.e. 14%) as a colourless oil, b.p. 120°C/0.5 mbar, (Found: MH^+, 206.1545. $C_{13}H_{19}NO$ requires MH, 206.1545); υ_{max}(film)/cm^{-1} 2975, 1645, 1452; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.29 (5H, m, ArH), 5.79 (1H, m CH=), 5.08 (2H, m, $=CH_2$), 5.0 (1H, broad s, NH), 4.72 (1H, q, J=6.6 Hz, OCH), 3.07 (1H, m, CHN), 2.25 (2H, m, $CH_2CH=CH_2$), 1.43 (3H, d, J=6.6 Hz, Me), 1.01 (3H, d, J=6.6 Hz, *Me*CHNH); δ_C (62.9 MHz; $CDCl_3$) 143.8, 135.4, 128.3, 127.3, 126.18, 117.0, 81.2, 55.4, 38.5, 21.9, 17.5; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.73 (1H, q, J=6.6 Hz, OCH), 1.44 (3H, d, J=6.6 Hz, Me), 1.09 (3H, d, J=6.6 Hz, *Me*CHNH); δ_C (62.9 MHz; $CDCl_3$) 135.1, 126.15, 117.2, 81.1, 55.6, 38.2, 22.0, 18.0; *m/z* (EI) 206 (MH^+, 4%), 164 (10), 105 (100), 60 (68).

*1-Phenyl-*N*-(1-phenylethoxy) but-3-enylamine hydrochloride* **5c.HCl**

To a solution of crude **5c** (1.12 g, 4.2 mmol) in ether (10 mL) was added HCl in ether (1M; 10 mL, 10 mmol). The precipitated gum was filtered and recrystallised (light petroleum-ether) to afford a single diastereomer of the *title compound* (0.47 g, 42%) as colourless crystals, m.p. 133-135°C, (Found: C, 71.23; H, 7.42; N, 4.85. $C_{18}H_{22}NOCl$ requires C, 71.25; H, 7.31; N, 4.62); υ_{max}(Nujol)/cm^{-1} 2924, 2478, 1579, 1452; δ_H (250 MHz; $CDCl_3$) 11.9 (2H, broad s, NH_2), 7.37 (10H, m, ArH), 5.45 (1H, q, J=6.2 Hz, OCH), 5.40 (1H, m, CH=), 4.99 (2H, m, $=CH_2$), 4.20 (1H, dd, J=11.2 and 4.5 Hz, CHN), 3.11 (1H, m, CH_2CH=Me), 2.96 (1H, m, $CH_2CH=CH_2$), 1.56 (3H, d, J=6.2 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 138.5, 132.1, 131.5, 129.6, 129.4, 128.9, 128.64, 128.58, 126.9, 119.2, 83.0, 65.4, 34.0, 21.3; *m/z* (EI) 226 (13%), 131 (16), 122 (58), 105 (100), 77 (55), 65 (10), 51 (34), 39 (27).

Preparation of O*-(1-Phenylethyl) Ketoxime Ethers*

O*-(1-Phenylethyl) valerophenone oxime* **6a**

To a round bottomed flask fitted with a nitrogen inlet were added valerophenone (0.59 g, 3.65 mmol) and ethanol (10 mL), the solution was then cooled to 0°C. (±)-O-(1-Phenylethyl)hydroxylamine **1** (0.50 g, 3.65 mmol) was then added dropwise. The solution was allowed to warm to room temperature and was stirred for 12 h. The ethanol was removed under reduced pressure and the residue partitioned between water (10 mL) and dichloromethane (10 mL). The mixture was separated and the aqueous portion was washed with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (20 mL) and dried ($MgSO_4$). Filtration and evaporation gave the *title compound* **6a** (0.985 g, 96%, E:Z 100:0) as a colourless oil,

(Found: MH^+, 282.1858. $C_{19}H_{23}NO$ requires MH, 282.1858); υ_{max}(film)/cm^{-1} 2958, 1451; δ_H (250 MHz; $CDCl_3$) 7.60 (2H, m, ArH), 7.34 (8H, m, ArH), 5.36 (1H, q, J=6.6 Hz, OCH), 2.82 (2H, dd, J=7 and 8.4 Hz, CH_2C=N), 1.62 (3H, d, J=6.6 Hz, Me), 1.50 (4H, m, $(CH_2)_2$), 0.94 (3H, t, J=7.2 Hz $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 158.5, 143.7, 136.9, 128.9, 128.3, 128.2, 127.3, 126.33, 126.25, 81.1, 28.7, 26.4, 22.9, 22.2, 13.9; *m/z* (CI) 282 (MH^+, 100), 162 (37), 122 (18), 105 (18).

Similarly prepared were the following:-

1-*Phenyl*-O-*(1-phenylethyl)*-1-*but-3-enone oxime* **6b**
(89%, E:Z 100:0) as a colourless oil, (Found MH^+, 266.1545. $C_{18}H_{19}NO$ requires MH, 266.1545); υ_{max}(film)/cm^{-1} 2978, 1645, 1445; δ_H (250 MHz; $CDCl_3$) 7.59 (2H, m, ArH), 7.34 (8H, m, ArH), 5.91 (1H, m, CH=), 5.38 (1H, q, J=6.6 Hz, OCH), 5.12 (2H, m, $=CH_2$) 3.57 (2H, m, CH_2C=N), 1.61 (3H, d, J=6.6 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 155.2, 143.6, 146.9, 132.5, 129.0, 128.31, 128.25, 127.3, 126.34, 126.26, 117.0, 81.3, 31.7, 22.2; *m/z* (CI) 266 (MH^+, 100%), 146 (23), 122 (16), 105 (8), 74 (9).

2,2-Dimethyl-O-*(1-phenylethyl)-3-heptanone oxime* **6c**
(50%, E:Z 100:0) as a colourless oil, (Found: MH^+, 262.2171. $C_{17}H_{27}NO$ requires MH, 262.2171); υ_{max}(film)/cm^{-1} 2965, 1454, 1365; δ_H (250 MHz; $CDCl_3$) 7.35 (5H, m, ArH), 5.21 (1H, q, J=6.6 Hz, OCH), 2.60 (2H, m, CH_2-C=N), 1.55 (3H, d, J=6.6 Hz, Me), 1.55 (2H, m, CH_2), 1.37 (2H, m, CH_2), 1.11 (9H, s, CMe_3), 0.98 (3H, t, J=7.2 Hz $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 166.5, 144.2, 128.0, 126.7, 126.1, 80.0, 37.5, 28.9, 27.8, 26.1, 23.5, 22.1, 13.8; *m/z* (CI) 262 (MH^+, 100%), 248 (9), 142 (20), 122 (17), 105 (23).

2,2-Dimethyl-O-*(1-phenylethyl)-3-hex-5-enone oxime* **6d**
(97%, E:Z 100:0) as a colourless oil, b.p. 120°C/2 mbar, (Found: MH^+, 246.1858. $C_{16}H_{23}NO$ requires MH, 246.1858); υ_{max}(film)/cm^{-1} 2971, 1648, 1454, 1363; δ_H (250 MHz; $CDCl_3$) 7.27 (5H, m, ArH), 5.92 (1H, m, CH=), 5.17 (1H, q, J=6.6 Hz, OCH), 5.03 (2H, m, $=CH_2$), 3.09 (2H, m, CH_2C=N), 1.52 (3H, d, J=6.6 Hz, Me), 1.07 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 163.2, 143.8, 133.7, 128.0, 127.0, 126.2, 116.1, 80.2, 37.6, 31.0, 27.9, 22.0; *m/z* (CI) 246 (MH^+, 100%), 105 (6).

2-Methyl-O-*(1-phenylethyl)-3-heptanone oxime* **6e**
(99%, E:Z 76:24) as a colourless oil, (Found: MH^+, 248.2014. $C_{16}H_{25}NO$ requires MH, 248.2014); υ_{max}(film)/cm^{-1} 2964, 1467, 1365, 1084; (E isomer) δ_H (250 MHz; $CDCl_3$) 7.24 (5H, m, ArH), 5.13 (1H, q, J=6.6 Hz, OCH), 2.41 (1H, septet, J=6.9 Hz, C*H*Me_2), 2.25 (2H, m, CH_2C=N), 1.47 (3H, d, J=6.6 Hz, Me), 1.37 (4H, m, $(CH_2)_2$), 1.01 (3H, d, J=6.9 Hz, CH*Me*Me), 1.00 (3H, d, J=6.9 Hz, CHMe*Me*), 0.85 (3H, t, J=7.2 Hz $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 165.1, 144.0, 128.0, 127.0, 126.1, 80.0, 33.6, 28.5, 26.7, 23.2, 22.2, 20.2, 13.8; (Z isomer) δ_H (250 MHz; $CDCl_3$) 3.30 (1H, septet, J=6.9 Hz, C*H*Me_2), 2.07 (2H, m, CH_2C=N), 1.07 (3H, d, J=6.9 Hz, CH*Me*Me), 1.06 (3H, d, J=6.9 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 164.7, 30.3, 29.0, 27.4, 22.5, 19.1, 19.0; *m/z* (CI) 248 (MH^+, 100%), 128 (29), 122 (12), 105 (20).

2-Methyl-O-*(1-phenylethyl)-3-hex-5-enone oxime* **6f**
(79%, E:Z 79:21) as a colourless oil (Found: MH^+, 232.1701. $C_{16}H_{23}NO$ requires MH, 232.1701); υ_{max}(film)/cm^{-1} 2957, 1622, 1443; (E isomer) δ_H (250 MHz; $CDCl_3$) 7.27 (5H, m, ArH), 5.88 (1H, m, CH=), 5.19 (1H, q, J=6.6 Hz, OCH), 5.07 (2H, m, $=CH_2$), 3.08 (2H, m, CH_2C=N), 2.48 (1H, septet, J=6.9 Hz, C*H*Me_2), 1.51 (3H, d, J=6.6 Hz, Me), 1.05 (3H, d, J=6.9 Hz, CH*Me*Me), 1.04 (3H, d, J=6.9 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 161.9, 134.9, 133.0, 128.06, 127.0, 126.1, 116.6, 80.2, 33.6, 31.8, 22.2, 20.10, 20.05; (Z isomer) δ_H (250 MHz; $CDCl_3$) 3.36 (1H, septet, J=6.9 Hz, C*H*Me_2), 2.89 (2H, m,

CH_2-C=N), 1.09 (3H, d, *J*=6.9 Hz, CH*Me*Me), 1.07 (3H, d, *J*=6.9 Hz, CHMe*Me*); δ_C (62.9 MHz; $CDCl_3$) 128.13, 127.1, 126.2, 35.3, 27.6, 19.0, 18.96; *m/z* (CI) 232 (MH^+, 62%), 105 (100), 77 (4).

O-*(1-Phenylethyl)-2-hexanone oxime* **6g**
(85%, E:Z 60:40) as a colourless oil, (Found: MH^+, 220.1701. $C_{14}H_{21}NO$ requires MH, 220.1701); υ_{max}(film)/cm^{-1} 2959, 1453; (E isomer) δ_H (250 MHz; $CDCl_3$) 7.29 (5H, m, ArH), 5.21 (1H, q, *J*=6.6 Hz, OCH), 2.14 (2H, m, CH_2C=N), 1.90 (3H, s, MeC=N), 1.53 (3H, d, *J*=6.6 Hz, Me), 1.32 (4H, m, $(CH_2)_2$), 0.88 (3H, t, *J*=7.2 Hz $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 157.8, 144.3, 128.14, 127.05, 126.03, 80.03, 35.5, 28.6, 22.4, 22.2, 14.1, 13.8; (Z isomer) δ_H (250 MHz; $CDCl_3$) 5.22 (1H, q, *J*=6.6 Hz, OCH), 2.42 (2H, m, CH_2C=N), 1.85 (3H, s, MeC=N), 1.54 (3H, d, *J*=6.6 Hz, Me), 1.45 (4H, m, $(CH_2)_2$), 0.99 (3H, t, *J*=7.2 Hz $(CH_2)_3$*Me*); δ_C (62.9 MHz; $CDCl_3$) 158.3, 144.1, 127.0, 126.00, 80.01, 29.1, 27.8, 22.7, 22.4, 19.9, 13.9; *m/z* (CI) 220 (MH^+, 100%), 122 (12), 116 (8), 105 (19), 100 (39).

Reduction of O-*(1-Phenylethyl) Ketoximes*

1-Phenyl-N-*(1-phenylethoxy)-1-pentylamine* **5a**
To a dry round bottomed flask and pressure equalising dropping funnel were added ketoxime ether **6a** (0.281 g, 1 mmol), methanol (15 mL), bromocresol green (5 drops) and sodium cyanoborohydride (0.095 g, 1.5 mmol). Methanolic HCl was added *via* the dropping funnel to keep the solution acidic. The reaction mixture was stirred at room temperature for 2 h and was monitored by TLC. If the starting material had not been consumed then more reducing agent (1.5 mmol) was added. The reaction was quenched with water (1 mL) and the solvent removed *in vacuo*. The residue was partitioned between water (10 mL) and dichloromethane (10 mL) and the layers separated. The aqueous portion was washed with dichloromethane (2 x 10 mL) and the combined organic extracts were washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude mixture was purified by column chromatography on silica gel with dichloromethane-light petroleum (1:2) as eluent to furnish the title compound (0.150 g, 53%, d.e. 19%) as a colourless oil with identical spectroscopic properties as the *alkoxyamine* **5a** prepared by the addition of *n*-butyllithium to the aldoxime **2a**.

Similarly were prepared the following:-

2,2-Dimethyl-N-*(1-phenylethoxy)-3-heptylamine* **5e**
Obtained from the reduction of ketoxime ether **6c** (65%, d.e. ~10%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **5e** prepared by the addition of *n*-butyllithium to the aldoxime **2b**.

2-Methyl-N-*(1-phenylethoxy)-3-heptylamine* **5g**
Obtained from the reduction of ketoxime ether **6e** (56%, d.e. ~10%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **5g** prepared by the addition of *n*-butyllithium to the aldoxime **2c**.

N-*(1-Phenylethoxy)-2-hexylamine* **5i**
Obtained from the reduction of the ketoxime ether **6g** (95%, d.e. ~5%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **5i** prepared by the addition of *n*-butyllithium to the aldoxime **2d**.

1-Phenyl-N-*(1-phenylethoxy) but-3-enylamine***5c**
Obtained from the reduction of ketoxime ether **6b** (45%, d.e. 12%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **5c** prepared by the addition of allylmagnesium bromide to the aldoxime **2a**.

2,2-Dimethyl-N-(1-phenylethoxy)-3-hex-5-enylamine **5f**
Obtained from the reduction of ketoxime ether **6d** (65%, d.e. <5%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **5f** prepared by the addition of allylmagnesium bromide to the aldoxime **2b**.

2-Methyl-N-(1-phenylethoxy)-3-hex-5-enylamine **5h**
Obtained from the reduction of ketoxime ether **6f** (53%, d.e. <5%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **5h** prepared by the addition of allylmagnesium bromide to the aldoxime **2c**.

1-Phenyl butylamine **8**
Zinc powder (3.86 g, 59 mmol) was added to a solution of the alkoxyamine **5a** (0.84 g, 2.96 mmol) in acetic acid (8 mL) and water (7 mL). The solution was placed in a sonic bath for 2 h at 40°C. The mixture was extracted with ether (2 x 20 mL), the aqueous phase was basified (pH >13) with saturated sodium carbonate solution and extracted with dichloromethane (3 x 30 mL). The dichloromethane was dried (K_2CO_3), filtered and evaporated to furnish the title compound **8** (0.4 g, 84%, e.e. 68%) as a colourless oil, $[\alpha]_D$ +8.7° (*c*=20.15, $CDCl_3$) (lit.,[4,25] $[\alpha]_D$ +14.1° (*neat*) for material with 85% e.e.; $[\alpha]_D$= +11.7° (c=1, $CHCl_3$) for materail with 92% e.e.). In order to recover the chiral alcohol, the ether extracts were washed, dried, and evaporated to give the crude 1-phenylethyl alcohol (87%), $[\alpha]_D$ = +42° (c=0.83, MeOH).

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