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Asymmetric synthesis of *N*-protected amino acids by the addition of organolithium carboxyl synthons to ROPHy/SOPHy-derived aldoximes and ketoximes †

Tracey S. Cooper,[a] Pierre Laurent,[a] Christopher J. Moody *[a] and Andrew K. Takle[b]

[a] *Department of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD*

[b] *Department of Medicinal Chemistry, Neurology and GI Centre of Excellence for Drug Discovery, GlaxoSmithKline Research & Development Ltd., New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW*

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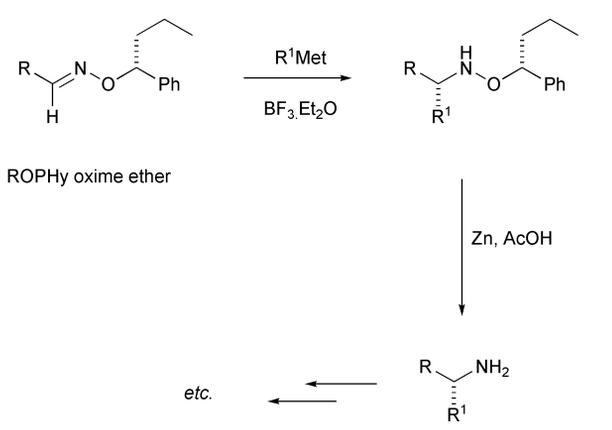
A new asymmetric synthesis of α-amino acids is described in which the key step is the highly diastereoselective addition of organolithium carboxyl synthons (2-furyllithium, phenyllithium, vinyllithium) to (*R*)- and (*S*)-*O*-(1-phenylbutyl) oximes **2** to give hydroxylamines **3**, with vinyllithium being the most satisfactory nucleophilic reagent. Subsequent reductive cleavage of the N–O bond in hydroxylamines **3**, followed by *N*-protection, and oxidative cleavage of the carboxyl precursor gave a range of *N*-protected amino acids and esters. The method was exemplified by the synthesis of a range of derivatives of non-proteinogenic amino acids such as 4-bromophenylalanine, *tert*-leucine, norvaline, cyclohexyl- and aryl-glycines, 2-amino-8-oxodecanoic acid (Aoda) and α-methylvaline.

Introduction

The development of new methodology for the asymmetric synthesis of α-amino acids, both natural and unnatural, continues to attract the attention of chemists worldwide.[2–9] Many of these methods involve stereoselective additions to C=N bonds,[10–16] and in this context we have recently reported the highly diastereoselective addition of organometallic reagents to the C=N bond of chiral oxime ethers to give non-racemic hydroxylamines.[17,18] This subsequently resulted in the development of oxime ethers derived from (*R*) and (*S*) *O*-(1-phenylbutyl)-hydroxylamines, which we term ROPHy and SOPHy by analogy with Enders' RAMP and SAMP hydrazones, as useful reagents for asymmetric synthesis, and their application in the asymmetric synthesis of chiral amines (Scheme 1).[1,17,18] The methodology has been applied to the asymmetric synthesis of various nitrogen containing compounds including the hemlock piperidine alkaloids (−)-coniine and (+)-pseudoconhydrine,[19] β-amino acids,[20] 1-(2-thiazolyl)ethylamines,[21] including the cytotoxic thiazole-containing peptide virenamide B,[22] and, in combination with ring-closing metathesis, a range of nitrogen heterocycles, including iminosugars.[1,23] We now report the details of a new route to α-amino acids based on the highly diastereoselective addition of organolithium carboxyl synthons to a range of *O*-(1-phenylbutyl) oximes.



Scheme 1

Results and discussion

In order to adapt our asymmetric synthesis of protected amines (Scheme 1) into a route to *N*-protected amino acids, two strategies were considered (Scheme 2). The first involved the use of an oxime ether **1** which incorporates the carboxylic acid precursor, R_A; addition of organometallic reagents, followed by cleavage of the N–O bond, and conversion of R_A into a carboxyl group would then give the required amino acid. Alternatively the carboxyl synthon can be added as an organometallic reagent, R_AMet (Scheme 2b), to the oxime ether **2**, the two routes being stereocomplementary, since one enantiomer of the 1-phenylbutyl auxiliary can give both enantiomers of the α-amino acid. The former strategy (Scheme 2a) has been the subject of a previous article,[24] and therefore we now report details of the second approach.

In order to investigate the viability of such an approach, a wide range of *O*-(1-phenylbutyl) oxime ethers was required. These were prepared by condensation of the relevant aldehyde or ketone with (*R*)- or (*S*)-*O*-(1-phenylbutyl)hydroxylamine, obtained by hydrazine hydrate cleavage of the corresponding *N*-phthaloyl derivatives, as previously described.[18] A range of oxime ethers **2** derived from aliphatic aldehydes (oximes **2a**–**2h**), a dialkyl ketone (oxime **2i**), aromatic aldehydes (oximes **2j**–**2m**), and two aromatic ketones (oximes **2n**, **2o**) was thus prepared (Table 1). The starting carbonyl compounds were chosen to provide a variety of substituents in the final α-amino acids, including α-methyl quaternary amino acids from the methyl ketoximes **2i**, **2n**, and **2o**, and naturally occurring non-proteinogenic α-amino acids such as 2-amino-8-oxodecanoic acid (Aoda) and 4-bromophenylalanine from the aldoxime ethers **2g** and **2h** respectively. The aldehyde starting material for oxime ether **2g** was prepared as shown in Scheme 3.

Several nucleophilic carboxyl synthons R_A were considered as suitable reagents to add to oxime ethers **2**. However, preliminary experiments quickly established that oxime ethers did not undergo addition of cyanide (in the form of Et_2AlCN)

† Chiral oxime ethers in asymmetric synthesis. Part 6.[1]

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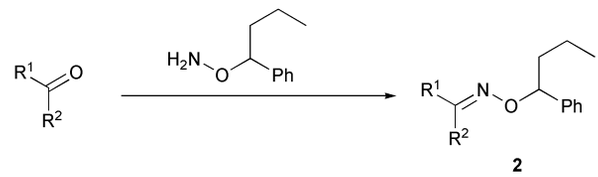
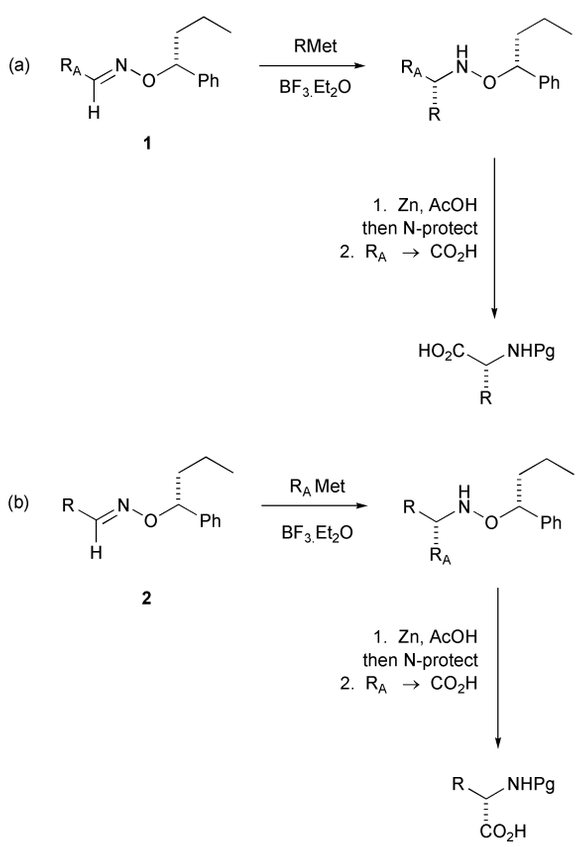
Table 1 Preparation of (*R*)- and (*S*)-*O*-(1-phenylbutyl) oximes **2**



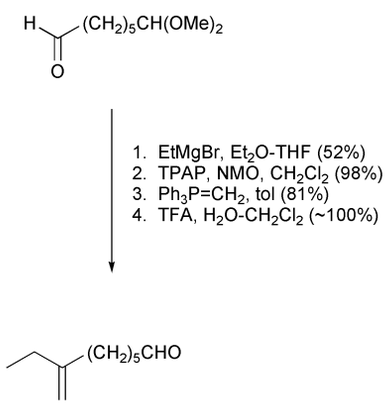
2

Oxime	R^1	R^2	Configuration	Yield/%
2a	*n*-Pr	H	*S*	73[a]
2b	*i*-Pr	H	*S*	57[b]
2c	$H_2C{=}CH(CH_2)_2$	H	*S*	56[c]
2d	*t*-Bu	H	*S*	93[d]
2e	CMe_2Et	H	*S*	33
2f	*c*-Hex	H	*S*	90[c]
2g	$EtC(=CH_2)(CH_2)_5$	H	*R*	47 (+36% *Z*-isomer)
2h	4-$BrC_6H_4CH_2$	H	*R*	40
2i(*S*)	*i*-Pr	Me	*S*	61
2i(*R*)	*i*-Pr	Me	*R*	68
2j	Ph	H	*S*	93[c]
2k	4-$MeOC_6H_4$	H	*R*	87[d]
2l	2,5-$Me_2C_6H_3$	H	*S*	93
2m	3-F,2-MeC_6H_3	H	*S*	94
2n	Ph	Me	*S*	48[d]
2o	4-BrC_6H_4	Me	*S*	30

[a] Ref. 19. [b] (*R*)-enantiomer described in ref. 20. [c] Ref. 20. [d] Ref. 18.



Scheme 2 [R_A = carboxylic acid precursor].



Scheme 3

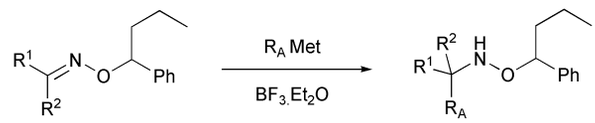
or acetylide (in the form of TMSC≡CLi) nucleophiles. For example, Et_2AlCN did not add to the pivaldehyde derived oxime ether **2d** under conditions reported to be successful for other C=N electrophiles.[13] Presumably this illustrates the poor reactivity of such oxime ethers to all but the most reactive nucleophiles, although in the case of **2d** there is additional steric hindrance. Therefore attention turned to other nucleophilic carboxyl synthons.

The group R_A that was chosen for initial study was the furan group, since 2-furyllithium is readily generated, and oxidation of the furan ring with a range of reagents has been reported to give the carboxylic acid.[25,26] The strategy has been used in the synthesis of carbohydrates,[27,28] and, more relevantly, in other routes to amino acids.[29,30] Thus 2-furyllithium was generated using a literature method,[30] and added to the oxime ether in toluene at −78 °C in the presence of boron trifluoride etherate according to our normal protocol.[1] The results were generally disappointing (Table 2, Entries 1–3); the aldoxime ether **2h** underwent addition of 2-furyllithium to give the hydroxylamine **3a** in modest yield (40%) and reasonable diastereomeric excess (de) (83%). However, the additions to the ketoxime ethers **2i(*S*)** and **2o** proceeded poorly, although the latter gave the hydroxylamine **3c** with excellent diastereocontrol. Additions to the aromatic aldoxime ethers **2j**–**2l** proved unsatisfactory.

The second organometallic carboxyl synthon investigated was phenyllithium. The benzene ring can be cleaved oxidatively to give a carboxylic acid, and this strategy has already found use in the synthesis of α-amino acids from chiral α-alkylbenzylamine derivatives.[14,31–34] Therefore phenyllithium was added to the aldoxime ethers **2b**, **2d** and **2e** under the usual conditions. The additions proceeded with excellent diastereoselectivity to give the hydroxylamines **3d**–**3f**, although the yields were poor (Table 2, Entries 4–6).

Finally the use of vinyl organometallic reagents as carboxyl synthons was investigated. Vinylmagnesium bromide (as supplied commercially in THF) did not add to the oxime ethers **2**,

Table 2 Addition of organolithium carboxyl synthons to oxime ethers **2** to give hydroxylamines **3**

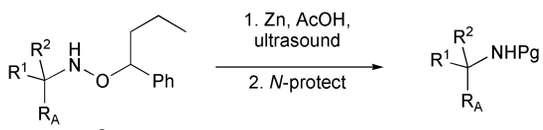


2 **3**

Entry	Oxime ether	R^1	R^2	R_A	Hydroxylamine	Configuration[a]	Yield/%	de/%[b]
1	**2h**	4-$BrC_6H_4CH_2$	H	2-furyl	**3a**	*S,R*	40	83
2	**2i(S)**	*i*-Pr	Me	2-furyl	**3b**	*R,S*	31	52
3	**2o**	4-BrC_6H_4	Me	2-furyl	**3c**	*R,S*	14	>95
4	**2b**	*i*-Pr	H	Ph	**3d**	*R,S*	38	95
5	**2d**	*t*-Bu	H	Ph	**3e**	*R,S*	31	>98
6	**2e**	CMe_2Et	H	Ph	**3f**	*R,S*	32	>98
7	**2a**	*n*-Pr	H	H_2C=CH	**3g**	*R,S*	87	84
8	**2c**	H_2C=$CH(CH_2)_2$	H	H_2C=CH	**3h**	*R,S*	77	94
9	**2f**	*c*-Hex	H	H_2C=CH	**3i**	*S,S*	74	92
10	**2g**	$EtC(=CH_2)(CH_2)_5$	H	H_2C=CH	**3j**	*S,R*	76	>95
11	**2i(R)**	*i*-Pr	Me	H_2C=CH	**3k**	*S,R*	54	>95
12	**2j**	Ph	H	H_2C=CH	**3l**	*S,S*	46	98
13	**2k**	4-$MeOC_6H_4$	H	H_2C=CH	**3m**	*R,R*	50	91
14	**2l**	2,5-$Me_2C_6H_3$	H	H_2C=CH	**3n**	*S,S*	16	95
15	**2m**	3-F,2-MeC_6H_3	H	H_2C=CH	**3o**	*S,S*	10	95
16	**2n**	Ph	Me	H_2C=CH	**3p**	*S,S*	10	64

[a] The configurations refer to the new chiral center, assigned on the basis of our previous work, and the starting chiral auxiliary respectively. [b] Determined from the ^{1}H-NMR spectrum of the crude hydroxylamine **3** before chromatography.

Table 3 Conversion of hydroxylamines **3** into *N*-protected amines **4**



3 **4**

Entry	Hydroxylamine	R^1	R^2	R_A	Amine	Pg	Configuration	Yield/%	ee/%[a]
1	**3a**	4-$BrC_6H_4CH_2$	H	2-furyl	**4a**	Boc	*S*	72	83
2	**3d**	*i*-Pr	H	Ph	**4b**	Ac	*R*	38	98
3	**3e**	*t*-Bu	H	Ph	**4c**	Ac	*R*	28	>98
4	**3f**	CMe_2Et	H	Ph	**4d**	Ac	*R*	6	>98
5	**3g**	*n*-Pr	H	H_2C=CH	**4e**	Cbz	*R*	89	nd
6	**3h**	H_2C=$CH(CH_2)_2$	H	H_2C=CH	**4f**	Cbz	*R*	53	nd
7	**3i**	*c*-Hex	H	H_2C=CH	**4g**	Cbz	*S*	52	nd
8	**3j**	$EtC(=CH_2)(CH_2)_5$	H	H_2C=CH	**4h**	Cbz	*S*	70	97
9	**3k**	*i*-Pr	Me	H_2C=CH	**4i**	Cbz	*S*	80	nd
10	**3l**	Ph	H	H_2C=CH	**4j**	Ac	*S*	9	90
11	**3m**	4-$MeOC_6H_4$	H	H_2C=CH	**4k**	CBz	*R*	85	nd

[a] Determined by HPLC on a chiral stationary phase by comparison with the racemate; nd = not determined at this stage—measured at amino ester stage in the case of **4e** and **4f**.

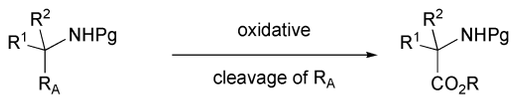
THF being known to be generally deleterious to such reactions. However vinyllithium, generated from tetravinyltin by the literature protocol,[35] added smoothly to a range of oxime ethers **2** to give the corresponding hydroxylamines **3g**–**3p**. With the exception of the aromatic oxime ethers **2l**–**2n**, the yields are acceptable, and for the most part, the diastereoselectivity of the addition reaction is good (Table 2, Entries 7–16). Hence vinyllithium proved the most satisfactory of the various organometallic carboxyl synthons investigated.

In all the addition reactions of organolithium reagents described in Table 2, the stereochemistry of the new chiral centre was assigned on the basis of our previous work, and, in some cases, by the subsequent conversion of the hydroxylamines **3** into α-amino acids of known configuration (see below). The diastereoselectivity of the addition was determined from the ^{1}H-NMR spectrum of the crude hydroxylamine product before chromatography. No attempt was made to investigate other auxiliaries (*cf.* ref. 18) even in cases where the addition reaction failed.

With a range of chiral hydroxylamines **3** containing a carboxylic acid precursor, R_A, in hand, their conversion into α-amino acid derivatives was undertaken. This was achieved by initial cleavage of the N–O bond using our previously described zinc/acetic acid/ultrasound method, and was exemplified for the furan derivative **3a**, the phenyl derivatives **3d**–**3f**, and the vinyl derivatives **3g**–**3m**. The resulting amines were not isolated but were immediately converted into their *tert*-butyl or benzyl carbamates or *N*-acetyl derivatives by reaction with di-*tert*-butyl dicarbonate, benzyl chloroformate or acetic anhydride respectively. The *N*-protected amines **4** were isolated in varying yield (Table 3), and their enantiomeric purity established by comparison with the independently synthesized racemate by HPLC on a chiral stationary phase.

The conversion of the R_A substituent in the *N*-protected amines **4** into a carboxylic acid (or ester) was carried out under standard oxidative conditions. Thus the furan ring in **4a** was oxidatively cleaved using Ru(VIII),[25,30] to give *N*-Boc 4-bromophenylalanine **5a** in modest yield. Likewise the phenyl ring in **4c**

Table 4 Oxidative cleavage of the R_A group in amines **4** to give amino acids **5**



4 **5**

Entry	Amine	R_A	Method[a]	Amino acid	R^1	R^2	Pg	R	Configuration	Yield/%
1	**4a**	2-furyl	A	**5a**	4-$BrC_6H_4CH_2$	H	Boc	H	*S*	33
2	**4c**	Ph	B	**5b**	*t*-Bu	H	Ac	H	*R*	63[b]
3	**4e**	H_2C=CH	C	**5c**	*n*-Pr	H	Cbz	Me	*R*	59[c]
4	**4f**	H_2C=CH	C	**5d**	$MeO_2CCH_2CH_2$	H	Cbz	Me	*R*	40[d]
5	**4g**	H_2C=CH	C	**5e**	*c*-Hex	H	Cbz	Me	*R*	70
6	**4h**	H_2C=CH	B	**5f**	$EtCO(CH_2)_5$	H	Cbz	H	*S*	39
7	**4i**	H_2C=CH	B	**5g**	*i*-Pr	Me	Cbz	H	*S*	38
8	**4j**	H_2C=CH	A	**5h**	Ph	H	Ac	H	*R*	24
9	**4k**	H_2C=CH	C	**5i**	4-$MeOC_6H_4$	H	Cbz	Me	*S*	58

[a] Method A: $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O; Method B: $RuCl_3$, H_5IO_6, CCl_4–MeCN–H_2O; Method C: O_3, NaOH, MeOH, CH_2Cl_2, −78 °C. [b] This conversion is reported for the (*S*)-enantiomer in ref. 14. [c] 86% ee as determined by HPLC. [d] 93% ee as determined by HPLC.

was cleaved with Ru(VIII) to give *N*-acetyl *tert*-leucine **5b** in 63% yield; this transformation has previously been reported for the (*S*)-enantiomer.[14] The vinyl groups in amines **4e**–**4k** were cleaved to the carboxylic acid using Ru(VIII) or using Marshalls' ozonolysis procedure which leads directly to the methyl ester.[36] Hence the vinyl compounds **4e**, **4g** and **4k** were ozonized in a mixture of methanolic sodium hydroxide and dichloromethane to give the corresponding *N*-Cbz methyl esters of the amino acids norvaline **5c**, cyclohexylglycine **5e** and 4-methoxyphenylglycine **5i** in reasonable yield (Table 3, Entries 3, 5, 9). Similar treatment of amine **4f** resulted in cleavage of both double bonds and the formation of dimethyl *N*-Cbz glutamate **5d** (Table 3, Entry 4). The double bonds in amines **4h**–**4j** were cleaved using Ru(VIII) to give the carboxylic acids **5f**–**5h** (Table 3, Entries 6–8). Oxidation of **4h** gave *N*-Cbz 2-amino-8-oxodecanoic acid (Aoda) **5f**, a component of the cyclic peptide apicidin,[37] in modest yield, whereas similar oxidation of **4i** gave the *N*-protected quaternary amino acid, α-methylvaline **5g**. Finally Ru(VIII) oxidation of **4j** gave *N*-acetylphenylglycine **5h** in poor yield, possible due to competing oxidation of the phenyl ring. The oxidative cleavage reactions are summarized in Table 4, and the amino acid derivatives thus obtained are shown in Fig. 1.

Thus we have extended the use of chiral ROPHy and SOPHy derived oximes in the asymmetric synthesis of α-amino acids, and exemplified their use by the synthesis of a range of derivatives of non-proteinogenic amino acids such as 4-bromophenylalanine, *tert*-leucine, norvaline, cyclohexyl- and aryl-glycines, 2-amino-8-oxodecanoic acid (Aoda) and α-methylvaline. The method complements other approaches to the asymmetric synthesis of α-amino acids by addition of nucleophiles to C=N bonds.

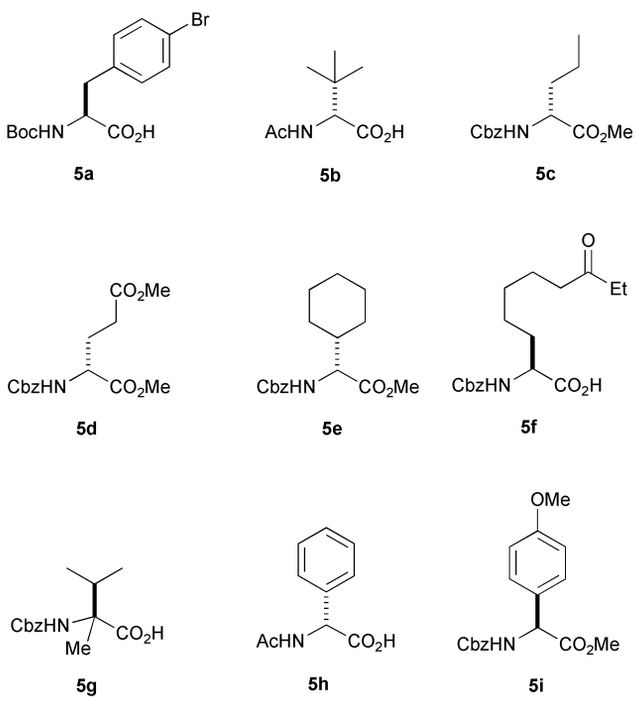


Fig. 1

Experimental

For general experimental details, see ref. 1. Hydroxylamines **3** were characterized as diastereomeric mixtures; the NMR data refer to the major diastereomer.

General procedure for the preparation of oxime ethers 2

A suspension of (*R*)- or (*S*)-*N*-(1-phenylbutoxy)phthalimide[18] (3.0 g, 10.17 mmol) in ethanol (50 mL) was heated until the phthalimide dissolved. Hydrazine hydrate (0.6 mL, 12.4 mmol) was added at this elevated temperature and the reaction mixture was heated under reflux for a further 1 h. The solution was then allowed to cool to room temperature. The aldehyde or ketone (12 to 30 mmol) was added at room temperature and the reaction mixture stirred overnight. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel (eluting with ether–light petroleum (1 : 20) unless otherwise stated).

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)butyraldehyde oxime 2a. Prepared as described previously.[19]

(*E*)-(*S*)-(+)-*O*-(1-Phenylbutyl)isobutyraldehyde oxime 2b. Prepared as described previously for the (*R*)-enantiomer.[20]

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)pent-4-enaldehyde oxime 2c. Prepared as described previously.[20]

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)pivaldedehyde oxime 2d. Prepared as described previously.[18]

(*E*)-(*S*)-(+)-*O*-(1-Phenylbutyl)-2,2-dimethylbutyraldehyde oxime 2e. Obtained from the condensation of (*S*)-*O*-(1-phenylbutyl)hydroxylamine with 2,2-dimethylbutyraldehyde as a colourless oil (33%); $[\alpha]_D^{24}$ +16.0 (*c* 1.24, $CHCl_3$); (Found: MH^+, 248.2015. $C_{16}H_{25}NO$ + H requires 248.2014); ν_{max}(film)/

cm^{-1} 2955, 2868, 1444, 1024, 927, 697; δ_H (300 MHz; $CDCl_3$) 7.35–7.27 (6 H, m, ArH, HC=N), 5.07 (1 H, t, *J* 6.9, OCH), 1.95 (1 H, m, C*H*H), 1.73 (1 H, m, CH*H*), 1.40 (4 H, m, CH_2), 1.03 (3 H, s, Me), 1.01 (3 H, s, Me), 0.95 (3 H, t, *J* 7.4, Me), 0.76 (3 H, t, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$) 157.9 (CH), 142.5 (C), 128.0 (CH), 127.1 (CH), 126.8 (CH), 84.3 (CH), 38.1 (CH_2), 36.7 (C), 33.5 (CH_2), 25.0 (Me), 24.6 (Me), 18.8 (CH_2), 14.0 (Me), 8.5 (Me); *m*/*z* (CI) 248 (MH^+, 100%), 166 (8), 150 (36), 132 (3), 115 (25), 108 (7), 100 (53).

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)cyclohexanecarboxaldehyde oxime 2f. Prepared as described previously.[20]

(*E*)-(*R*)-(−)-*O*-(1-Phenylbutyl)-7-ethyloct-7-enaldehyde oxime 2g. (a) 7,7-Dimethoxyheptanal[38] (5.5 g, 31.6 mmol) was dissolved in THF (150 mL) under nitrogen and cooled to 0 °C. Ethylmagnesium bromide (3 M in ether; 21 mL, 63.2 mmol) was added dropwise at this temperature, and the mixture stirred until all starting material was consumed. The reaction mixture was quenched at this temperature with aqueous saturated ammonium chloride solution (50 mL), and allowed to warm to room temperature. The mixture was extracted with ether (3 × 50 mL), combined, dried (K_2CO_3), filtered and evaporated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate–light petroleum (1 : 5) to give 9,9-dimethoxynonan-3-ol (3.355 g, 52%) as a colourless oil; δ_H (300 MHz; $CDCl_3$) 4.35 (1 H, t, *J* 5.7, C*H*($OMe)_2$), 3.51 (1 H, m, C*H*OH), 3.31 (6 H, s, CH(O*Me*)$_2$), 1.59–1.30 (12 H, m, 6 × CH_2), 0.93 (3 H, t, *J*7.4, CH_2*Me*).

Solid TPAP (289 mg, 5 mol%, 0.82 mmol) was added in one portion to a stirred mixture of the above alcohol (3.355 g, 16.42 mmol), NMO (2.885 g, 24.63 mmol) and powdered 4 Å molecular sieves (8 g) in dry dichloromethane (33 mL) at room temperature under nitrogen. On completion (2 h monitored by TLC) the reaction mixture was filtered through a short pad of silica, eluting with ethyl acetate. The filtrate was evaporated to give crude 9,9-dimethoxynonan-3-one as a colourless oil (3.243 g, 98%) which was used without further purification; ν_{max}(film)/cm^{-1} 2981, 2940, 2858, 2827, 1711, 1455, 1414, 1373, 1194, 1132, 1050, 958, 738; δ_H (300 MHz; $CDCl_3$) 4.34 (1 H, t, *J* 5.7, C*H*($OMe)_2$), 3.30 (6 H, s, CH(O*Me*)$_2$), 2.41 (4 H, m, CH_2(CO)CH_2), 1.57 (4 H, m, 2 × CH_2), 1.32 (4 H, m, 2 × CH_2), 1.04 (3 H, t, *J* 7.4, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 211.9 (C), 104.6 (CH), 52.8 (Me), 42.4 (CH_2), 36.1 (CH_2), 32.5 (CH_2), 29.3 (CH_2), 24.6 (CH_2), 24.0 (CH_2), 8.0 (Me).

(b) Methyltriphenylphosphonium bromide (14.565 g, 40.77 mmol) was dissolved in toluene (90 mL) under nitrogen and cooled to 0 °C. *n*-Butyllithium (1.6 M in hexane; 25.5 mL, 40.77 mmol) was added dropwise at this temperature and allowed to warm to room temperature for 30 min and then cooled to 0 °C. This solution was slowly added to a solution of 9,9-dimethoxynonan-3-one (2.750 g, 13.59 mmol) in toluene (55 mL) under nitrogen at 0 °C. The reaction was the allowed to warm to room temperature and stirred for 5 h and acetone (50 mL) was added to quench the reaction. The solution was filtered through a short pad of silica, eluting with ethyl acetate. The residue was purified by column chromatography on silica gel eluting with ethyl acetate–light petroleum (1 : 9) to give 8,8-dimethoxy-2-ethyloct-1-ene (2.196 g, 81%) as a colourless oil; ν_{max}(film)/cm^{-1} 3068, 2935, 2853, 2827, 1644, 1455, 1383, 1358, 1194, 1122, 1076, 1046, 963, 886; δ_H (300 MHz; $CDCl_3$) 4.68 (2 H, br, =CH_2), 4.36 (1 H, t, *J* 5.7, C*H*($OMe)_2$), 3.31 (6 H, s, CH(O*Me*)$_2$), 2.00 (4 H, m, 2 × CH_2), 1.64–1.21 (8 H, m, 4 × CH_2), 1.02 (3 H, t, *J*7.5, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 151.8 (C), 107.7 (CH_2), 104.7 (CH), 52.8 (Me), 36.4 (CH_2), 32.7 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 28.0 (CH_2), 24.7 (CH_2), 12.6 (Me); a satisfactory mass spectrum could not be obtained.

(c) 8,8-Dimethoxy-2-ethyloct-1-ene (2.180 g, 10.88 mmol) was dissolved in chloroform (60 mL) and aqueous trifluoroacetic acid (50%, 30 mL) was added at 0 °C and then the reaction was allowed to warm to rt. After 5 h, the solution was diluted in dichloromethane (130 mL) and carefully washed successively with a saturated solution of sodium hydrogen carbonate (40 mL), brine (50 mL), water (50 mL) and dried (K_2CO_3), filtered and evaporated to give 7-ethyloct-7-enal (quantitative yield) as an oil which was not further purified for the next step; ν_{max}(film)/cm^{-1} 3078, 2966, 2935, 2853, 2715, 1716, 1639, 1460, 1368, 1214, 1158, 1117, 881; δ_H (300 MHz; $CDCl_3$) 9.77 (1 H, t, *J* 1.7, CHO), 4.70 (1 H, br s, =C*H*H), 4.69 (1 H, br s, =CH*H*), 2.44 (2 H, dt, *J* 7.3, 1.7, CH_2CHO), 2.01 (4 H, m, CH_2C(=CH_2)CH_2), 1.64 (2 H, m, CH_2), 1.51–1.27 (4 H, m, 2 × CH_2), 1.02 (3 H, t, *J* 7.5, Me).

The crude aldehyde was condensed with (*R*)-*O*-(1-phenylbutyl)hydroxylamine (7.12 mmol) according to the general method to give the *title compound* (1.005 g, 47%) as a colourless oil; $[a]_D^{23}$ −29.2 (*c* 1.30, $CHCl_3$); (Found: M^+, 301.2408. $C_{20}H_{31}NO$ requires 301.2405); ν_{max}(film)/cm^{-1} 3088, 3063, 3032, 2960, 2930, 2873, 2855, 1644, 1496, 1450, 1363, 1107, 1061, 1025, 974, 917, 887, 758, 697; δ_H (300 MHz; $CDCl_3$) 7.42 (1 H, *J* 6.3, N=CH), 7.29 (5 H, m, ArH), 5.01 (1 H, t, *J* 6.9, OCH), 4.68 (1 H, d, *J* 1.0, C*H*H=), 4.66 (1 H, d, *J* 1.0, CH*H*=), 2.13 (2 H, q, *J* 7.1, CH_2), 2.06–1.83 (5 H, m, 2 × CH_2, C*H*H), 1.69 (1 H, m, CH*H*), 1.50–1.19 (8 H, m, 4 × CH_2), 1.01 (3 H, t, *J* 7.4, Me), 0.92 (3 H, t, *J* 7.4, Me); δ_C (75 MHz; $CDCl_3$) 151.4 (C), 151.2 (CH), 142.7 (C), 128.2 (CH), 127.2 (CH), 126.7 (CH), 107.5 (CH_2), 84.5 (CH), 38.4 (CH_2), 36.2 (CH_2), 29.4 (CH_2), 28.73 (CH_2), 28.68 (CH_2), 27.4 (CH_2), 26.6 (CH_2), 18.9 (CH_2), 14.0 (Me), 12.4 (Me); *m*/*z* (EI) 301 (M^+, 3%), 284 (54), 272 (48), 258 (26), 134 (98), 107 (42), 92 (100), 77 (44), 55 (50).

Also obtained was *(Z)-(R)-(−)-7-O-(1-phenylbutyl)-7-ethyloct-7-enaldehyde oxime* as a colourless oil (0.770 g, 36%); ν_{max}(film)/cm^{-1} 3088, 3063, 3032, 2960, 2930, 2873, 2855, 1644, 1496, 1450, 1363, 1107, 1061, 1025, 974, 917, 887, 758, 697; δ_H (300 MHz; $CDCl_3$) 7.29 (5 H, m, ArH), 6.61 (1 H, *J* 5.5, CHN), 5.04 (1 H, t, *J* 6.8, OCH), 4.70 (2 H, m, CH_2), 2.40 (2 H, m, CH_2), 2.07–1.84 (5 H, m, 2 × CH_2, C*H*H), 1.71 (1 H, m, CH*H*), 1.54–1.23 (8 H, m, 4 × CH_2), 1.03 (3 H, t, *J* 7.4, Me), 0.93 (3 H, t, *J* 7.4, Me); δ_C (75 MHz; $CDCl_3$) 152.0 (CH), 151.4 (C), 143.1 (C), 128.2 (CH), 127.2 (CH), 126.4 (CH), 107.6 (CH_2), 84.8 (CH), 38.6 (CH_2), 36.1 (CH_2), 29.1 (CH_2), 28.71 (CH_2), 27.5 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 18.9 (CH_2), 14.0 (Me), 12.4 (Me).

(*E*)-(*R*)-(−)-*O*-(1-Phenylbutyl)-4-bromophenylacetaldehyde oxime 2h. Obtained from the condensation of (*R*)-*O*-(1-phenylbutyl)hydroxylamine with 4-bromophenylacetaldehyde as a colourless oil (40%); $[a]_D^{24}$ −32.6 (*c* 1.4, CH_2Cl_2); (Found: MH^+, 346.0811. $C_{18}H_{20}{}^{79}BrNO$ + H requires 346.0807); ν_{max}(film)/cm^{-1} 3028, 1488, 1452, 1358, 1307, 1200; δ_H (300 MHz; $CDCl_3$) 7.50 (1 H, t, *J* 6.6, HC=N), 7.40 (2 H, d, *J* 8.5, ArH), 7.38–7.26 (5 H, m, ArH), 6.98 (2 H, d, *J* 8.5, ArH), 5.10 (1 H, t, *J* 6.9, OCH), 3.40 (2 H, d, *J* 6.6, CH_2PhBr), 1.93 (1 H, m, C*H*H), 1.74 (1 H, m, CH*H*), 1.41 (2 H, m, CH_2), 0.97 (3 H, t, *J* 7.3, Me); δ_C (75 MHz; $CDCl_3$) 148.7 (CH), 142.7 (C), 137.3 (C), 135.5 (C), 131.7 (CH), 130.5 (CH), 128.3 (CH), 127.4 (CH), 126.7 (CH), 84.9 (CH), 38.3 (CH_2), 35.3 (CH_2), 18.9 (CH_2), 14.0 (Me); *m*/*z* (CI) 346/344 (MH^+, 28%), 268 (8), 217 (6), 200 (28), 168 (18), 150 (100), 137 (3), 120 (18), 108 (6), 91 (1).

(*E*)-(*S*)-(+)-*O*-(1-Phenylbutyl)-3-methylbutan-2-one oxime 2i(S). Obtained from the condensation of (*S*)-*O*-(1-phenylbutyl)hydroxylamine with 3-methylbutan-2-one as a pale yellow oil (61%); $[a]_D^{23}$ +38.7 (*c* 1.06, $CHCl_3$); (Found: MH^+, 234.1861. $C_{15}H_{23}NO$ + H requires 234.1858); ν_{max}(film)/cm^{-1} 3032, 2960, 1449, 1372, 1234, 1034, 922, 758, 702; δ_H (300 MHz; $CDCl_3$) 7.36–7.22 (5 H, m, ArH), 5.04 (1 H, t, *J* 6.7, OCH), 2.45 (1 H, heptet, *J* 6.8, C*H*($Me)_2$), 1.89 (1 H, m, C*H*H), 1.84 (3 H, s, Me), 1.72 (1 H, m, CH*H*), 1.37 (2 H, m, CH_2), 1.03 (3 H, d, *J* 6.8,

Me), 1.00 (3 H, d, *J* 6.8, Me), 0.92 (3 H, t, *J* 7.4, Me); δ_C (75 MHz; $CDCl_3$) 161.2 (C), 143.3 (C), 128.0 (CH), 126.9 (CH), 126.4 (CH), 84.1 (CH), 38.7 (CH_2), 34.1 (CH), 19.9 (Me), 19.8 (Me), 18.8 (CH_2), 14.1 (Me), 11.1 (Me); *m*/*z* (CI) 234 (MH^+, 100%), 150 (2), 125 (1), 108 (3), 86 (8).

(*E*)-(*R*)-(−)-*O*-(1-Phenylbutyl)-3-methylbutan-2-one oxime 2i(R). Obtained from the condensation of (*R*)-*O*-(1-phenylbutyl)hydroxylamine with 3-methylbutan-2-one as a colourless oil (68%); $[a]_D^{25}$ −30.8 (*c* 1.04, $CHCl_3$); remaining data as for above enantiomer.

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)benzaldehyde oxime 2j. Prepared as described previously.[20]

(*E*)-(*R*)-(+)-*O*-(1-Phenylbutyl)-4-methoxybenzaldehyde oxime 2k. Prepared as described previously.[18]

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)-2,5-dimethylbenzaldehyde oxime 2l. Obtained from the condensation of (*S*)-*O*-(1-phenylbutyl)hydroxylamine with 2,5-dimethylbenzaldehyde as a colourless oil (93%); $[a]_D^{22}$ −63.0 (*c* 1.19, $CHCl_3$); (Found: MH^+, 282.1863. $C_{19}H_{23}NO$ + H requires 282.1858); ν_{max}(film)/cm^{-1} 3027, 2950, 2924, 2873, 1495, 1449, 1029, 947, 809, 702; δ_H (300 MHz; $CDCl_3$) 8.36 (1 H, s, N=CH), 7.42 (1 H, s, ArH), 7.30 (5 H, m, ArH), 7.02 (2 H, br s, ArH), 5.20 (1 H, t, *J* 6.9, OCH), 2.32 (3 H, s, Me), 2.27 (3 H, s, Me), 2.02 (1 H, m, C*H*H), 1.80 (1 H, m, CH*H*), 1.44 (2 H, m, CH_2), 0.95 (3 H, t, *J* 7.4, Me); δ_C (75 MHz; $CDCl_3$) 147.7 (CH), 142.4 (C), 135.5 (C), 133.6 (C), 131.8 (C), 130.6 (CH), 130.3 (CH), 128.2 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 85.4 (CH), 38.3 (CH_2), 20.9 (Me), 19.4 (Me), 18.9 (CH_2), 14.0 (Me); *m*/*z* (FAB) 282 (MH^+, 19%), 281 (100), 280 (32), 150 (54), 148 (11), 133 (100), 132 (19), 115 (7), 105 (15).

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)-3-fluoro-2-methylbenzaldehyde oxime 2m. Obtained from the condensation of (*S*)-*O*-(1-phenylbutyl)hydroxylamine with 3-fluoro-2-methylbenzaldehyde as a colourless oil (94%); $[a]_D^{23}$ −49.5 (*c* 1.07, $CHCl_3$); (Found: C, 75.7; H, 7.2; N, 4.8. $C_{18}H_{20}FNO$ requires C, 75.8; H, 7.1; N, 4.9%); ν_{max}(film)/cm^{-1} 3057, 2950, 2929, 2873, 1567, 1449, 1239, 1019, 947; δ_H (300 MHz; $CDCl_3$) 8.35 (1 H, s, N=CH), 7.32 (6 H, s, ArH), 7.08 (1 H, m, ArH), 6.98 (1 H, m, ArH), 5.19 (1 H, t, *J* 6.9, OCH), 2.26 (3 H, d, *J* 2.0, Me), 2.02 (1 H, m, C*H*H), 1.80 (1 H, m, CH*H*), 1.56–1.32 (2 H, m, CH_2), 0.95 (3 H, t, *J* 7.4, Me); δ_C (75 MHz; $CDCl_3$) 161.3 (CF, d, J_{CF} 241.6), 146.7 (CH, d, J_{CF} 4.0), 142.2 (C), 132.8 (C, d, J_{CF} 4.7), 128.3 (CH), 127.5 (CH), 126.9 (CH), 126.7 (CH, d, J_{CF} 8.9), 123.8 (C, d, J_{CF} 17.4), 122.6 (CH, d, J_{CF} 3.3), 115.8 (CH, d, J_{CF} 23.3), 85.7 (CH), 38.1 (CH_2), 18.9 (CH_2), 14.0 (Me), 10.7 (Me, d, J_{CF} 4.0); *m*/*z* (CI) 286 (MH^+, 14%), 266 (6), 182 (21), 155 (8), 154 (100), 133 (88), 91 (32).

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)acetophenone oxime 2n. Prepared as described previously.[18]

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)-4-bromoacetophenone oxime 2o. Obtained from the condensation of (*S*)-*O*-(1-phenylbutyl)-hydroxylamine with 4-bromoacetophenone as a pale yellow oil (30%); $[a]_D^{24}$ −74.7 (*c* 1.62, $CDCl_3$); (Found: MH^+, 346.0811. $C_{18}H_{20}{}^{79}BrNO$ + H requires 346.0807); ν_{max}(film)/cm^{-1} 3037, 2955, 2934, 2868, 1608, 1480, 1454, 1316, 1004, 922, 814, 691; δ_H (300 MHz; $CDCl_3$) 7.45–7.22 (9 H, m, ArH), 5.22 (1 H, dd, *J* 6.3, 7.1 OCH), 2.27 (3 H, s, Me), 2.01 (1 H, m, C*H*H), 1.81 (1 H, s, CH*H*), 1.42 (2 H, m, CH_2), 0.96 (3 H, t, *J* 7.4, Me); δ_C (75 MHz; $CDCl_3$) 153.2 (C), 142.8 (C), 135.7 (C), 131.3 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 126.6 (CH), 123.1 (C), 85.5 (CH), 38.5 (CH_2), 18.9 (CH_2), 14.1 (Me), 12.6 (Me); *m*/*z* (CI) 346/344 (MH^+, 100%), 269 (10), 268 (51), 200 (42), 168 (6), 166 (11), 150 (49), 120 (32), 108 (12), 91 (4), 52 (18).

General procedure for the addition of organometallic reagents

The oxime ether **2** (3.9 mmol, 1 eq.) was dissolved in toluene (10 mL) under nitrogen and cooled to −78 °C or −90 °C. Boron trifluoride etherate (11.8 mmol, 3 eq.) was added and the mixture stirred for 15 min. The organometallic reagent (11.8 mmol, 3 eq.) was added dropwise over 30 min at this temperature, and the mixture stirred until all starting material was consumed. The reaction mixture was quenched at this temperature with aqueous saturated ammonium chloride solution (10 mL), and allowed to warm to room temperature. The mixture was extracted with ether (3 × 15 mL), combined, dried (K_2CO_3), filtered and evaporated. The residue was purified by column chromatography on silica gel (eluting with ether–light petroleum (1 : 20) unless otherwise stated).

Addition of 2-furyllithium

2-Furyllithium was prepared in diethyl ether following a literature protocol.[30]

(1*S*,1′*R*)-(−)-*N*-(1-Phenylbutoxy)-2-(4-bromophenyl)-1-(2-furyl)ethylamine 3a. Obtained from the addition of 2-furyllithium to (*R*)-*O*-(1-phenylbutyl)-4-bromophenylacetaldehyde oxime **2h** as a yellow oil (40%, 83% *de*); $[a]_D^{24}$ −42.5 (*c* 1.13, $CHCl_3$); (Found: MH^+, 414.1068. $C_{22}H_{24}{}^{79}BrNO_2$ + H requires 414.1069); ν_{max}(film)/cm^{-1} 3021, 2954, 2925, 2872, 1490, 1447, 1071, 734, 701; δ_H (300 MHz; $CDCl_3$) 7.40–7.22 (8 H, m, ArH, fur-H5), 6.92 (2 H, d, *J* 8.3, ArH), 6.16 (1 H, m, fur-H4), 6.13 (1 H, m, fur-H3), 5.45 (1 H, br s, NH), 4.46 (1 H, dd, *J* 6.2, 7.5, OCH), 4.22 (1 H, t, *J* 7.1, *H*CNH), 3.02 (1 H, dd, *J* 7.1, 13.7, ArC*H*H), 2.97 (1 H, dd, *J* 7.1, 13.7, ArCH*H*), 1.72 (1 H, m, CH_2), 1.51 (1 H, m, CH_2), 1.30 (2 H, m, CH_2), 0.86 (3 H, t, *J* 7.1, Me); δ_C (75 MHz; $CDCl_3$) 153.8 (C), 142.8 (C), 141.5 (CH), 136.9 (C), 131.3 (CH), 130.8 (CH), 128.2 (CH), 127.3 (C), 126.6 (CH), 120.3 (C), 110.2 (CH), 107.7 (CH), 85.5 (CH), 60.2 (CH), 38.4 (CH_2), 36.8 (CH_2), 19.0 (CH_2), 14.0 (Me); *m*/*z* (CI) 416/414 (MH^+, 23%), 336 (5), 268 (26), 266 (40), 264 (12), 188 (12), 168 (16), 150 (100), 133 (2), 108 (6), 96 (56), 91 (2).

(2*R*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-2-(2-furyl)-3-methyl-2-butylamine 3b. Obtained from the addition of furyllithium to (*S*)-*O*-(1-phenylbutyl)-3-methylbutan-2-one oxime **2i(S)** as a colourless oil (31%, 52% *de*); $[a]_D^{24}$ −31.9 (*c* 1.22, $CHCl_3$); (Found: M^+, 285.2096. $C_{19}H_{27}NO$ requires 285.2093); ν_{max}-(film)/cm^{-1} 3032, 2960, 2934, 2868, 1454, 1362, 1152, 1014, 912, 702; δ_H (300 MHz; $CDCl_3$) 7.37–7.25 (6 H, m, ArH, fur-H5), 6.33 (1 H, dd, *J* 1.7, 3.3, fur-H4), 6.19 (1 H, m, fur-H3), 5.38 (1 H, br s, NH), 4.43 (1 H, dd, *J* 5.6, 7.8, OCH), 2.24 (1 H, heptet, *J* 6.9, C*H*($Me)_2$), 1.69 (1 H, m, C*H*H), 1.47 (1 H, m, CH*H*), 1.33 (3 H, s, Me), 1.30 (1 H, m, C*H*H), 1.20 (1 H, m, CH*H*), 0.89 (3 H, d, *J* 8.8, Me), 0.85 (3 H, m, Me), 0.77 (3 H, d, *J* 8.8, Me); δ_C (75 MHz; $CDCl_3$) 158.2 (C), 143.5 (C), 140.6 (CH), 128.1 (CH), 127.0 (CH), 126.5 (CH), 109.8 (CH), 106.8 (CH), 85.0 (CH), 63.1 (C), 38.9 (CH_2), 33.0 (CH), 18.9 (CH_2), 17.9 (Me), 17.1 (Me), 16.9 (Me), 14.1 (Me); *m*/*z* (EI) 285 (M^+, 4%), 279 (7), 263 (18), 256 (26), 234 (100), 230 (22), 219 (32), 218 (69), 213 (18), 204 (94).

(1*R*,1′*S*)-(+)-*N*-(1-Phenylbutoxy)-1-(4-bromophenyl)-1-(2-furyl)ethylamine 3c. Obtained from the addition of furyllithium to (*S*)-*O*-(1-phenylbutyl)-4-bromoacetophenone oxime **2o** as a colourless oil (14%, ~95% *de*); $[a]_D^{20}$ +20.5 (*c* 1.22, $CHCl_3$); (Found: MH^+, 414.1068. $C_{22}H_{24}{}^{79}BrNO_2$ + H requires 414.1069); ν_{max}(film)/cm^{-1} 2960, 2924, 2868, 1495, 1449, 1070, 1014, 819, 697; δ_H (300 MHz; $CDCl_3$) 7.40–7.19 (10 H, m, ArH, fur-H5), 6.36 (1 H, dd, *J* 2.1, 3.3, fur-H4), 6.30 (1 H, d, *J* 3.3, fur-H3), 5.65 (1 H, br s, NH), 4.49 (1 H, dd, *J* 5.9, 7.8, OCH), 1.71 (3 H, s, Me), 1.68 (1 H, m, C*H*H), 1.48 (1 H, m, CH*H*), 1.28 (1 H, m, C*H*H), 1.12 (1 H, m, CH*H*), 0.81 (3 H, t, *J* 7.3, Me); δ_C (75 MHz; $CDCl_3$) 157.3 (C), 148.2 (C), 142.8 (CH),

141.5 (C), 131.0 (CH), 128.6 (CH), 128.2 (CH), 127.2 (CH), 126.7 (CH), 121.1 (C), 110.1 (CH), 107.8 (CH), 85.4 (CH), 63.1 (C), 38.4 (CH_2), 24.5 (Me), 18.9 (CH_2), 14.0 (Me); *m*/*z* (CI) 414/412 (MH^+, 0.1%), 245 (4), 244 (7), 242 (19), 215 (94), 213 (100), 197 (72), 196 (34), 183 (24), 133 (65), 120 (5), 107(15), 91 (15).

Additions of phenyllithium

Phenyllithium was used as commercially supplied in cyclohexane–ether.

(1*R*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-2-methyl-1-phenylpropylamine 3d. Obtained from the addition of phenyllithium to (*S*)-*O*-(1-phenylbutyl)isobutyraldehyde oxime **2b** as a colourless oil (38%, 95% *de*); $[a]_D^{22}$ −64.9 (*c* 1.17, $CHCl_3$); (Found: MH^+, 298.2171. $C_{20}H_{27}NO$ + H requires 298.2171); ν_{max}(film)/cm^{-1} 3027, 2960, 1495, 1454, 1362, 1024, 753; δ_H (300 MHz; $CDCl_3$) 7.40–7.24 (10 H, m, ArH), 5.59 (1 H, d, *J* 7.7, NH), 4.34 (1 H, dd, *J* 5.3, 8.3, OCH), 3.72 (1 H, d, *J* 7.7, CH), 1.85 (1 H, heptet, *J* 6.8, C*H*($Me)_2$), 1.56 (1 H, m, C*H*H), 1.33 (1 H, m, CH*H*), 1.09 (1 H, m, C*H*H), 0.90 (3 H, d, *J* 6.7, Me), 0.85 (1 H, m, CH*H*), 0.67 (3 H, d, *J* 6.7, Me), 0.67 (3 H, t, *J* 7.3, Me); δ_C (100 MHz; $CDCl_3$) 143.6 (C), 141.7 (C), 128.4 (CH), 128.2 (CH), 127.7 (CH), 127.1 (CH), 126.8 (CH), 126.5 (CH), 85.1 (CH), 71.9 (CH), 38.7 (CH_2), 31.0 (CH), 20.0 (Me), 19.3 (Me), 18.7 (CH_2), 13.8 (Me); *m*/*z* (CI) 298 (MH^+, 34%), 166 (5), 150 (100), 133 (4), 106 (10), 72 (1).

(1*R*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-2,2-dimethyl-1-phenylpropylamine 3e. Obtained from the addition of phenyllithium to (*S*)-*O*-(1-phenylbutyl)pivaldehyde oxime **2d** as a colourless solid (31%, >98% *de*); mp 39–40 °C; $[a]_D^{24}$ −67.1 (*c* 1.46, $CHCl_3$); (Found: MH^+, 312.2322. $C_{21}H_{29}NO$ + H requires 312.2327); ν_{max}(Nujol)/cm^{-1} 3027, 2955, 2863, 1449, 1362, 1050, 1004, 697; δ_H (300 MHz; $CDCl_3$) 7.45–7.28 (10 H, m, ArH), 5.74 (1 H, s, NH), 4.41 (1 H, dd, *J* 5.0, 8.9, OCH), 3.82 (1 H, s, CH), 1.49 (1 H, m, C*H*H), 1.31 (1 H, m, CH*H*), 0.86 (2 H, m, CH_2), 0.86 (9 H, s, 3 × Me), 0.61 (3 H, t, *J* 7.4, Me); δ_C (100 MHz; $CDCl_3$) 143.8 (C), 141.1 (C), 129.2 (CH), 128.2 (CH), 127.2 (CH), 127.1 (CH), 126.7 (CH), 126.5 (CH), 85.2 (CH), 74.5 (CH), 38.7 (CH_2), 33.6 (C), 27.2 (Me), 18.6 (CH_2), 13.7 (Me); *m*/*z* (CI) 312 (MH^+, 1%), 254 (37), 133 (41), 121 (99), 90 (98), 76 (44).

(1*R*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-2,2-dimethyl-1-phenylbutylamine 3f. Obtained from the addition of phenyllithium to (*S*)-*O*-(1-phenylbutyl)-2,2-dimethylbutyraldehyde oxime **2e** as a colourless oil (32%, >98% *de*); $[a]_D^{21}$ −55.2 (*c* 1.05, $CHCl_3$); (Found: MH^+, 326.2491. $C_{22}H_{31}NO$ + H requires 326.2484); ν_{max}(film)/cm^{-1} 3021, 2960, 2868, 1598, 1490, 1449, 1362, 1301, 1198, 1024, 906, 697; δ_H (300 MHz; $CDCl_3$) 7.39–7.26 (10 H, m, ArH), 5.73 (1 H, s, NH), 4.40 (1 H, dd, *J* 4.9, 8.8, OCH), 3.89 (1 H, s, *H*CNH), 1.47 (1 H, m, C*H*H), 1.24 (1 H, m, CH*H*), 1.21 (2 H, m, CH_2), 0.95 (2 H, m, CH_2) 0.84 (3 H, t, *J* 7.4, Me), 0.82 (3 H, s, Me), 0.76 (3 H, s, Me), 0.63 (3 H, t, *J* 7.2, Me); δ_C (75 MHz; $CDCl_3$) 143.8 (C), 140.9 (C), 129.3 (CH), 128.2 (CH), 127.1 (CH), 127.1 (CH), 126.6 (CH), 126.4 (CH), 85.1 (CH), 72.7 (CH), 38.7 (CH_2), 36.2 (C), 31.9 (CH_2), 23.7 (Me), 23.6 (Me), 18.6 (CH_2), 13.7 (Me), 8.0 (Me); *m*/*z* (CI) 326 (MH^+, 30%), 254 (100), 194 (15), 176 (36), 161 (65), 133 (93), 122 (75), 105 (52), 91 (25).

Addition of vinyllithium

Vinyllithium was prepared in ether by transmetallation of tetravinyltin using methyllithium according to the literature procedure.[35] The additions of vinyllithium were carried out at −90 °C.

(3*R*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-3-hex-1-enylamine 3g. Obtained from the addition of vinyllithium to (*S*)-*O*-(1-phenylbutyl)butyraldehyde oxime **2a** as a colourless oil (87%, 84% de); $[a]_D^{26}$ −90.5 (*c* 0.74, $CHCl_3$); (Found: MH^+, 248.2017. $C_{16}H_{25}NO$ + H requires 248.2014); ν_{max}(film)/cm^{-1} 3257, 3083, 3063, 3022, 2955, 2930, 2868, 1455, 1373, 1358, 1107, 1061, 1030, 994, 912, 758, 697; δ_H (300 MHz; $CDCl_3$) 7.30 (5 H, m, ArH), 5.76 (1 H, ddd, *J* 17.5, 10.3, 8.1, =CH), 5.21 (3 H, m, NH, $=CH_2$), 4.55 (1 H, dd, *J* 7.7, 6.0, OCH), 3.35 (1 H, br q, *J* 6.7, NCH), 1.78 (1 H, m, C*H*H), 1.58–1.15 (7 H, m, CH*H*, 3 × CH_2), 0.89 (3 H, t, *J* 8.6, Me), 0.85 (3 H, t, *J* 7.1, Me); δ_C (75 MHz; $CDCl_3$) 143.3 (C), 139.8 (CH), 128.3 (CH), 127.2 (CH), 126.6 (CH), 116.4 (CH_2), 85.5 (CH), 64.2 (CH), 38.7 (CH_2), 33.9 (CH_2), 19.1 (CH_2), 19.0 (CH_2), 14.1 (Me), 14.0 (Me); *m*/*z* (CI) 248 (MH^+, 53%), 236 (13), 149 (36), 133 (100), 116 (16), 107 (23), 98 (9), 91 (12).

(3*R*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-3-hepta-1,6-dienylamine 3h. Obtained from the addition of vinyllithium to (*S*)-*O*-(1-phenylbutyl)pent-4-enaldehyde oxime **2c** as a colourless oil (77%, 94% de); $[a]_D^{26}$ −83.5 (*c* 0.85, $CHCl_3$); (Found: MH^+, 260.2012. $C_{17}H_{25}NO$ + H requires 260.2014); ν_{max}(film)/cm^{-1} 3257, 3078, 3027, 2955, 2925, 2863, 1690, 1644, 1598, 1501, 1450, 1358, 1301, 1199, 1107, 1061, 1030, 994, 907, 758, 697; δ_H (300 MHz; $CDCl_3$) 7.29 (5 H, m, ArH), 5.75 (2 H, m, 2 × =CH), 5.17 (2 H, m, $=CH_2$), 4.95 (2 H, m, $=CH_2$), 4.54 (1 H, dd, *J* 7.5, 5.9, OCH), 3.36 (1 H, q, *J* 7.2, NCH), 2.02 (2 H, m, CH_2), 1.77 (1 H, m, C*H*H), 1.60–1.19 (5 H, m, CH*H*, 2 × CH_2), 0.89 (3 H, t, *J* 7.2, Me), NH signal not observed; δ_C (75 MHz; $CDCl_3$) 143.2 (C), 139.4 (CH), 138.2 (CH), 128.3 (CH), 127.3 (CH), 126.6 (CH), 116.8 (CH_2), 114.7 (CH_2), 85.5 (CH), 63.8 (CH), 38.7 (CH_2), 30.9 (CH_2), 30.0 (CH_2), 19.2 (CH_2), 14.1 (Me); *m*/*z* (CI) 260 (MH^+, 95%), 215 (50), 169 (18), 128 (100).

(1*S*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-1-cyclohexylprop-2-enylamine 3i. Obtained from the addition of vinyllithium to (*S*)-*O*-(1-phenylbutyl)cyclohexanecarboxaldehyde oxime **2f** as a colourless oil (74%, 92% de); $[a]_D^{27}$ −72.3 (*c* 0.83, $CHCl_3$); (Found: M^+, 287.2248. $C_{19}H_{29}NO$ requires 287.2249); ν_{max}(film)/cm^{-1} 3263, 3064, 3030, 2958, 2926, 2853, 1494, 1451, 1106, 1061, 1028, 996, 916, 760, 700; δ_H (300 MHz; $CDCl_3$) 7.29 (5 H, m, ArH), 5.76 (1 H, ddd, *J* 17.0, 10.7, 8.7, =CH), 5.28 (1 H, br s, NH) 5.13 (2 H, m, $=CH_2$), 4.53 (1 H, dd, *J* 7.7, 5.8, OCH), 3.12 (1 H, dd, *J* 8.7, 6.6, NCH), 1.84–0.89 (15 H, m, CH, 7 × CH_2), 0.88 (3 H, t, *J* 7.2, Me); δ_C (75 MHz; $CDCl_3$) 143.4 (C), 138.2 (CH), 128.2 (CH), 127.2 (CH), 126.7 (CH), 117.2 (CH_2), 85.3 (CH), 69.6 (CH), 39.0 (CH), 38.7 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 26.5 (CH_2), 26.23 (CH_2), 26.20 (CH_2), 19.2 (CH_2), 14.1 (Me); *m*/*z* (FI) 287 (M^+, 100%), 202 (21), 133 (8).

(3*S*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-9-ethyl-3-deca-1,9-dienylamine 3j. Obtained from the addition of vinyllithium to (*E*)-(*R*)-*O*-(1-phenylbutyl)-7-ethyloct-7-enaldehyde oxime **2g** as a colourless oil (76%, >95% de); $[a]_D^{25}$ +72.3 (*c* 1.01, $CHCl_3$); (Found: MH^+, 330.2792. $C_{22}H_{35}NO$ + H requires 330.2797); ν_{max}(film)/cm^{-1} 3258, 3078, 3022, 2960, 2925, 2873, 2848, 1639, 1491, 1455, 1358, 1102, 1061, 1030, 989, 912, 886, 758, 697; δ_H (300 MHz; $CDCl_3$) 7.30 (5 H, m, ArH), 5.76 (1 H, ddd, *J* 17.3, 10.2, 7.9, =CH), 5.15 (3 H, m, NH, $=CH_2$), 4.67 (2 H, m, $=CH_2$), 4.54 (1 H, dd, *J* 7.5, 5.8, OCH), 3.33 (1 H, q, *J* 6.9, NCH), 1.97 (4 H, m, 2 × CH_2), 1.78 (1 H, m, C*H*H), 1.59–1.14 (11 H, m, CH*H*, 5 × CH_2), 1.01 (3 H, t, *J* 7.4, Me), 0.89 (3 H, t, *J* 7.3, Me); δ_C (75 MHz; $CDCl_3$) 151.7 (C), 143.3 (C), 139.8 (CH), 128.3 (CH), 127.3 (CH), 126.6 (CH), 116.5 (CH_2), 107.4 (CH_2), 85.5 (CH), 64.4 (CH), 38.7 (CH_2), 36.2 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 25.7 (CH_2), 19.2 (CH_2), 14.1 (Me), 12.4 (Me); *m*/*z* (CI) 330 (MH^+, 100%), 198 (11), 180 (8), 133 (9).

(3*S*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-3,4-dimethyl-3-pent-1-enylamine 3k. Obtained from the addition of vinyllithium to (*R*)-3-*O*-(1-phenylbutyl)-3-methylbutan-2-one oxime **2i(R)** as a colourless oil (54%, >95% de); $[a]_D^{26}$ +117.3 (*c* 0.81, $CHCl_3$);

(Found: C, 78.5; H, 10.9; N, 5.3. $C_{17}H_{27}NO$ requires C, 78.1; H, 10.4; N, 5.3%); ν_{max}(film)/cm^{-1} 2960, 2924, 2873, 1449, 1362, 922, 702; δ_H (300 MHz; $CDCl_3$) 7.30 (5 H, m, ArH), 5.93 (1 H, dd, *J* 17.7, 11.1, =CH), 5.11 (1 H, dd, *J* 11.1, 1.3, =C*H*H), 5.05 (1 H, dd, *J* 17.7, 1.3, =CH*H*), 5.04 (1 H, br, NH), 4.55 (1 H, dd, *J* 7.9, 5.5, OCH), 1.93 (1 H, heptet, *J* 6.9, C*H*Me$_2$), 1.76 (1 H, m, C*H*H), 1.62–1.21 (3 H, m, CH*H*, CH_2), 1.06 (3 H, s, CMe), 0.89 (6 H, m, CH*Me*$_2$), 0.80 (3 H, d, *J* 6.9, Me); δ_C (75 MHz; $CDCl_3$) 143.6 (C), 142.0 (CH), 128.2 (CH), 127.1 (CH), 126.5 (CH), 113.9 (CH_2), 85.2 (CH), 63.7 (C), 39.0 (CH_2), 32.4 (CH), 19.2 (CH_2), 17.5 (Me), 17.4 (Me), 17.1 (Me), 14.1 (Me); *m*/*z* (FI) 262 (MH^+, 24%), 261 (100), 202 (8), 97 (8).

(1*S*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-3-phenyl-3-prop-1-enylamine 3l. Obtained from the addition of vinyllithium to (*S*)-*O*-(1-phenylbutyl)benzaldehyde oxime **2j** as a colourless oil (46%, 98% *de*); $[\alpha]_D^{26}$ −56.8 (*c* 0.54, $CHCl_3$); (Found: C, 81.4; H, 8.6; N, 4.7. $C_{19}H_{23}NO$ requires C, 81.1; H, 8.2; N, 5.0%); ν_{max}(film)/cm^{-1} 3027, 2950, 2934, 2868, 1490, 1460, 917, 753, 697; δ_H (300 MHz; $CDCl_3$) 7.42–7.25 (10 H, m, ArH), 6.11 (1 H, ddd, *J* 7.1, *J* 10.1, *J* 17.3, *H*C=CH_2), 5.40 (1 H, s, NH), 5.25 (2 H, m, CH=C*H*$_2$), 4.62 (2 H, m, OCH, NCH), 1.81 (1 H, m, C*H*H), 1.57 (1 H, m, CH*H*), 1.37 (2 H, m, CH_2), 0.91 (3 H, t, *J* 7.2, Me); δ_C (75 MHz; $CDCl_3$) 143.0 (C), 139.8 (C), 138.6 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 126.7 (CH), 116.8 (CH_2), 85.4 (CH), 68.2 (CH), 38.5 (CH_2), 19.1 (CH_2), 14.0 (Me); *m*/*z* (FI) 281 (M^+, 100%), 191 (13), 148 (93), 133 (18).

(1*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-1-(4-methoxyphenyl)-1-prop-2-enylamine 3m. Obtained from the addition of vinyllithium to (*R*)-*O*-(1-phenylbutyl)-4-methoxybenzaldehyde oxime **2k** as a colourless oil (50%, 91% de); $[\alpha]_D^{27}$ +36.1 (*c* 0.83, $CHCl_3$); (Found: C, 77.5; H, 8.5; N, 4.4. $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%); (Found: MH^+, 312.1971. $C_{20}H_{25}NO_2$ + H requires 312.1963); ν_{max}(film)/cm^{-1} 3257, 3063, 3030, 2958, 2933, 2872, 2836, 1610, 1512, 1454, 1303, 1247, 1176, 1036, 918, 828, 760, 700; δ_H (300 MHz; $CDCl_3$) 7.26 (5 H, m, ArH), 7.15 (2 H, m, ArH), 6.79 (2 H, m, ArH), 6.07 (1 H, ddd, *J* 17.3, 10.2, 7.0, =CH), 5.35–5.15 (3 H, m, NH, =CH_2), 4.58 (1 H, dd, *J* 7.7, 6.0, OCH), 4.49 (1 H, d, *J* 7.0, NCH), 3.75 (3 H, s, OMe), 1.79 (1 H, m, C*H*H), 1.60–1.16 (3 H, m, CH*H*, CH_2), 0.88 (3 H, t, *J* 7.3, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 159.3 (C), 143.3 (C), 139.1 (CH), 132.2 (C), 129.3 (CH), 128.5 (CH), 127.5 (CH), 126.9 (CH), 116.7 (CH_2), 114.0 (CH), 85.7 (CH), 67.8 (CH), 55.5 (Me), 38.8 (CH_2), 19.4 (CH_2), 14.3 (Me); *m*/*z* (CI) 312 (MH^+, 6%), 204 (4), 180 (12), 162 (17), 147 (100), 133 (15), 91 (8).

(1*S*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-3-(2,5-dimethylphenyl)-3-prop-1-enylamine 3n. Obtained from the addition of vinyllithium to (*S*)-*O*-(1-phenylbutyl)-2,5-dimethylbenzaldehyde oxime **2l** as a yellow oil (16%, 95% *de*); $[\alpha]_D^{26}$ −43.1 (*c* 1.16, $CHCl_3$); (Found: MH^+, 310.2163. $C_{21}H_{27}NO$ + H requires 310.2171); ν_{max}(film)/cm^{-1} 3431, 3027, 2955, 2919, 1613, 1454, 968; δ_H (400 MHz; $CDCl_3$) 7.35–7.03 (8 H, m, ArH), 6.79 (1 H, br s, NH), 6.56 (1 H, dd, *J* 10.6, 17.5, C*H*=CH_2), 5.34 (1 H, dd, *J* 0.9, 10.6, CH=C*H*H), 5.19 (1 H, m, NHC*H*), 5.08 (1 H, t, *J* 6.8, OCH), 4.94 (1 H, dd, *J* 0.9, 17.5, CH=CH*H*), 2.33 (3 H, s, Me), 1.78 (1 H, m, C*H*H), 1.58 (1 H, m, CH*H*), 1.42 (3 H, s, Me), 0.94 (2 H, m, CH_2), 0.84 (3 H, t, *J* 7.3, Me); δ_C (100 MHz; $CDCl_3$) 134.5 (C), 134.2 (CH), 132.0 (C), 130.7 (C), 129.4 (CH), 128.8 (CH), 128.2 (CH), 128.0 (CH), 127.0 (CH), 126.6 (C), 126.4 (CH), 122.9 (CH_2), 85.4 (CH), 30.9 (CH), 26.9 (CH_2), 20.9 (Me), 18.88 (Me), 18.83 (CH_2), 13.9 (Me); *m*/*z* (CI) 310 (MH^+, 0.1%), 290 (6), 204 (12), 177 (13), 176 (100), 158 (23), 133 (90), 132 (11), 107 (4), 96 (26).

(1*S*,1′*S*)-(+)-*N*-(1-Phenylbutoxy)-3-(3-fluoro-2-methylphenyl)-3-prop-1-enylamine 3o. Obtained from the addition of vinyllithium to (*S*)-*O*-(1-phenylbutyl) 3-fluoro-2-methylbenzaldehyde oxime **2m** as a yellow oil, (10%, 95% *de*); $[\alpha]_D^{26}$ +30.3 (*c* 0.89, $CDCl_3$); (Found: MH^+, 314.1891. $C_{20}H_{24}FNO$ + H requires 314.1920); ν_{max}(film)/cm^{-1} 3032, 2955, 2924, 2873, 1582, 1465, 1239, 917, 789, 697; δ_H (400 MHz; $CHCl_3$) 7.31–7.24 (5 H, m, ArH), 7.03 (2 H, m, ArH), 7.02 (1 H, m, ArH), 6.00 (1 H, ddd, *J* 6.8, 13.5, 17.1, C*H*=CH_2), 5.35 (1 H, br s, NH), 5.23 (2 H, m, CH=C*H*$_2$), 4.78 (1 H, d, *J* 6.8, NHC*H*), 4.58 (1 H, dd, *J* 6.2, 7.6, OCH), 2.16 (3 H, d, *J* 2.1, Me), 1.78 (1 H, m, C*H*H), 1.55 (1 H, m, CH*H*), 1.37 (1 H, m, C*H*H), 1.26 (1 H, m, CH*H*), 0.92 (3 H, t, *J* 7.3, Me); δ_C (100 MHz; $CDCl_3$) 161.3 (CF, d, J_{CF} 241.8), 142.9 (C), 140.1 (C), 137.6 (CH), 128.2 (CH), 127.3 (CH), 126.6 (CH, d, J_{CF} 4.7), 126.5 (CH, d, J_{CF} 2.8), 123.3 (C), 122.7 (CH, d, J_{CF} 3.1), 117.1 (CH_2), 113.9 (C, d, J_{CF} 23.2), 85.5 (CH), 63.8 (CH, d, J_{CF} 2.6), 38.4 (CH_2), 18.8 (CH_2), 14.0 (Me), 10.0 (Me, d, J_{CF} 6.1); *m*/*z* (CI) 312 (M + NH_4^+, 4%), 223 (3), 222 (12), 210 (4), 182 (23), 164 (19), 149 (100), 133 (100), 132 (24), 91 (20).

(2*S*,1′*S*)-(−)-*N*-(1-Phenylbutoxy)-2-phenyl-2-but-3-enylamine 3p. Obtained from the addition of vinyllithium to (*S*)-*O*-(1-phenylbutyl)acetophenone oxime**2n** as a colourless oil (10%, 64% *de*); $[\alpha]_D^{26}$ −5.3 (*c* 4.73, $CHCl_3$); (Found: MH^+, 296.2016. $C_{20}H_{25}NO$ + H requires 296.2014); ν_{max}(film)/cm^{-1} 3411, 2960, 2924, 2852, 1603, 1454, 1372, 1029; δ_H (300 MHz; $CDCl_3$) 7.33–7.25 (10 H, m, ArH), 6.33 (1 H, dd, *J* 10.8, 17.6, C*H*=CH_2), 5.25 (1 H, br s, NH), 5.20 (2 H, ddd, *J* 1.1, 10.8, 23.3, CH=C*H*$_2$), 4.54 (1 H, dd, *J* 5.7, 8.0, OCH), 1.47 (3 H, s, Me), 1.44 (1 H, m, C*H*H), 1.25 (1 H, m, CH*H*), 0.93 (2 H, m, CH_2), 0.88 (3 H, t, *J* 7.2, Me); δ_C (75 MHz; $CDCl_3$) 149.4 (C), 143.0 (CH), 135.5 (C), 128.2 (CH), 127.8 (CH), 127.1 (CH), 126.7 (CH), 126.7 (CH), 126.4 (CH), 114.0 (CH_2), 85.3 (CH), 64.3 (C), 38.7 (CH_2), 28.2 (Me), 18.8 (CH_2), 14.1 (Me); *m*/*z* (CI) 296 (MH^+, 33%), 268 (15), 226 (7), 164 (10), 163 (19), 133 (73), 131 (100), 91 (54).

General method for the cleavage of the N–O bond and preparation of *N*-protected amines

Zinc dust (2.61 g, 40 mmol) was added to a mixture of the hydroxylamine (1 mmol) in acetic acid : water (1 : 1; 6.5 mL). The mixture was placed in a sonic bath at 40 °C and the reaction followed by TLC until completion (typically 2–6 h). The zinc was filtered and washed with ether. The filtrate was basified with sodium hydrogen carbonate solution (sat.) and the aqueous layer was extracted with dichloromethane (8 × 15 mL). The extracts were combined, dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in dichloromethane (7 mL) and treated with:

(i) di-*tert*-butyl dicarbonate (0.87 g, 4 mmol) and DMAP (cat.) and stirred for 12 h,

or (ii) sodium carbonate (0.21 g, 2 mmol) was added to the residue dissolved in THF : water (1 : 1; 10 mL), cooled to 0 °C and treated with benzyl chloroformate. The mixture was warmed to room temperature and stirred for 12 h,

or (iii) the residue was dissolved in anhydrous pyridine (10 mL) and treated with excess acetic anhydride and stirred for 12 h.

The mixture was extracted with dichloromethane (4 × 10 mL), combined, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography to give the Boc-, Cbz and acetyl-protected amines. The enantiomeric purity of the protected amines was determined by HPLC on a chiral stationary phase, typically ChiralPak AD with hexane–isopropanol (99 : 1) as eluant, by comparison with the independently synthesized racemate.

(*S*)-(−)-*N*-(*tert*-Butoxycarbonyl)-1-(4-bromophenyl)-1-(2-furyl)ethylamine 4a. Obtained by the zinc mediated N–O bond cleavage and subsequent *N*-protection of hydroxylamine **3a** as a colourless oil (72% over two steps, 83% *ee*); $[\alpha]_D^{24}$ −5.9 (*c* 1.07, $CHCl_3$); (Found: MH^+, 366.0712. $C_{17}H_{20}{}^{79}BrNO_3$ + H

requires 366.0706); ν_{max}(film)/cm^{-1} 3359, 2979, 1678, 1519, 1365, 1250, 1167, 1009, 810, 735; δ_H (300 MHz; $CDCl_3$) 7.36 (1 H, d, *J* 1.4, fur-H5), 7.34 (2 H, d, *J* 8.2, ArH), 6.89 (2 H, d, *J* 8.2, ArH), 6.26 (1 H, dd, *J* 1.4, 3.2, fur-H4), 6.01 (1 H, d, *J* 3.2, fur-H3), 4.98 (1 H, br s, NH), 4.80 (1 H, m, NHC*H*), 3.06 (2 H, d, *J* 6.8, ArCH_2), 1.41 (9 H, s, 3 × Me); δ_C (75 MHz; $CDCl_3$) 154.8 (C), 153.4 (C), 141.7 (CH), 136.1 (C), 131.3 (CH), 131.0 (CH), 120.4 (C), 110.2 (CH), 106.6 (CH), 53.3 (CH), 49.8 (C), 40.1 (CH_2), 28.3 (Me); *m*/*z* (ES) 356/354 (MH^+, 40%), 282 (30), 281 (100), 267 (32), 265 (18), 225 (6), 222 (11), 221 (67), 73 (68), 55(42).

(*R*)-(+)-*N*-Acetyl-2-methyl-1-phenylpropylamine 4b. Obtained by the zinc mediated N–O bond cleavage and subsequent *N*-protection of hydroxylamine **3d** as a colourless solid (38% over two steps, 98% *ee*); mp 135–136 °C (lit.,[39] mp 120 °C; lit.,[40] mp 119–120 °C); $[\alpha]_D^{24}$ +105.5 (*c* 1.1, $CHCl_3$) (lit.,[39] $[\alpha]_D^{20}$ +135 (*c* 3.8, MeOH); lit.,[40] $[\alpha]_D$ +72.3 (*c* 3.8, MeOH)); (Found: MH^+, 192.1388. $C_{12}H_{17}NO$ + H requires 192.1388); ν_{max}(Nujol)/cm^{-1} 3426, 3272, 3078, 2960, 2924, 1649, 1557, 1454, 702; δ_H (300 MHz; $CDCl_3$) 7.36–7.20 (5 H, m, ArH), 5.85 (1 H, m, NH), 4.76 (1 H, t, *J* 8.5, CH), 2.00 (4 H, m, MeCO, C*H*$(Me)_2$), 0.97 (3 H, d, *J* 6.6, Me), 0.83 (3 H, d, *J* 6.6, Me); δ_C (75 MHz; $CDCl_3$) 169.3 (C), 141.6 (C), 128.5 (CH), 127.1 (CH), 126.9 (CH), 59.1 (CH), 33.4 (Me), 23.5 (CH), 19.7 (Me), 18.8 (Me); *m*/*z* (CI) 192 (MH^+, 100%), 148 (6), 141 (18), 108 (2), 106 (7), 94 (2), 77 (13), 72 (3).

(*R*)-(+)-*N*-Acetyl-2,2-dimethyl-1-phenylpropylamine 4c. Obtained by the zinc mediated N–O bond cleavage and subsequent *N*-protection of hydroxylamine **3e** as a colourless solid (28% over two steps, >98% *ee*); mp 175–176 °C (lit.,[14] *S*-enantiomer mp 177–177.5 °C); $[\alpha]_D^{24}$ +42.7 (*c* 1.03, $CHCl_3$) (lit.,[41] $[\alpha]_D^{26}$ +77; lit.,[14] *S*-enantiomer $[\alpha]_D^{28}$ −92.0 (*c* 2.05, EtOH)); (Found: M^+, 205.1463. $C_{13}H_{19}NO$ requires 205.1467); ν_{max}(Nujol)/cm^{-1} 3313, 2960, 2914, 1644, 1547, 1367, 1101, 727; δ_H (300 MHz; $CDCl_3$) 7.35–7.20 (5 H, m, ArH), 6.18 (1 H, d, *J* 9.6, NH), 4.85 (1 H, d, *J* 9.6, CH), 2.03 (3 H, s, Me), 0.94 (9 H, s, 3 × Me); δ_C (75 MHz; $CDCl_3$) 169.3 (C), 140.1 (C), 128.1 (CH), 127.7 (CH), 127.0 (CH), 61.5 (CH), 34.8 (C), 26.6 (Me), 23.5 (Me); *m*/*z* (FI) 205 (M^+, 100%), 149 (15), 148 (11), 57 (7).

(*R*)-(+)-*N*-Acetyl-2,2-dimethyl-1-phenylbutylamine 4d. Obtained by the zinc mediated N–O bond cleavage and subsequent *N*-protection of hydroxylamine **3f** as a colourless solid (6% over two steps, >98% *ee*); mp 125–126 °C; $[\alpha]_D^{24}$ +35.1 (*c* 0.37, $CHCl_3$); (Found: MH^+, 220.1703. $C_{14}H_{21}NO$ + H requires 220.1701); ν_{max}(Nujol)/cm^{-1} 3308, 2965, 2924, 1644, 1536, 1378, 1101, 732; δ_H (300 MHz; $CDCl_3$) 7.36–7.22 (5 H, m, ArH), 6.15 (1 H, m, NH), 4.90 (1 H, d, *J* 9.6, CH), 2.01 (3 H, s, MeCO), 1.29 (2 H, m, CH_2), 0.90 (3 H, s, Me), 0.89 (3 H, t, *J* 7.4, Me), 0.83 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 169.0 (C), 140.0 (C), 128.2 (CH), 127.7 (CH), 126.9 (CH), 60.2 (CH), 37.3 (C), 31.8 (CH_2), 23.6 (Me), 23.1 (Me), 22.9 (Me), 8.2 (Me); *m*/*z* (CI) 220 (MH^+, 100%), 162 (6), 161 (45), 149 (32), 148 (44), 106 (32), 105 (77), 88 (8), 60 (17).

(*R*)-(−)-*N*-Benzyloxycarbonyl-3-hex-1-enylamine 4e. Obtained from cleavage of the N–O bond of hydroxylamine **3g** and subsequent protection. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (3 : 7) to give the pure product as a colourless solid (89% over two steps); mp 55–56 °C; $[\alpha]_D^{26}$ −10.1 (*c* 0.79, $CHCl_3$); (Found: C, 72.2; H, 8.3; N, 5.9. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%); (Found: MH^+, 234.1514. $C_{14}H_{19}NO_2$ + H requires 234.1494); ν_{max}(KBr)/cm^{-1} 3323, 3063, 2959, 2925, 2863, 1683, 1537, 1460, 1306, 1262, 1075, 917; δ_H (300 MHz; $CDCl_3$) 7.37–7.11 (5 H, m, ArH), 5.67 (1 H, m, =CH), 5.29 (1 H, br d, *J* 7.9, NH), 5.20–4.91 (4 H, m, CH_2Ph, =CH_2), 4.15 (1 H, br, NCH), 1.53–1.20 (4 H, m, 2 × CH_2), 0.88 (3 H, t, *J* 6.9, Me); δ_C (75 MHz; $CDCl_3$) 155.9 (C), 138.9 (CH), 136.7 (C), 128.4 (CH), 127.94 (CH), 127.89 (CH), 114.3 (CH_2), 66.4 (CH_2), 53.1 (CH), 37.0 (CH_2), 18.9 (CH_2), 13.8 (Me); *m*/*z* (CI) 234 (MH^+, 10%), 190 (12), 173 (6), 152 (19), 146 (7), 119 (7), 91 (100).

(*R*)-(−)-*N*-Benzyloxycarbonyl-3-hepta-1,6-dienylamine 4f. Obtained from cleavage of the N–O bond of hydroxylamine **3h** and subsequent protection. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (1 : 4) to give the pure product as a colourless solid (53% over two steps); mp 36–38 °C; $[\alpha]_D^{26}$ −8.4 (*c* 0.83, $CHCl_3$); (Found: M^+, 245.1431. $C_{15}H_{19}NO_2$ requires 245.1416); ν_{max}(KBr)/cm^{-1} 3319, 3078, 3032, 2981, 2930, 2848, 1685, 1639, 1532, 1450, 1296, 1255, 1071, 989, 912, 753, 697; δ_H (300 MHz; $CDCl_3$) 7.35 (5 H, m, ArH), 5.89–5.68 (2 H, m, 2 × =CH), 5.22–4.94 (6 H, m, CH_2Ph, 2 × =CH_2), 4.70 (1 H, br d, *J* 5.7, NH), 4.20 (1 H, br m, NCH), 2.11 (2 H, q, *J* 7.4, CH_2), 1.60 (2 H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 156.0 (C), 138.6 (C), 137.8 (CH), 136.7 (CH), 128.7 (CH), 128.3 (CH), 115.4 (CH_2), 115.1 (CH_2), 66.8 (CH_2), 53.1 (CH), 34.3 (CH_2), 30.1 (CH_2), one ArCH not observed; *m*/*z* (EI) 245 (M^+, 16%), 216 (27), 204 (54), 201 (19), 172 (22), 154 (32), 147 (25), 110 (21), 100 (12), 91 (100).

(*S*)-(−)-*N*-Benzyloxycarbonyl-1-cyclohexylprop-2-enylamine 4g. Obtained from cleavage of the N–O bond of hydroxylamine **3i** and subsequent protection. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (7 : 13) to give the pure product as a colourless solid (52% over two steps); mp 74–76 °C; $[\alpha]_D^{27}$ −32.2 (*c* 0.87, $CHCl_3$); (Found: C, 75.0; H, 8.5; N, 5.0. $C_{17}H_{23}NO_2$ requires C, 74.7; H, 8.5; N, 5.1%); (Found: M^+, 273.1736. $C_{17}H_{23}NO_2$ requires 273.1729); ν_{max}(KBr)/cm^{-1} 3331, 3078, 2917, 2851, 1683, 1653, 1539, 1450, 1296, 1250, 1020, 912, 656; δ_H (300 MHz; $CDCl_3$) 7.34 (5 H, m, ArH), 5.74 (1 H, ddd, *J* 16.7, 10.4, 6.0, =CH), 5.15 (4 H, m, CH_2Ph, =CH_2), 4.75 (1 H, br d, *J* 8.5, NH), 4.04 (1 H, br m, NCH), 1.81–1.56 (5 H, m, CH, 2 × CH_2), 1.42 (1 H, br, C*H*H), 1.29–0.86 (5 H, m, CH*H*, 2 × CH_2); δ_C (75 MHz; $CDCl_3$) 156.0 (C), 137.2 (C), 136.6 (CH), 128.5 (CH), 128.1 (CH), 115.4 (CH_2), 66.7 (CH_2), 58.2 (CH), 42.2 (CH), 29.3 (CH_2), 28.6 (CH_2), 26.3 (CH_2), 26.10 (CH_2), 26.08 (CH_2); one ArCH not observed; *m*/*z* (FI) 273 (M^+, 100%), 190 (10), 91 (4), 83 (11).

(*S*)-(+)-*N*-Benzyloxycarbonyl-9-ethyl-3-deca-1,9-dienylamine 4h. Obtained from cleavage of the N–O bond of hydroxylamine **3j** and subsequent protection. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (1 : 10) to give the pure product as a colourless oil (70% over two steps, 97% ee); $[\alpha]_D^{21}$ +12.9 (*c* 1.16, $CHCl_3$); (Found: MH^+, 316.2279. $C_{20}H_{29}NO_2$ + H requires 316.2276); ν_{max}(film)/cm^{-1} 3329, 3068, 3034, 2965, 2933, 2858, 1701, 1645, 1527, 1456, 1338, 1240, 1070, 992, 919, 888, 736, 697; δ_H (300 MHz; $CDCl_3$) 7.34 (5 H, m, ArH), 5.74 (1 H, ddd, *J* 17.0, 10.4, 5.8, =CH), 5.13 (4 H, m, CH_2Ph, =CH_2), 4.71 (3 H, m, =CH_2, NH), 4.16 (1 H, br, NCH), 1.99 (4 H, m, 2 × CH_2), 1.59–1.21 (8 H, m, 4 × CH_2), 1.01 (3 H, t, *J* 7.5, Me); δ_C (75 MHz; $CDCl_3$) 155.8 (C), 151.5 (C), 138.7 (CH), 136.6 (C), 128.5 (CH), 128.1 (CH), 114.6 (CH_2), 107.5 (CH_2), 66.7 (CH_2), 53.4 (CH), 36.1 (CH_2), 35.1 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 25.5 (CH_2), 12.4 (Me), one ArCH not observed; *m*/*z* (CI) 316 (MH^+, 95%), 272 (60), 255 (25), 224 (27), 163 (28), 152 (33), 146 (23), 91 (100).

(*S*)-(+)-*N*-Benzyloxycarbonyl-3,4-dimethyl-3-pent-1-enylamine 4i. Obtained from cleavage of the N–O bond of hydroxylamine **3k** and subsequent protection. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (3 : 7) to give the pure product as a colourless oil (80% over two steps); $[\alpha]_D^{25}$ +24.6 (*c* 1.22, $CHCl_3$); (Found: C, 73.5; H, 9.0; N, 5.7. $C_{15}H_{21}NO_2$ requires C, 72.8; H,

8.6; N, 5.7%); (Found: MH^+, 248.1646. $C_{15}H_{21}NO_2$ + H requires 248.1650); ν_{max}(film)/cm^{-1} 3350, 3088, 3063, 3032, 2967, 2870, 1729, 1500, 1455, 1248, 1214, 1069, 1009, 917; δ_H (300 MHz; $CDCl_3$) 7.33 (5 H, m, ArH), 5.91 (1 H, dd, *J* 17.5, 10.5, =CH), 5.19–4.97 (4 H, m, CH_2Ph, =CH_2), 4.83 (1 H, s, NH), 2.07 (1 H, br, C*H*Me_2), 1.37 (3 H, s, CMe), 0.87 (6 H, dd, *J* 6.8, 4.9, CH*Me*$_2$); δ_C (75 MHz; $CDCl_3$) 154.9 (C), 141.5 (CH), 136.9 (C), 128.7 (CH), 128.3 (CH), 128.2 (CH), 113.7 (CH_2), 66.3 (CH_2), 59.6 (C), 35.5 (CH), 20.5 (Me), 17.4 (Me), 17.2 (Me); *m*/*z* (CI) 248 (MH^+, 56%), 204 (33), 187 (11), 152 (13), 119 (11), 97 (21), 91 (100).

(*S*)-(−)-*N*-Acetyl-1-phenylprop-2-enylamine 4j. Obtained by the zinc mediated N–O bond cleavage and subsequent *N*-protection of hydroxylamine **3l** as a colourless solid (9% over two steps, 90% *ee*); mp 72–73 °C (lit.,[42] racemate mp 66 °C); $[\alpha]_D^{24}$ −72.2 (*c* 1.69, $CDCl_3$); (Found: MH^+, 176.1076. $C_{11}H_{13}NO$ + H requires 176.1075); ν_{max}(Nujol)/cm^{-1} 3431, 3247, 3057, 2919, 2847, 1649, 1536, 1367, 1137, 702; δ_H (300 MHz; $CHCl_3$) 7.32–7.23 (5 H, m, ArH), 6.05 (1 H, br s, NH), 5.95 (2 H, m, C*H*=CH_2), 5.19 (2 H, m, CH=CH_2), 1.96 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 169.1 (C), 140.5 (C), 137.2 (CH), 128.7 (CH), 127.7 (CH), 127.2 (CH), 115.7 (CH_2), 55.1 (CH), 30.9 (Me); *m*/*z* (CI) 192 (MH^+, 100%), 148 (6), 141 (18), 108 (2), 106 (7), 94 (2), 77 (13), 72 (3).

(*R*)-(+)-*N*-Benzyloxycarbonyl-1-(4-methoxyphenyl)prop-2-enylamine 4k. Obtained from cleavage of the N–O bond of hydroxylamine **3m** and subsequent protection. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (3 : 7) to give the pure product as a colourless solid (85% over two steps); mp 74–76 °C; $[\alpha]_D^{28}$ +61.8 (*c* 0.73, $CHCl_3$); (Found: C, 72.8; H, 6.3; N, 4.6. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%); (Found: MH^+, 298.1456. $C_{18}H_{19}NO_3$ + H requires 298.1443); ν_{max}(KBr)/cm^{-1} 3307, 3027, 2996, 2935, 2832, 1685, 1532, 1512, 1301, 1247, 1173, 1025; δ_H (300 MHz; $CDCl_3$) 7.39–7.05 (7 H, m, ArH), 6.82 (2 H, d, *J* 9.2, ArH), 5.94 (1 H, m, =CH), 5.44 (6 H, m, CH_2Ph, =CH_2, NH, NCH), 3.73 (3 H, s, OMe); δ_C (75 MHz; $CDCl_3$) 159.2 (C), 155.9 (C), 138.0 (CH), 136.6 (C), 133.0 (C), 128.6 (CH), 128.4 (CH), 128.3 (CH), 115.6 (CH_2), 114.2 (CH), 67.0 (CH_2), 56.7 (CH), 55.4 (Me); one ArCH not observed; *m*/*z* (CI) 298 (MH^+, 3%), 254 (6), 237 (17), 206 (30), 190 (14), 147 (100), 100 (12), 91 (29).

Oxidations

(*S*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(4-bromophenyl)alanine 5a. Sodium metaperiodate (163 mg, 0.762 mmol) in CCl_4 : CH_3CN : H_2O (2 : 3 : 3, v/v) and $RuCl_3 \cdot 3H_2O$ (1.3 mg, 0.00635 mmol) were stirred vigorously for 20 min, and furan **4a** (45 mg, 0.127 mmol) was then added and the mixture turned black. Sodium metaperiodate was then added until the yellow colouration was restored. The mixture was then stirred for a further 20 min. An acid–base extraction, drying over $MgSO_4$, evaporation and trituration with ether gave the *title compound* as a colourless solid (14.4 mg, 33%); mp 116–117 °C (lit.,[43] racemate mp 117–118 °C); $[\alpha]_D^{24}$ +20.0 (*c* 0.25, MeOH) (lit.,[43] $[\alpha]_D^{20}$ +9.6 (*c* 2, EtOAc)); ν_{max}(KBr)/cm^{-1} 3424, 2361, 1693, 1489, 1396, 1366, 1251, 1163, 1071, 1011; δ_H (300 MHz; $CDCl_3$) 7.42 (2 H, d, *J* 8.2, ArH), 7.06 (2 H, d, *J* 8.2, ArH), 4.96 (1 H, d, *J* 7.0, NH), 4.59 (1 H, m, NHC*H*), 3.15 (1 H, m, C*H*HAr), 3.02 (1 H, m, CH*H*Ar), 1.42 (9 H, s, 3 × Me); CO_2H not observed.

(*R*)-*N*-Acetyl-*tert*-leucine 5b. Prepared in 63% yield by oxidative cleavage of (*R*)-(+)-*N*-acetyl-2,2-dimethyl-1-phenylpropylamine **4c** exactly as described for the (*S*)-enantiomer.[14]

General procedure for the preparation of *N*-Cbz-protected amino esters by ozonolysis of vinyl compounds. Ozone was passed through a solution of the vinyl compound (**4e**–**4g**, **4k**) (0.37 mmol, 1 eq.) sodium hydroxide (1.85 mmol, 5 eq.) in dichloromethane (12 mL) and methanol (5 mL) at −78 °C. After 2 h diethyl ether (5 mL) and water (5 mL) were added and the reaction mixture allowed to warm to room temperature. The mixture was exhaustively extracted with diethyl ether (5 × 5 mL). The extracts were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude ester.

(*R*)-(−)-Methyl 2-benzyloxycarbonylaminopentanoate 5c (*N*-Cbz-norvaline methyl ester). Obtained from ozonolysis of olefin **4e**. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (1 : 2) to give the pure product as a colourless oil (59%, 86% ee); (lit.,[44] racemate, oil); $[\alpha]_D^{26}$ −2.3 (*c* 0.86, $CHCl_3$); (Found: C, 63.6; H, 7.5; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2; N, 5.3%); (Found: M^+, 265.1311. $C_{14}H_{19}NO_4$ requires 265.1314); ν_{max}(film)/cm^{-1} 3345, 3068, 3032, 2960, 2868, 1718, 1523, 1456, 1347, 1260, 1214, 1107, 1061, 1025; δ_H (300 MHz; $CDCl_3$) 7.44–7.20 (5 H, m, ArH), 5.34 (1 H, br d, *J* 7.0, NH), 5.10 (2 H, s, CH_2Ph), 4.38 (1 H, q, *J* 7.0, NCH), 3.73 (3 H, s, OMe), 1.88–1.52 (2 H, m, CH_2), 1.47–1.21 (2 H, m, CH_2), 0.92 (3 H, t, *J* 7.2, Me); δ_C (75 MHz; $CDCl_3$) 173.4 (C), 156.1 (C), 136.5 (C), 128.7 (CH), 128.4 (CH), 128.3 (CH), 67.2 (CH_2), 53.9 (CH), 52.5 (Me), 34.9 (CH_2), 18.7 (CH_2), 13.8 (Me); *m*/*z* (FI) 265 (M^+, 100%), 221 (3), 179 (5).

(*R*)-(+)-Dimethyl *N*-benzyloxycarbonylglutamate 5d. Obtained from ozonolysis of diene **4f**. The crude product was purified by column chromatography on silica gel, eluting with light petroleum–ether (2 : 3) to give the pure product as a colourless oil (40%, 93% ee); $[\alpha]_D^{26}$ +23.2 (*c* 0.99, MeOH) (lit.,[45] *S*-enantiomer $[\alpha]_D^{20}$ −22.2 (*c* 1, MeOH)); δ_H (300 MHz; $CDCl_3$) 7.44–7.18 (5 H, m, ArH), 5.49 (1 H, d, *J* 7.5, NH), 5.10 (2 H, s, CH_2Ph), 4.41 (1 H, q, *J* 7.5, NCH), 3.74 (3 H, s, OMe), 3.65 (3 H, s, OMe), 2.52–2.31 (2 H, m, CH_2), 2.29–2.09 (1 H, m, C*H*H), 2.07–1.87 (1 H, m, CH*H*); δ_C (75 MHz; $CDCl_3$) 173.4 (C), 172.6 (C), 156.2 (C), 136.4 (C), 128.8 (CH), 128.5 (CH), 128.4 (CH), 67.4 (CH_2), 53.6 (CH), 52.9 (Me), 52.1 (Me), 30.2 (CH_2), 27.9 (CH_2).

(*R*)-(−)-Methyl 2-benzyloxycarbonylamino-2-cyclohexylethanoate 5e. Obtained from ozonolysis of olefin **4g**. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (1 : 4) to give the pure product as a colourless oil (70%); $[\alpha]_D^{28}$ −18.7 (*c* 1.07, $CHCl_3$) (lit.,[45] *S*-enantiomer $[\alpha]_D^{28}$ +17.38 (*c* 1.07, $CHCl_3$)); (Found: C, 66.6; H, 7.4; N, 4.3. $C_{17}H_{23}NO_4$ requires C, 66.9; H, 7.6; N, 4.6%); (Found: MH^+, 306.1721. $C_{17}H_{23}NO_4$ + H requires 306.1705); ν_{max}(film)/cm^{-1} 3350, 3032, 2929, 2854, 1724, 1522, 1451, 1341, 1213, 1061, 1025; δ_H (300 MHz; $CDCl_3$) 7.48–7.19 (5 H, m, ArH), 5.39 (1 H, d, *J* 8.8, NH), 5.10 (2 H, s, CH_2Ph), 4.29 (1 H, dd, *J* 8.8, 5.3, NCH), 3.72 (3 H, s, OMe), 1.87–1.46 (6 H, m, 3 × CH_2), 1.36–0.90 (5 H, m, CH, 2 × CH_2); δ_C (75 MHz; $CDCl_3$) 172.8 (C), 156.4 (C), 136.5 (C), 128.8 (CH), 128.4 (CH), 67.2 (CH_2), 59.0 (CH), 52.3 (Me), 41.2 (CH), 29.6 (CH_2), 28.2 (CH_2), 26.2 (CH_2); one ArCH not observed; *m*/*z* (CI) 306 (MH^+, 7%), 262 (65), 246 (11), 202 (11), 170 (88), 138 (6), 119 (8), 91 (100).

(*S*)-(+)-2-Benzyloxycarbonylamino-8-oxodecanoic acid 5f (*N*-Cbz-Aoda). The diene **4h** (100 mg, 0.320 mmol) was stirred at room temperature in carbon tetrachloride (1.5 mL), acetonitrile (1.5 mL) and water (2 mL) with periodic acid (456 mg, 2.000 mmol) for 10 min. $RuCl_3 \cdot 3H_2O$ (1 mg, 0.006 mmol, 2 mol%) was added and the reaction mixture stirred at room temperature for 3 h. Water (5 mL) and dichloromethane (5 mL) were added and the aqueous layer was basified to pH 9 with saturated aqueous sodium hydrogen carbonate solution. The solution was extracted with dichloromethane (3 × 5 mL) and the aqueous layer was acidified (pH 1) with hydrochloride

acid (2 M). The solution was further extracted with dichloromethane (3 × 5 mL). The last dichloromethane organic layers were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel, eluting with acetic acid–dichloromethane–light petroleum (1 : 1 : 8) to give the pure product as a colourless oil (42 mg, 39%); $[\alpha]_D^{25}$ +6.9 (*c* 1.30, $CHCl_3$) (lit.,[37] not given); (Found: MH^+, 336.1808. $C_{18}H_{25}NO_5$ + H requires 336.1811); ν_{max}(film)/cm^{-1} 3329, 3063, 3027, 2939, 2858, 2576, 1712, 1522, 1456, 1404, 1342, 1217, 1050; δ_H (300 MHz; $CDCl_3$) 7.43–7.22 (5 H, m, ArH), 7.08 (1 H, br s, OH), 6.22 (1 H, br, NH, minor rotamer), 5.42 (1 H, d, *J* 7.9, NH, major rotamer), 5.10 (2 H, AB, *J* 11.5, C*H*$_2$Ph), 4.35 (1 H, m, NCH, major rotamer), 4.25 (1 H, br, NCH, minor rotamer), 2.39 (4 H, m, 2 × CH_2), 1.86 (1 H, m, C*H*H), 1.75–1.45 (3 H, m, CH*H*, CH_2), 1.44–1.18 (4 H, m, 2 × CH_2), 1.03 (3 H, t, *J* 7.3, Me); δ_C (75 MHz; $CDCl_3$) *major rotamer* 212.7 (C), 176.8 (C), 156.5 (C), 136.3 (C), 128.7 (CH), 128.3 (CH), 128.2 (CH), 67.2 (CH_2), 54.0 (CH), 42.3 (CH_2), 36.1 (CH_2), 32.3 (CH_2), 28.8 (CH_2), 25.2 (CH_2), 23.7 (CH_2), 8.0 (Me); *m*/*z* (ES) 693 (2 M + Na, 25%), 688 (2 M + NH_4, 25), 358 (M + Na, 45), 353 (M + NH_4, 75), 336 (MH^+, 100), 292 (35).

(*S*)-(+)-2-Benzyloxycarbonylamino-2,3-dimethylbutanoic acid 5g (*N*-Cbz-α-methylvaline). The olefin **4i** (100 mg, 0.400 mmol) was stirred at room temperature in carbon tetrachloride (1.5 mL), acetonitrile (1.5 mL) and water (2 mL) with periodic acid (456 mg, 2.00 mmol) for 10 min. $RuCl_3 \cdot 3H_2O$ (2 mg, 0.008 mmol, 2 mol%) was added and the solution heated at 50 °C for 5 h. Water (5 mL) and dichloromethane (5 mL) were added and the aqueous layer was basified to pH 9 with saturated aqueous sodium hydrogen carbonate solution. The solution was extracted with dichloromethane (3 × 5 mL) and the aqueous layer was acidified (pH 1) with hydrochloride acid (2 M). The solution was further extracted with dichloromethane (3 × 5 mL). The last dichloromethane organic layers were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel, eluting with acetic acid–dichloromethane–light petroleum (1 : 1 : 8) to give the pure product as a colourless oil (40 mg, 38%); $[\alpha]_D^{23}$ +16.3 (*c* 0.80, $CHCl_3$); (Found: MH^+, 266.1391. $C_{14}H_{19}NO_4$ + H requires 266.1392); ν_{max}(film)/cm^{-1} 3409, 3327, 3062, 3031, 2971, 2639, 2547, 1715, 1507, 1456, 1410, 1343, 1258, 1069; δ_H (300 MHz; $CDCl_3$) 9.72 (1 H, br, OH), 7.33 (5 H, m, ArH), 5.39 (1 H, br s, NH), 5.09 (2 H, s, C*H*$_2$Ph), 2.21 (1 H, br m, C*H*Me$_2$), 1.56 (3 H, s, CMe), 0.96 (6 H, dd, *J* 9.2, 7.0, CH*Me*$_2$); δ_C (75 MHz; $CDCl_3$) 178.9 (C), 155.7 (C), 136.4 (C), 128.8 (CH), 128.44 (CH), 128.38 (CH), 67.1 (CH_2), 63.2 (C), 35.0 (CH), 19.1 (Me), 17.5 (Me), 17.4 (Me); *m*/*z* (FI) 265 (M^+, 100%), 220 (7), 114 (18), 108 (31).

(*R*)-(−)-*N*-Acetylphenylglycine 5h. (*S*)-(−)-*N*-Acetyl-1-phenylprop-2-enylamine **4j** (30 mg, 0.17 mmol) was dissolved in CCl_4 : CH_3CN : H_2O (2 : 2 : 3; v/v; 3 mL), sodium metaperiodate (147.6 mg, 0.69 mmol) and $RuCl_3 \cdot 3H_2O$ (cat.) was added and the mixture was stirred for 2 h. The product was extracted with ethyl acetate (3 × 5 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography to give the *title compound* as a colourless solid (8 mg, 24%); mp 188–189 °C (lit.,[46] 190–191 °C); $[\alpha]_D^{20}$ −100.0 (*c* 0.80, MeOH) (lit.,[46] $[\alpha]_D^{22}$ −215.5 (*c* 1.30, 95% EtOH)); (400 MHz; CD_3OD) 7.45–7.35 (5 H, m, ArH), 5.41 (1 H, s, NHC*H*), 2.00 (3 H, s, Me); N*H* and CO_2H not observed; δ_C (100 MHz; $CDCl_3$) 171.4 (C), 169.3 (C), 136.9 (C), 128.3 (CH), 127.8 (CH), 127.3 (CH), 57.1 (CH), 20.8 (Me).

(*S*)-(+)-Methyl 2-benzyloxycarbonylamino-2-(4-methoxyphenyl)ethanoate 5i. Obtained from ozonolysis of olefin **4k**. The crude product was purified by column chromatography on silica gel, eluting with ether–light petroleum (1 : 2) to give the pure product as a colourless solid (58%); mp 54–56 °C (lit.,[47] racemate, not given); $[\alpha]_D^{28}$ +106.9 (*c* 0.58, $CHCl_3$); (Found: C, 65.1; H, 5.8; N, 4.1. $C_{18}H_{19}NO_5$ requires C, 65.6; H, 5.8; N, 4.3%); (Found: M^+, 329.1252. $C_{18}H_{19}NO_5$ requires 329.1263); ν_{max}(KBr)/cm^{-1} 3383, 3012, 2971, 2945, 2889, 2843, 1739, 1700, 1516, 1434, 1314, 1256, 1208, 1179, 1050; δ_H (300 MHz; $CDCl_3$) 7.43–7.11 (7 H, m, ArH), 6.87 (2 H, d, *J* 8.7, ArH), 5.83 (1 H, d, *J* 6.4, NH), 5.31 (1 H, d, *J* 7.1, NCH), 5.08 (2 H, AB, *J* 12.1, C*H*$_2$Ph), 3.78 (3 H, s, OMe), 3.71 (3 H, s, OMe); δ_C (75 MHz; $CDCl_3$) 171.8 (C), 160.0 (C), 155.6 (C), 136.4 (C), 128.9 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 114.6 (CH), 67.3 (CH_2), 57.6 (CH), 55.5 (Me), 53.0 (Me); *m*/*z* (FI) 329 (M^+, 100%).

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