Conformational preference in aromatic amides bearing chiral *ortho* substituents: its origin and application to relayed stereocontrol

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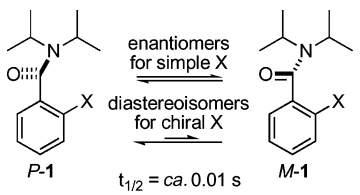
Tertiary aromatic amides bearing stereogenic centres *ortho* to the amide group may adopt two diastereoisomeric conformations which interconvert slowly on the NMR timescale at ambient temperature, and are therefore detectable by NMR. Certain classes of stereogenic centre—particularly sulfoxides, ephedrine-derived oxazolidines, and proline-derived imidazolidines—strongly bias the population of the two conformers. We propose a model, supported by molecular mechanics calculations, which rationalises the sense and magnitude of the conformational selectivity attained in terms of the steric and electronic properties of the controlling centre. The control over conformation may be exploited either by trapping the favoured conformer as an atropisomer, or by using it to relay information about the stereochemistry of the controlling centre.

Introduction

Tertiary aromatic amides bearing at least one *ortho* substituent, such as **1**, adopt conformations in which the ring and the amide group lie more or less perpendicular.[1,2] Given an unsymmetrically substituted aromatic ring, this feature gives rise to enantiomeric conformers *P*-**1** and *M*-**1** (Scheme 1) and we[3–9] and others[10,11] have studied the rate at which these conformers interconvert. In many 2,6-disubstituted amides,[1,3] the rate of conformer interconversion is, in principle[12] (and in many cases, in practice[3,5,7,9,10,13–16]), slow enough for them to become atropisomers, separable into axially chiral stereoisomers. 2-Substituted benzamides **1** with only one *ortho* substituent are typically not atropisomeric (Scheme 1),[3,†] but Ar–CO rotation in such compounds is nonetheless slow on the NMR timescale (a half-life for Ar–CO rotation of the order of 0.01 s), a feature which allows dynamic NMR methods to be used as a means of determining rotational barriers.[3,4]



Scheme 1 Conformers of tertiary benzamides.

Given an unsymmetrically and chirally substituted ring, the two conformers of **1** about the Ar–CO bond become diastereoisomeric, with their relative stability and therefore the ratio in the equilibrating mixture determined by the relative importance of the diastereoisomeric interactions between the chiral axis and chiral substituent X. In previous publications we have reported scattered observations that this effect can lead to surprisingly high levels of conformational control, mainly in 1-naphthamides.[17] These observations have covered such chiral groups as 1-silylethyl[18,19] and 1-stannylethyl[20,21] groups, 1-hydroxyalkyl[3,6] and 1-aminoalkyl[22,23] groups, sulfinyl groups[9,15,24] and oxazolidinyl[14,25,26] and imidazolidinyl[14,27] groups derived by condensation of aldehydes with (−)-ephedrine or with a diamine derived from (−)-proline. In this paper, we now report in full our studies of the ability of these and other chiral groups to control the orientation of tertiary aromatic amides in general, and offer a qualitative and quantitative rationalisation for some of the observations by molecular modelling, and we show how the conformational control achieved can be applied to the use of amides to relay stereochemical control.

Earlier observations

We have previously shown, in a series of publications,[1,6,19,21,22,28,29] that the perpendicular architecture of an aromatic amide is able to exert kinetic stereochemical control over the formation of new stereogenic centres, leading to the synthesis of atropisomeric diastereoisomers with high levels of stereoselectivity. Among the best of these stereoselective reactions is the lateral lithiation–electrophilic substitution of 2-ethyl naphthamide **2**,[19,21] which on stannylation gives the *anti* product *anti*-**3** (Scheme 2).[21] The first indication that the newly formed stereogenic centre was able to reverse the sense of stereocontrol in the reaction which formed it came when we were isolating the stannane *anti*-**3**:[20,21] even gentle heating was enough to promote its equilibration, by Ar–CO rotation, to the apparently more stable *syn* isomer. After 48 h at 65 °C in toluene, a 97 : 3 ratio of atropisomers in favour of the *syn* isomer was observed by integration of the NMR spectrum of the equilibrated mixture.[21]

2-Substituted tertiary naphthamides such as **2** typically exhibit barriers to Ar–CO rotation of >100 kJ mol^{-1}:[3,9] their Ar–CO conformers are atropisomeric (with a half-life for diastereoisomeric interconversion at room temperature typically of the order

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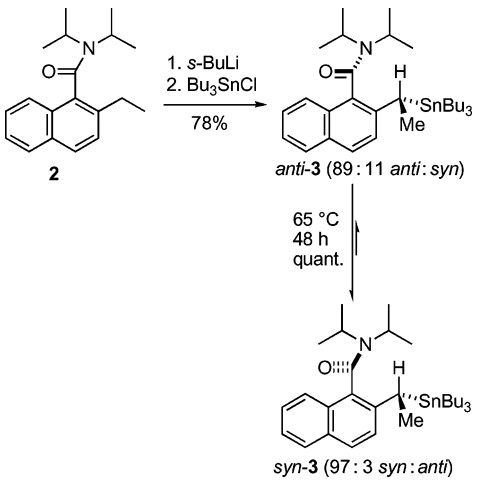
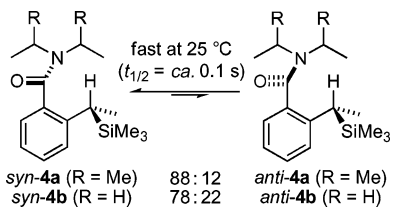
† The principal exceptions are peri-substituted naphthamides. See ref. 5.



Scheme 2 Equilibration between diastereoisomeric atropisomers.

of hours or more) and equilibrate only on heating. 2-Substituted, 6-unsubstituted tertiary benzamides **1** by contrast have barriers to Ar–CO rotation typically of only around 70 kJ mol^{-1}: their Ar–CO conformers interconvert rapidly at room temperature ($t_{1/2}$ *ca.* 0.01 s).[3] This rate is however still slow on the NMR timescale,[30] and NMR analysis of the benzamides **4**[7,31] bearing a chiral 2-substituent confirmed that indeed two conformers (Scheme 3) were clearly discernible in the NMR spectrum at, or for **4b** just below, room temperature. The ratio of conformers was easily established by integration of the spectra: **4a** shows two conformers in the ratio 88 : 12 at 23 °C, **4b** two conformers in the ratio 78 : 22 at −20 °C. Fig. 1 shows a portion of the NMR spectrum (the upfield C*H*Me$_2$ signal) of **4a**.



Scheme 3 Conformers of 2-(1-silyl)ethyl benzamide **4**.

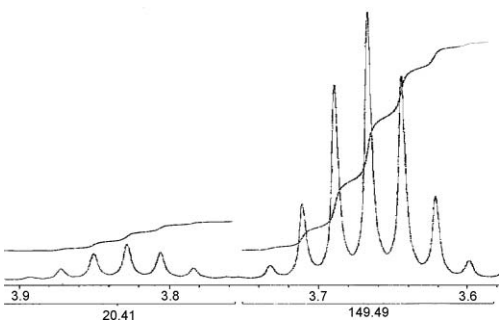


Fig. 1 A portion of the ^{1}H NMR spectrum of **4**, illustrating the presence of two diastereoisomeric conformers.

The X-ray crystal structure of **4a** led us to put forward a model to account for the conformational preference of **4a**[7,17] which we now propose to refine and use to rationalise conformational preferences in both 2-substituted benzamides of the general structure **6** and in

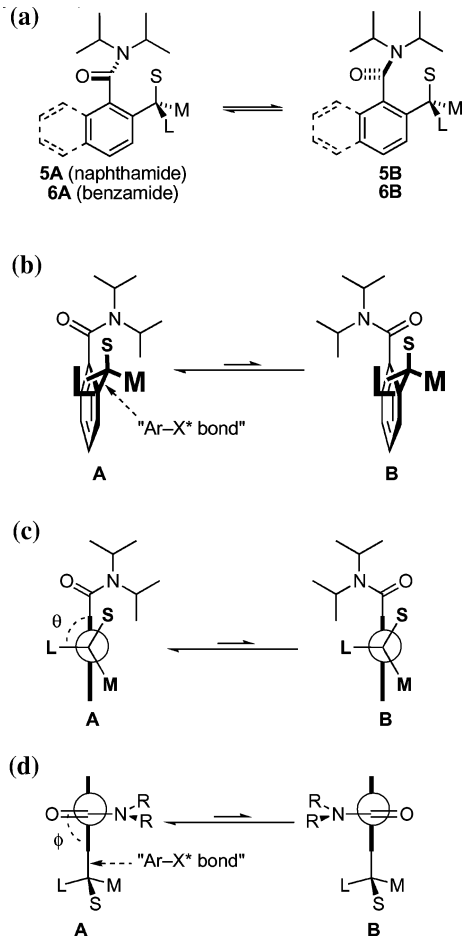


Fig. 2

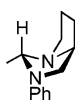
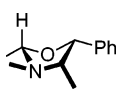
2-substituted naphthamides of the general structure **5** (Fig. 2a–c). In this model, S, M and L are the smallest, medium-sized and largest groups at the stereogenic centre, respectively. We propose that the favoured conformation, shown in Fig. 2 as **A**, is one in which the smallest group S more or less eclipses the amide Ar–CO bond while the largest group L occupies a position as far as possible from the amide's bulky *N*-substituents. Similar conformations are well established for chiral centres next to alkene π systems.[32] Fig. 2a illustrates the way we shall usually draw this conformer of **5** and **6**; Fig. 2b represents a perspective view of the same conformer; Fig. 2c represents this conformer in the form of a Newman projection along what we will term the "Ar–X* bond"; Fig. 2d shows the same conformation as a Newman projection along the Ar–CO bond. The angle θ may lie anywhere in the region of 90–120° and ϕ anywhere in the region of 90°: the difference in θ between Fig. 2b and 2c is due to the need for representational clarity and is not intended to carry any significance (*i.e.*, while the two show slightly different *conformations* they are intended to represent the same *conformer*[33]).

Results and analysis

Conformational control in aromatic amides bearing chiral 2-substituents

Several naphthamides **5** bearing chiral 2-substituents were available from diverse research projects, and Table 1 summarises

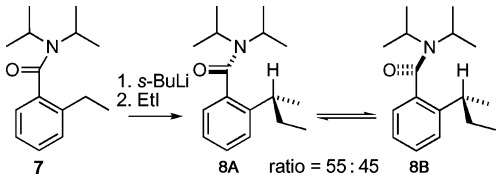
Table 1 Conformational preferences in naphthamides **5** bearing chiral 2-substituents

Entry	Compound		R	Ratio of diastereoisomers **A** : **B**	Solvent	T/°C	Reference
1	**5a**		—	60 : 40	Toluene	65	21
2	**5b**		—	94 : 6	Toluene	65	20
3	**5c**		Me	88 : 12	Toluene	60	21
4	**5d**		Bu	97 : 3	Toluene	65	21
5	**5e**		Me	62 : 38	Dioxane	62	3
6				56 : 44[a]	Dioxane	60	3
7	**5f**		Et	58 : 42	Dioxane	55	3
8	**5g**		Bu	51 : 49	Toluene	60	3
9				64 : 36	Dioxane	61.5	3
10				63 : 37[a]	Dioxane	61.5	3
11				65 : 35	EtOH	60	3
12	**5h**		Ph	64 : 36	Dioxane	60	3
13				59 : 41[a]	Dioxane	62	3
14	**5i**		*t*-Bu	11 : 89	Toluene	110	34
15	**5j**		Me	82 : 18	$CDCl_3$	60	22
16	**5k**		Bu	80 : 20	$CDCl_3$	60	22
17	**5l**		Me	62 : 38	$CDCl_3$	60	22
18	**5m**		Bu	47 : 53	$CDCl_3$	60	22
19	**5n**		—	>90 : 10	Toluene	110	14
20			—	>90 : 10	Toluene	110	14
21	**5o**		—	>95 : 5	Toluene	110	14
22			—	>95 : 5[a]	Toluene	110	14
23	**5p**		Me	99.5 : 0.5	$CDCl_3$	25	24
24	**5q**		*t*-Bu	>98 : 2	$CDCl_3$	25	24
25	**5r**		Ph	>98 : 2	$CDCl_3$	25	24
26	**5s**		*p*-Tol	>99 : 1	$CDCl_3$	25	24

[a] *N*,*N*-Diethylamide.

the ratios obtained when the atropisomeric diastereoisomers of these naphthamides were thermally equilibrated by heating in solution.

1. 2-Alkyl, 2-(1′-trialkylsilyl)ethyl and 2-(1′-trialkylstannyl)-ethyl substituents. The equilibrated ratios of atropisomers of the naphthamides in Table 1, entries 1–4, suggest that steric contrast between M and L is essential for good selectivity in these groups of compounds bearing electronically similar S, M and L groups. For example, while **5b**–**d**, with L = SiR_3 or SnR_3 and M = Me show high selectivity, in **5a**, with L = Et and M = Me, selectivity is poor. We made **8**, the benzamide analogue of **5a**, by lateral lithiation and ethylation of **7** (Scheme 4); its NMR spectrum at 23 °C in C_6D_6 showed two sets of peaks in a predictably almost unbiased ratio of 55 : 45. We confirmed that these represented diastereoisomeric conformers by variable temperature NMR (VT



Scheme 4 Conformers of a 2-*sec*-alkyl benzamide **8**.

NMR): coalescence between the pairs of peaks was observed at temperatures approaching 70 °C.

In order to investigate the validity of the conformational model shown in Fig. 2 when applied to compounds **4a** and **8** (and hence, by extension, **5a**–**d**) we modelled the two Ar–CO conformers **A** and **B** of **4a** and **8** using Macromodel (MM2*).[35] Fig. 3a shows a dihedral drive plot of energy against θ for the two Ar–CO conformers of **8** (**A** and **B**) and Fig. 3b the two Ar–CO conformers of **4a** (**A** and **B**)

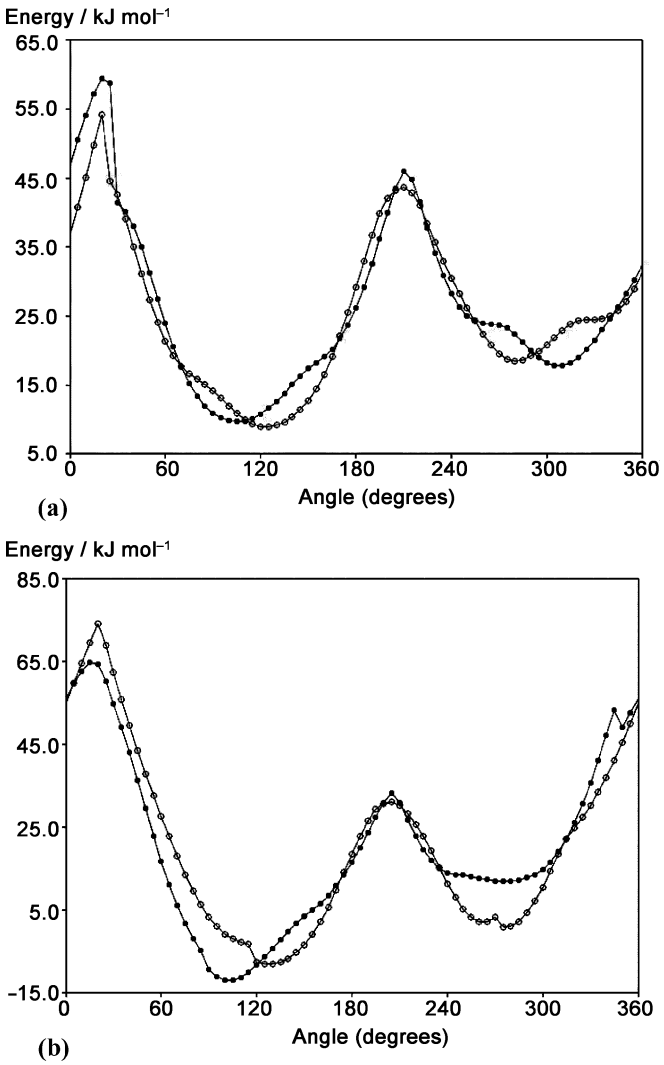


Fig. 3 (a) Plot of E *vs.* θ (see Fig. 2c) for **8A** (solid circles) and **8B** (open circles); (b) plot of E *vs.* θ (see Fig. 2c) for **4aA** (solid circles) and **4aB** (open circles).

The calculations confirm two features of our model. Firstly, for both Ar–CO conformers of both compounds, there are two stable conformations both with L more or less perpendicular to the plane of the ring. Of these, the favoured conformation approximates to that shown in Fig. 2, with $100° < \theta < 130°$ in both cases, in other words, H almost but not quite eclipsing the Ar–CO bond. Secondly, it confirms that in **4a** with L = SiR_3, the most stable conformations of the two Ar–CO conformers differ in energy by 4.05 kJ mol^{-1}, corresponding to a conformational ratio at 25 °C of 80 : 20. The same is not true for **8** with L = Et, in which the most stable conformations of the two Ar–CO conformers differ by only 1.51 kJ mol^{-1}, corresponding to a ratio of 55 : 45 at 25 °C. The absolute values of these figures are remarkably close to the experimentally determined ratios of 88 : 12 for **4a** and 55 : 45 for **8**.

In further support of the model in Fig. 2, though only insofar as the crystalline state gives an impression of conformation in solution, analysis of the X-ray crystal structures of some benzamides **4a** (shown in Fig. 4),[7] 6-diphenylphosphanyl-**4a**[7] and the related naphthamides **5a**[21] and **5c**[21] showed that the values of θ and ϕ (Figs. 2c, 2d) favoured by these compounds in the crystalline state (Table 2, entries 1–4) were more or less in agreement with our modelling. We are confident therefore that the model shown in Fig. 2 is fundamentally sound.

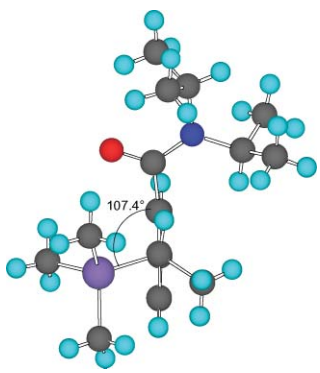


Fig. 4 View of X-ray crystal structure of **4a**[7] along the Ar–X* bond.

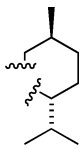
2. 2-(1′-Hydroxy)alkyl substituents. In the naphthamide series, thermal equilibration of the atropisomeric alcohols **5e**–**5h** (Table 1, entries 5–14) indicated a weak thermodynamic preference for atropisomer A, with the amide C=O and OH group *syn* when drawn as the conformer shown in Fig. 2.[3] The ratios showed a weak solvent dependence. Only in **5i**, in which R is a *t*-butyl group (Table 1, entry 14) was the "*anti*" atropisomer B favoured.

To establish the effect of a chiral 2-substituent on the conformation of benzamides or the analogous nicotinamides, we made the

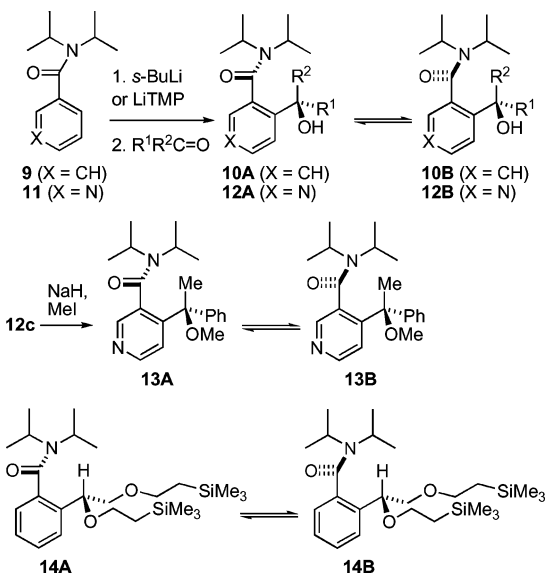
Table 2 Dihedral angles in selected X-ray crystal structures (see Fig. 2c, 2d)

Entry	Compound	θ (deg)	ϕ (deg)	Reference
1	**4a**	107.4	78.3	7
2	6-PPh_2–**4a**	101.3	88.3	7
3	**5a**	106.2	88.7	21
4	**5c**	99.5	89.7	21
5	**5o**	134.3	89.4	14
6	**33b**	132.8	86.9	This work
7	**33f**	133.2	80.8	This work
8	**33g**	127.9	86.4	This work

Table 3 Conformational preferences in benzamides and nicotinamides with hydroxyl-bearing 2-substituents

Entry	Compound	R^1	R^2	Yield (%)	Ratio of diastereoisomers **A** : **B**	Solvent
1	**12a**	Ph	H	67	50 : 50	$CDCl_3$
2	**10b**	Et	Me	59	50 : 50	$CDCl_3$
3	**12b**	Et	Me	83	50 : 50	$CDCl_3$
4	**10c**	Ph	Me	60	90 : 10	$CDCl_3$
5	**12c**	Ph	Me	61	90 : 10	$CDCl_3$
6					85 : 15	80 : 20 $CDCl_3$–CD_3OD
7					80 : 20	60 : 40 $CDCl_3$–CD_3OD
8					70 : 30	CD_3OD
9					60 : 40	d_6-DMSO
10					50 : 50	D_2O
11	**10d**			59	50 : 50	$CDCl_3$
12	**10e**			59	50 : 50	$CDCl_3$
13	**13**	Ph	Me	85	30 : 70	$CDCl_3$
14					30 : 70	CD_3OD
15	**14**	CH_2OR	H	40	34 : 66	$CDCl_3$

alcohols **10** and **12** by ortholithiation of **9**[36–38] or **11**[39] and addition to benzaldehyde, 2-butanone, acetophenone, norbornanone or fenchone (Scheme 5). Alcohol **12c** was methylated to give **13**. We also investigated the ether **14**, made from **9** by sequential double lithiation and quench with SEMCl.[40] Interconversion of the diastereoisomeric conformers is slow on the NMR timescale and integration of the NMR spectra of the products in a variety of solvents gave the conformational ratios shown in Table 3. We were unable to identify unambiguously the structure of the major conformer: assignments are made by analogy with the atropisomeric diastereoisomers in entries 5–14 of Table 1 and by assuming that the X-ray crystal structure of **10c** (Fig. 5) represents its favoured conformation in solution.



Scheme 5

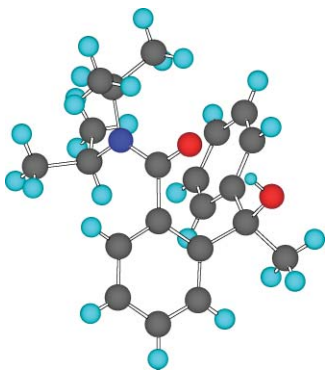


Fig. 5 X-Ray crystal structure of **10c**.

In cases where analogous pairs were made, the nicotinamides and benzamides had essentially identical conformational preferences, and comparing the nicotinamide **10a** with the naphthamide **5h** in Table 1, entry 12, showed a comparable lack of conformational bias. Neither was any significant conformational preference evident in the alcohols **10b**, **10d**, **10e** or **12b**, obtained by addition to ketones 2-butanone, norbornanone or menthone. However, addition of **9** or **11** to acetophenone gave alcohols **10c** and **12c** which showed a relatively strong bias towards one conformer in $CDCl_3$. Moving successively to more polar solvents (entries 5–10) gradually decreased the bias to, in water, just 1 : 1. This bias seems to be due principally to hydrogen bonding, rather than solely dipole effects, because alkylation to give **13** reduced (and possibly—we cannot be sure of the assignment—inverted) the preference from 90 : 10 to 30 : 70.‡ Furthermore, the X-ray crystal structure (Fig. 5) of **10c** shows the molecule adopting a conformation in the solid state approximating to **10cA** with an

‡ Hydrogen-bonding seems to have a powerful role to play in the conformational preferences of analogous compounds with the chiral hydroxyalkyl substituent in the 8-position. See ref. 6.

intramolecular hydrogen bond evident between the hydroxyl group and the amide carbonyl oxygen atom.

The surprisingly weak conformational preference in most of these compounds is presumably due to a balance between the conflicting demands of steric encumbrance, hydrogen bonding and dipole repulsion. We propose the model shown in Fig. 6 as a means of accounting for these effects, though the orientation of the groups R^1, R^2 and OH, particularly for conformer B, remains very much open to question. Two main features are clear. Firstly, intramolecular hydrogen bonding favours conformation A, and for **12c** the more hydrogen-bonding the solvent the less populated is conformer A (entries 5–10). Similarly, methylation of **12c** to yield **13** reduces the population of A (Table 3, entries 5 and 13) and removes this solvent dependence (Table 3, entries 8 and 14). Secondly, steric contrast seems relatively unimportant in this series, except when R^1 is *t*-Bu, when conformer B becomes favoured (Table 1, entry 14), presumably because of its more severe interaction with NR_2 in conformer A. Finally, in compounds **13** and **14**, where two of the substituents differ principally in electronegativity only, rather than size, the conformer with the C=O and C–O dipoles opposed appears to be weakly favoured (Table 3, entries 13–15). In general, stereogenic centres of these types offered relatively weak conformational preferences, and we did not pursue further the use of chiral alcohols or their derivatives as a means of attaining conformational control.

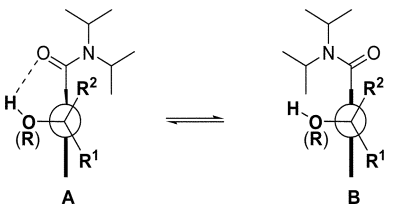


Fig. 6 Conformational preferences in 2-hydroxyalkyl benzamides and their derivatives.

3. 2-(1′-Amino)alkyl substituents. Comparing the conformational preference of the naphthamides **5j** and **5k** in entries 15 and 16 of Table 1 with those in entries 5 and 8, which differ only in the substitution of an NHMe for an OH substituent, shows that the preference for conformer A is stronger in the amine than in the alcohol. Increasing the bulk of the amino group by benzylation to yield **5l** and **5m** (entries 17, 18) has an effect contrary to what would be expected on steric grounds. It seems reasonable to propose therefore that the conformational preference of **5j** and **5k** is dictated by the potential for hydrogen bonding between C=O and N–H (Fig. 7) (though it is worth noting that no intramolecular

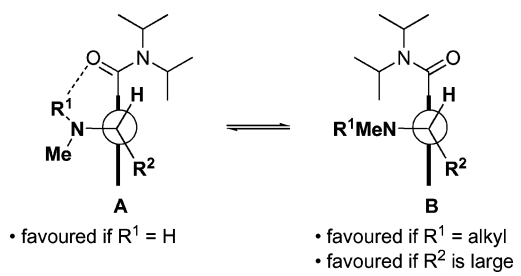


Fig. 7 Conformational preferences in 2-aminoalkyl benzamides and their derivatives.

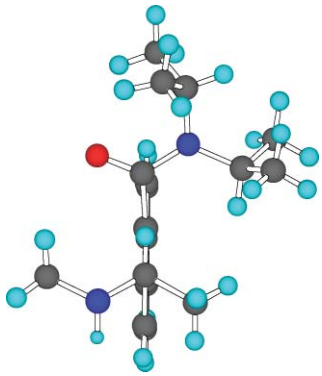
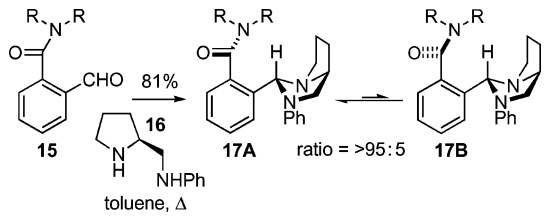


Fig. 8 View of X-ray crystal structure of **5j**[22] along the Ar–CH(Me)-NHMe bond.

hydrogen bond is evident in the X-ray crystal structure of **5j**:[22] Fig. 8 shows the X-ray crystal structure of **5j** viewed along the Ar–CH(Me)NHMe bond). Removing the potential for hydrogen bonding decreases the conformational preference, and indicates that the NMeBn group behaves as though it were relatively small.§

4. Proline-derived imidazolidines. Mukaiyama has demonstrated the use in asymmetric synthesis of imidazolidines formed by condensation of aldehydes with the proline-derived diamine **16**.[42,43] The R group of the aldehyde RCHO invariably lies *exo* on the bicylic imidazolidine.[43] In the naphthamide series, imidazolidine **5n**, derived by condensation of a 2-formylnaphthamide with diamine **16**, displays a strong (>90 : 10) conformational preference (Table 1, entry 19, 20) and is isolated as a single diastereoisomer at both the aminal centre and at the Ar–CO axis. Similarly, the room temperature NMR spectrum of the imidazolidine **17** contains a single set of sharp peaks strongly suggesting not only that the amide is a single diastereoisomer at the aminal centre, but also that it essentially adopts one Ar–CO conformation in solution, presumably (by analogy with the related naphthamide) **17A** (Scheme 6). Fig. 9 illustrates our rationalisation for this preference in both naphthamide **5n** and benzamides **17** and for comparison Fig. 10 shows the X-ray crystal structure of **5n**[14] viewed along the Ar–X* bond.



Scheme 6 Conformational control with a proline-derived diamine (R = Et).

The imidazolidine **17** (R = *i*-Pr) was modelled using the Macromodel[35] implementation of the MM2*, MM3 and MMFF forcefield. Two 5000-step Monte-Carlo conformational searches were carried out for each forcefield, the first search starting from **17A**, the second from **17B**. In each case the Ar–CO dihedral

§ In an accompanying paper (ref. 41) we show how the apparent small size of the NMeR group can be exploited to relay conformational control between remote atropisomeric axes.

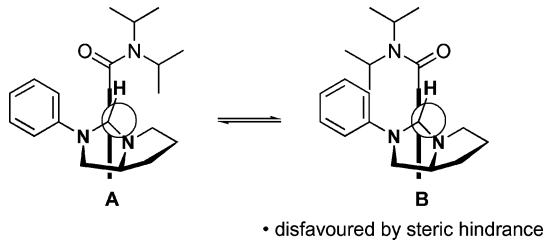


Fig. 9 Conformational preference in a proline-derived aminal.

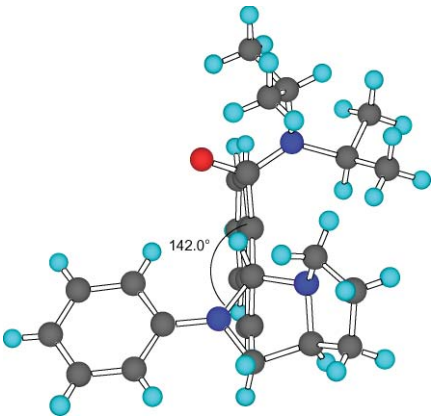
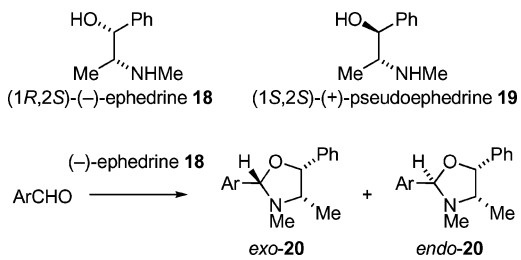


Fig. 10 View of the X-ray crystal structure of **5n**[14] along the Ar–X* bond ($\theta = 142.0$; $\phi = 76.7°$).

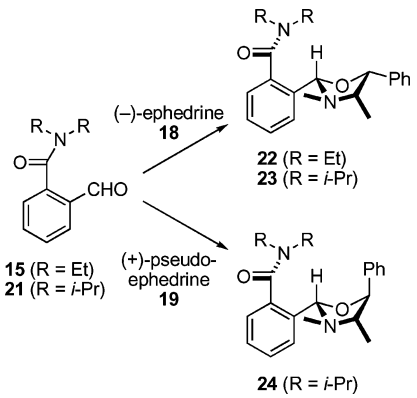
was constrained to ±90°. In this way two sets of conformers were generated, one set with Ar–CO orientation approximating to conformer **A** and one set with Ar–CO orientation corresponding conformer **B**. While all three force fields predict **17A** to be the lower energy conformer by at least 3.5 kJ mol^{-1}, only in MMFF is the energy difference (16.5 kJ mol^{-1}) sufficient to account for the observed thermodynamic selectivity (>95 : 5).

5. (−)-Pseudoephedrine- and (−)-ephedrine-derived oxazolidines. Condensation of (−)-ephedrine **18** or (+)-pseudoephedrine **19** with aldehydes is typically diastereoselective,[44–47] and with aromatic aldehydes the reaction creates a new stereogenic centre adjacent to the aromatic ring. Scheme 7 shows the reported products from condensation of ArCHO with (−)-ephedrine **18**: the major product (>90%) from benzaldehyde is *exo*-**20**, in which all of the substituents around the oxazolidine ring may lie pseudoequatorial. The minor product (<10%) is *endo*-**20**. Selectivity for the *exo* isomer is thermodynamic in nature,[45,47] and *endo*-**20** has been observed as the kinetic product of reactions with electron-deficient ArCHO, especially in alcoholic solvents.[47]



Scheme 7 Diastereoselective condensation of (−)-ephedrine with aldehydes.

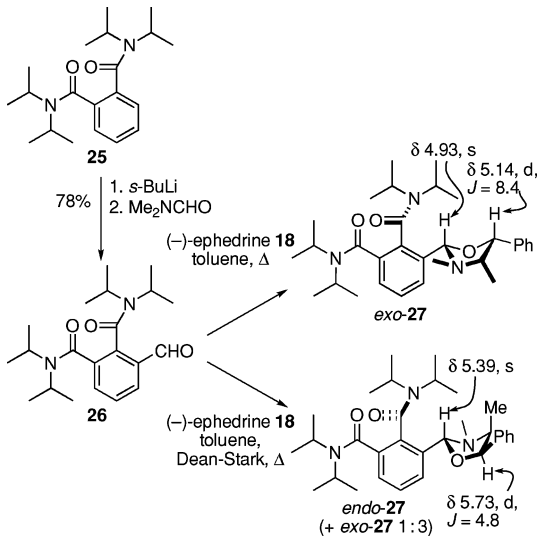
We condensed the aldehydes **15**, **21** and **26** with (−)-ephedrine **18** or (+)-pseudoephedrine **19** by refluxing in toluene for 24 h (Scheme 8). The oxazolidines **22**, **23** and **24** were formed from **15** and **21** as single diastereoisomers by NMR: there was no evidence for the presence of *endo* diastereoisomers (the distinctive NMR spectra of which[47] are discussed below). Moreover, the NMR spectra of the products showed single sharp sets of signals, indicating that the Ar–CO bond adopts essentially a single conformation, as is known to be the case when the Ar–CO atropisomers of the naphthamide analogues **5o** are allowed to equilibrate (Table 1, entries 21, 22). By analogy with the naphthamides **5o**, we assume the major Ar–CO conformers of **22** and **23** are as shown, and this conformation is evident in the X-ray crystal structure of derivatives of **22** (Table 2, entries 5–8). The conformation of the pseudoephedrine-derived product **23** was not assigned unambiguously, though the configuration of the new stereogenic centre at C2 of the oxazolidine ring is presumably controlled by the stereochemistry at the CH*Me* group, as is known for related compounds.[46]



Scheme 8 Condensation of an amidoaldehyde with ephedrine and pseudoephedrine.

The condensation of the diamide **26**, made *via* lithiation of **25**, with (−)-ephedrine was less straightforward. When the condensation was carried out simply by refluxing in toluene for 24 h, a single diastereosiomer of the product was formed which X-ray crystallography confirmed was the *exo* oxazolidine *exo*-**27** (Fig. 11a). The NMR spectrum of this compound was sharp and clean (see Fig. 12a) and it appears to exist in solution as a single conformer (>95 : 5), much like **23**. However, if the condensation was carried out using a Dean–Stark apparatus to remove water from the mixture, the crude product contained two diastereoisomers of the product in a 3 : 1 ratio, which were separable by flash chromatography. The major diastereoisomer was *exo*-**27**, but the minor diastereoisomer was shown by X-ray crystallography to be *endo*-**27**. The NMR spectra of the two oxazolidines **27** are shown in Fig. 12. The most distinctive differences (shown boxed in Fig. 12) between the two are the signals for H2 and H5 of the oxazolidine rings (Scheme 9). This spectroscopic feature has been noted previously,[47] and we now routinely make use of it to identify *endo* and *exo* oxazolidines.[48,49]

The differing stereoselectivities of the two condensations of **26** are presumably the result of kinetic *vs.* thermodynamic control. Agami[47] showed that condensation of aldehydes with (−)-ephedrine gives *exo* oxazolidines as the thermodynamic products



Scheme 9 Condensation of a diamidoaldehyde with ephedrine: kinetic and thermodynamic control.

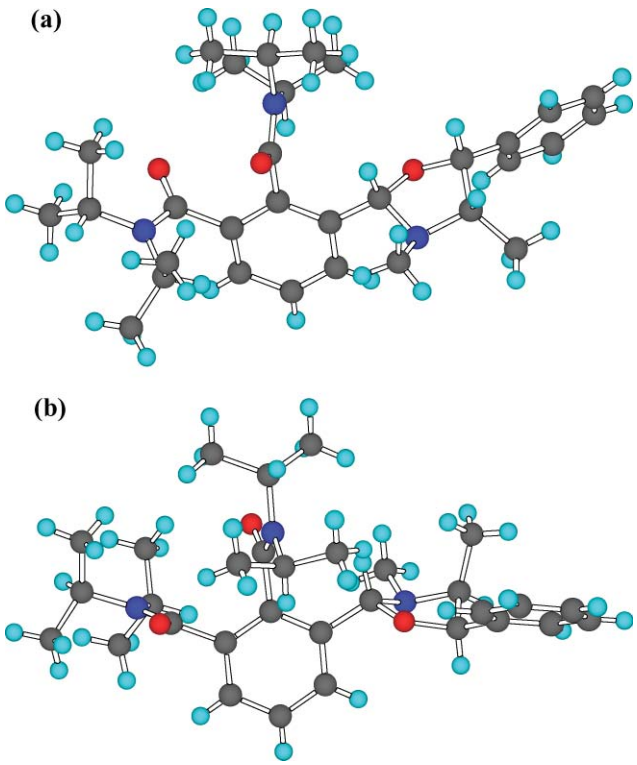


Fig. 11 (a) X-Ray crystal structure of *exo*-**27**; (b) X-ray crystal structure of *endo*-**27**.

but that reactions in polar solvents or with electron-deficient aldehydes yield initially *endo* oxazolidines, which only slowly epimerise to *exo*. The additional electron-withdrawing amide group of **26**, coupled with the rapid removal of water by the Dean–Stark apparatus, which would otherwise perhaps increase the rate of general acid catalysed epimerisation of the oxazolidine, must both contribute to the formation of the unexpected *endo* diastereoisomer. Resubjecting the *endo* oxazolidine *endo*-**27** to 1 h in refluxing toluene led to incomplete epimerisation to a 1 : 1 mixture of *endo* and *exo*-**27**.

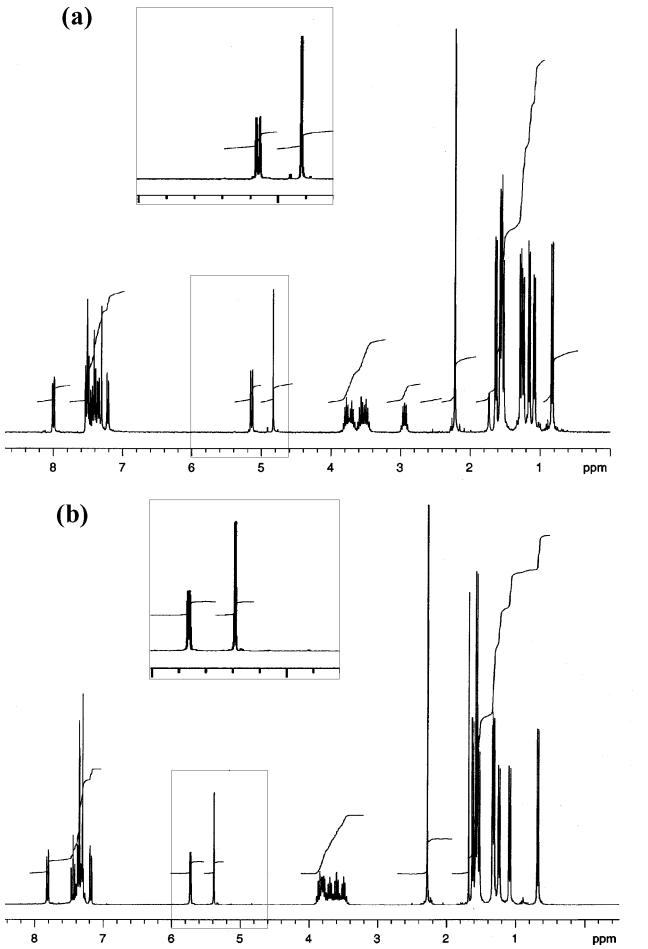


Fig. 12 (a) NMR spectrum of *exo*-**27**; (b) NMR spectrum of *endo*-**27**.

In order to clarify the reason for the preferred orientation of the amide bond in the amidooxazolidines **5o**, **5p**, **22**–**24** and *exo*-**27**, we used Macromodel[35] to carry out a Monte Carlo search of the conformations of **5o** with 3000 steps, finding 63 unique conformations, of which 26 minimised with good convergence. The global minimum of 34.1 kJ mol^{-1} was found 8 times, and corresponded to the conformation shown in Fig. 13a. The lowest energy conformation of opposite relative stereochemistry at the Ar–CO axis was 10.1 kJ mol^{-1} higher in energy, an energy difference corresponding to a conformational selectivity at 25 °C of >98 : 2 or at 110 °C of >96 : 4. Interestingly, the 10 kJ mol^{-1} difference in energy was made up almost entirely of a contribution from the electrostatic term. We therefore propose Fig. 13[14] as our rationalisation of the preferred Ar–CO conformation in **5o**, **5p**, **21**–**23** and *exo*-**27**, in which dipole repulsion between the amide

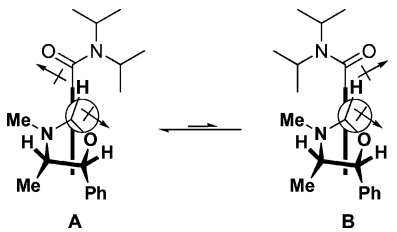


Fig. 13 Conformational preference in an ephedrine-derived oxazolidine.

C=O and the oxazolidine C–O is the principal factor governing the conformation. For comparison, Fig. 14 shows a corresponding view of the X-ray crystal structure of **5o**. We assume that a strong preference to place C=O *anti* to C–O is also at the root of the single conformation exhibited by *endo*-27.

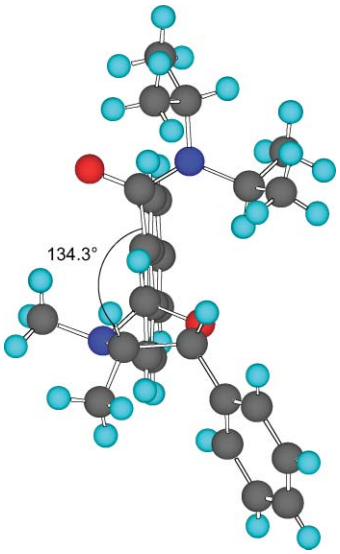
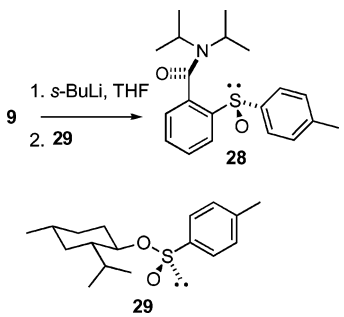


Fig. 14 View of X-ray crystal structure of **5o**[14] along Ar–X* bond (θ = 134.3; ϕ = 89.4°).

6. 2-Sulfinyl substituents. Naphthamides bearing 2-sulfinyl substituents are not atropisomeric because of the poor barrier to rotation offered by second row substituents,[7] but they exhibit extremely high levels of conformational control: for **5p** we found that one Ar–CO conformer is populated to a degree of >99.5% at ambient temperature.[24]

We made enantiomerically enriched sulfoxide **28** by ortholithiation of *N*,*N*-diisopropylnaphthamide **9** and reaction with (1*R*,2*S*,5*R*,S_S)-(−)-menthyl *p*-toluenesulfinate **29** (Scheme 10).[9,50,51]¶ The variable temperature NMR spectrum of **28** showed a single clean set of peaks at temperatures down to −50 °C in $CDCl_3$, and from this we deduce that **28**, like **5p**, exhibits a strong preference for the same single Ar–CO conformer, which we rationalise by proposing (on the basis of modelling studies[24]) that



Scheme 10 Synthesis of 2-sulfinyl benzamide **28**.

¶ Sulfoxide **25** has an optical rotation but we have not established beyond doubt that it is enantiomerically pure. Sulfoxide synthesis from **29** is not always reliably stereospecific: see ref. 52.

this conformation minimises interactions between the S–O and C=O dipoles (Fig. 16). The X-ray crystal structure of **28**[9] (Fig. 15) shows that this conformer is the one populated in the solid state.

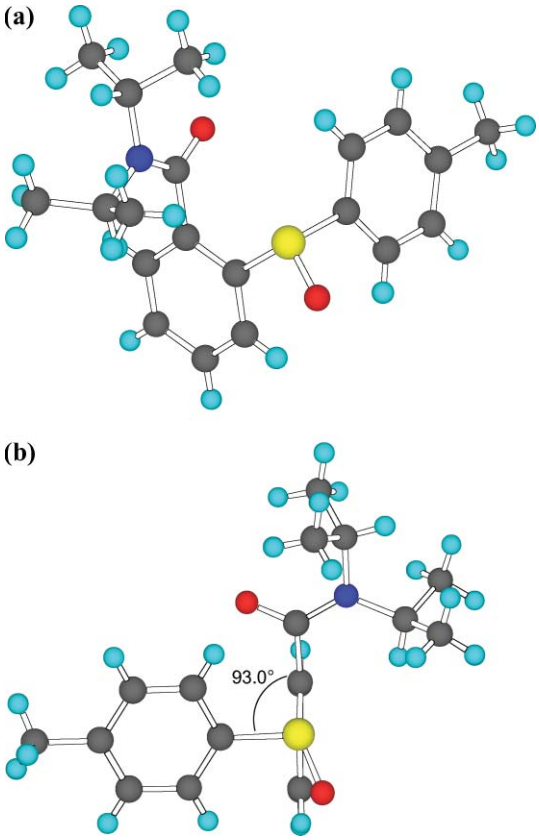


Fig. 15 (a) X-Ray crystal structure of **28**;[9] (b) view of the X-ray crystal structure of **28** along the Ar–S bond [reflected image shown for consistency with Fig. 16] (θ = 93.0; ϕ = 87.7°).

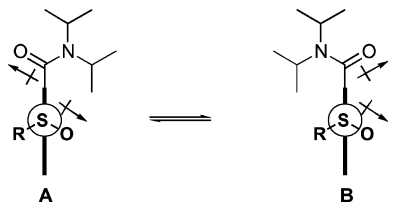
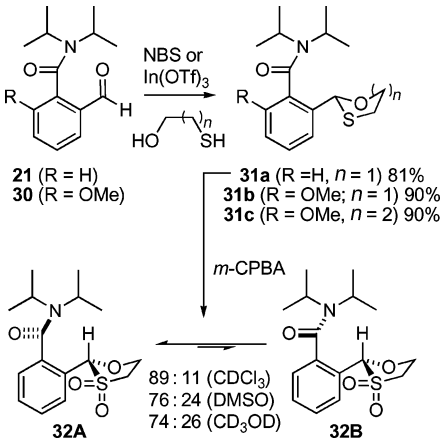


Fig. 16 Conformational preference in a 2-sulfinyl benzamide (for consistency, with other conformational diagrams in the paper, compounds shown are enantiomeric with **24**).

7. Oxathiolanes, oxathianes and oxathiolane *S*,*S*-dioxides. The outstanding levels of conformational control achieved with sulfoxides prompted us to investigate whether the electonegativity difference between S and O would similarly be able to control the orientation of an amide, opening up the possibility of using chiral hydroxythiols[53] to control amide stereochemistry in a manner analogous to our use of (−)-ephedrine. Aldehydes **21** and **30**[54] were condensed with 2-mercaptoethanol or 3-mercaptopropanol in the presence of NBS or indium triflate to yield the oxathianes and oxathiolanes **31a**–**c** (Scheme 11). The NMR spectrum of all three compounds showed two sets of peaks in a 1 : 1 ratio. For



Scheme 11 Formation of *S*,*O*-heterocycles.

31a, these must correspond to diastereoisomeric conformers (and indeed coalescence of the peaks at high temperature indicated that this was the case), indicating a total lack of conformational control. In **31b** and **31c** additional steric hindrance offers the possibility that the two sets of peaks are diastereoisomers,[3,54] and indeed two spots were visible in both cases by TLC. Separation by flash chromatography however did not give pure samples of each diastereoisomer, and within a few hours in chloroform, the ratio in each case returned to 1 : 1.

Oxathiolane **31a** was oxidised to the *S*,*S*-dioxide **32** with *m*-CPBA. The NMR spectrum of **32** in $CDCl_3$ showed two conformers in a ratio of 89 : 11 which coalesced on running the spectrum at higher temperatures. The ratio was lower in more polar solvents—76 : 24 in DMSO and 74 : 26 in methanol—suggesting that the conformational selectivity originates in dipole repulsion rather than steric hindrance, and we tentatively suggest that **32A** is favoured over **32B** (Fig. 17).

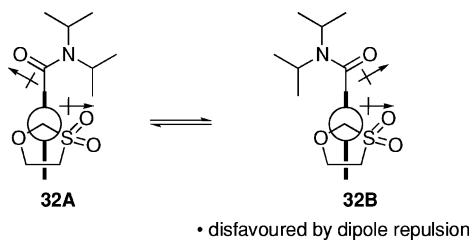


Fig. 17 Conformational preference in a 2-oxathiolanylbenzamide *S*,*S*-dioxide **32**.

Summary: achieving conformational control in benzamides

High levels of conformational control in benzamides **6** were achieved with (a) 2-(1-trialkylsilyl)ethyl groups (**4**); (b) 2-imidazolidinyl groups (**17**); (c) 2-oxazolidinyl groups (**22–24**, **27**) and (d) 2-sulfinyl groups **28**. In all cases, the chiral substituent is, or can easily be made, enantiomerically enriched or enantiomerically pure. The remainder of the paper describes "proof-of-concept" studies of some ways in which the controlled conformational preference of such amides may be exploited.

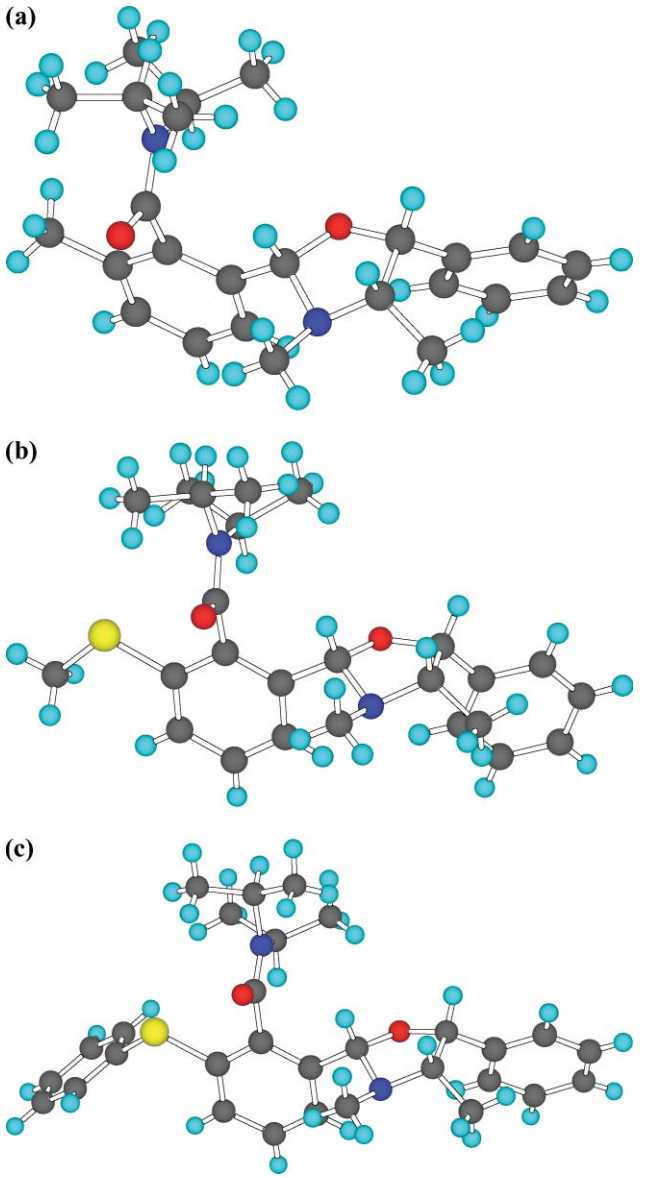


Fig. 18 (a) X-Ray crystal structure of **33b**; (b) X-ray crystal structure of **33f**; (c) X-ray crystal structure of **33g**.

Trapping conformational preference as atroposelectivity‖

While the two orientations of the amide group in a 2-substituted benzamide merely define two conformers of a single compound, in a 2,6-disubstituted benzamide the two orientations define two diastereoisomeric atropisomers. We therefore set out to convert the conformational selectivity exhibited by **17**, **22**, **23** and **28** into atroposelectivity by using ortholithiation[38,55,56] to introduce a 6-substituent *ortho* to the amide, trapping the preferred conformer as an atropisomer. A similar strategy has proved successful with enantiomerically pure amide **4b**,[7] and has been used to study the conformation of intermediates in atroposelective reactions.[19]

Of **17**, **22**, **23** and **28**, only the oxazolidines **22** and **23** could be successfully ortholithiated. Treatment of **17** or **28** with *s*-BuLi and a variety of electrophiles gave only complex mixtures of products.

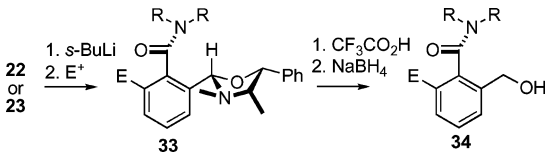
‖Preliminary report: see ref. 26.

Table 4 Trapping conformers as atropisomers

Entry	R	E^+	E	Yield **33** (%)	Yield **34** (%)	Ee **34** (%)
1	Et	MeI	Me	**33a** 58	—	—
2	*i*-Pr	MeI	Me	**33b** 55	**34b** 82	8
3	*i*-Pr	EtI	Et	**33c** 69	**34c** 87	28
4	*i*-Pr	Me_2NCHO	CHO	**33d** 89[40]	—	—
5	*i*-Pr	$Me_2C{=}O$	Me_2COH	**33e** 89	—	—
6	*i*-Pr	Me_2S_2	SMe	**33f** 39	**34f** 20	0
7	*i*-Pr	Ph_2S_2	SPh	**33g** 53	—	—

Sulfoxide **28** is presumably susceptible to nucleophilic attack at sulfur,[57] and was insufficiently acidic to be deprotonated by LiTMP or LDA.[55] Amides bearing additional organolithium-coordinating sites are known to behave problematically in ortholithiation reactions, often requiring large excesses of lithiating agent.[58]

Treatment of **22** or **23** with *s*-BuLi followed by the electrophiles listed in Table 4 however generally gave good yields of the 2,6-disubstituted benzamides **33a**–**g** which were isolated as single atropisomers with no traces of other diastereoisomers in the NMR spectra of the crude reaction mixtures (Scheme 12). The X-ray crystal structures of three of these products confirmed the expected orientation of the amide group, and are shown in Figs. 18a–c (see also Table 2, entries 5–8).

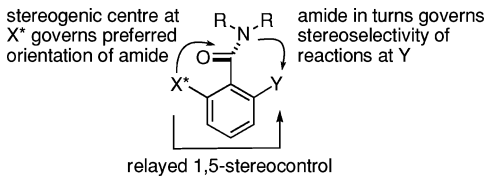


Scheme 12 Atroposelective synthesis *via* ephedrine-derived oxazolidines.

We hoped that hydrolysis under mild conditions would allow us to remove the ephedrine "auxiliary" and permit isolation of the 2,6-disubstituted amides in enantiomerically enriched form.[14,25] The sequence of reactions starting with **22** or **23** and culminating in such a deprotection would amount to a dynamic thermodynamic resolution.[59] The problem with the strategy is that, as noted previously,[14] while ephedrine-derived oxazolidines are rather stable to hydrolysis, the aldehyde products are relatively configurationally unstable at the Ar–CO bond. We therefore tried hydrolysing the oxazolidines **33b**, **33c** and **33f** with trifluoroacetic acid at 0 °C for as brief a time as possible, before neutralising and reducing the product aldehyde, still at 0 °C, and isolating the alcohols **34** (atropisomers carrying *ortho*-hydroxymethyl groups are typically more configurationally stable about their stereogenic axis than their aldehyde congeners[3,14,60]). Unfortunately, the best result which could be obtained was 28% ee for **34c**. Racemisation of the aldehyde intermediate is evidently still fast and further extension of this work was abandoned.

Using conformational preference to relay stereochemistry from centre to centre *via* an axis**

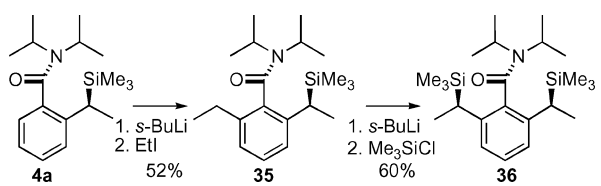
While it generally proved difficult to trap a conformational preference as a single atropisomer, we proposed that the induced conformational preference could still make its presence felt by its influence over the formation of a new stereogenic centre. It is well known that the orientation of an atropisomeric amide can exert powerful kinetic control over nucleophilic[6,13,22,29] and electrophilic[1,19,21] addition reactions. It seemed reasonable to suppose therefore that the conformation of an amide which, though lacking a kinetic barrier to Ar–CO rotation sufficiently high to be atropisomeric itself, is held in a preferred orientation, might allow the stereochemistry of the controlling centre to be relayed *via* the amide to control a new stereogenic centre relatively remote from the source of stereochemical information. We first reported on such a concept early in 1998,[61] and Davies,[62] Renaud[63] and Sibi[63] have since published conceptually related stereoselective reactions involving what they have termed "chiral relay". The strategy is illustrated schematically in Scheme 13.



Scheme 13 Stereochemical relay.

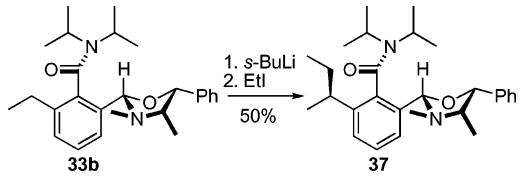
We decided to make use of two reactions known to be diastereoselective in the naphthamide series, namely (a) the diastereoselective lateral lithiation–electrophilic quench of 2-ethyl amides,[19,20] and (b) the chelation-controlled nucleophilic addition of aryl Grignard reagents to 2-formyl amides.[22,64] We employed derivatives of the conformationally uniform amides **4a** and **23** to probe this idea.

The racemic silane **4a** was treated with *s*-BuLi and the ortholithiated product quenched with ethyl iodide to yield **35** as a single diastereoisomer (Scheme 14). Diastereoselective lithiation with *s*-BuLi and electrophilic quench with Me_3SiCl gave a product **36**, again as a single diastereoisomer by NMR and with >10 : 1 selectivity by HPLC. The simplicity of the NMR spectrum of **36** (only two 6H doublets for the N*i*–Pr_2 group) indicated the presence of a plane of symmetry, and from the known conformational preference of **4a**[7] it is evident that **36** has the structure shown, in which information about the stereochemistry of the first

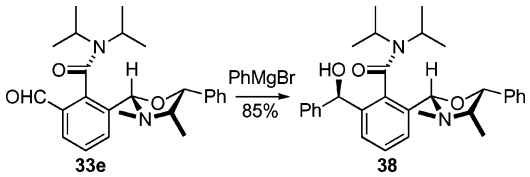


Scheme 14 Remote stereoselective silylation.

**Preliminary reports: see refs. 26 and 61.



Scheme 15 Remote stereoselective ethylation.



Scheme 16 Remote stereoselective addition to a carbonyl group.

silyl-bearing centre has been relayed through the amide axis to the second.

The same sequence of reactions starting from the conformationally uniform amide **23** gave, *via* **33b**, the oxazolidine **37**, again as a single diastereoisomer (Scheme 15). The sense of the stereoselective silylation was assumed to be the same as in the formation of **36**.[19,20] In both of these reactions, it is probable that the laterally lithiated derivative of **35** or **33b** has very low kinetic configurational stability about the Ar–CO bond on the timescale of the silylation,[65] and that the overall stereoselectivity is in fact the result of the continued thermodynamic influence of the fixed stereogenic centre over the amide axis in the lateral lithiation step.

Chelation-controlled nucleophilic addition of phenylmagnesium bromide[22] to the conformationally uniform aldehyde **33e** gave **38** (Scheme 16), again as a single diastereoisomer by NMR, with stereochemistry deduced from precedent.[22]

In all three of these reactions, 1,5-stereocontrol is delivered by relaying stereochemical information from a starting centre *via* the amide axis to a new centre in the final product 1,5-related to the source of stereochemical information. The operation of a stereochemical relay (also termed "chiral relay") effect has been deduced in other contexts, for example the alkylation of amino-acid derived diazines,[62] and in asymmetric Diels Alder reactions.[63] Uniquely in the reactions of these amides, however, is it possible to be certain, by NMR, of the conformational preference at the root of the relay effect. In future papers we shall show how amides can relay stereochemistry not only to new centres but also to further amide axes, leading to much more remote transmission of stereochemical information.

X-Ray crystallography

X-ray crystal structures described in this paper have been deposited with the Cambridge Crystallographic Database (ccdc@cam.ac.uk).‡‡ Details are as follows:

4a,[7] **5j**,[22] **5n**,[14] **5o**,[14] **33b**,[26] **33f**,[26] **33g**,[26] *exo*-**27**[26] and **28**[9] were published previously.

10c. Crystal data $C_{21}H_{27}NO_2$; $M = 325.44$; triclinic P-1; $a = 7.3320(14)$ Å; $b = 8.9703(18)$ Å; $c = 14.588(3)$ Å; $a = 73.464(4)°$; $b = 84.682(3)°$; $g = 77.268(3)°$; $V = 896.7(3)$ Å^3; $T = 100(2)$ K; $Z = 2$; $m = 0.076$ mm^{-1}; 5134 reflections; $R_{int} = 0.0348$; $R(F) = 0.0405$. CCDC reference number 286005

endo-**27**. Crystal data $C_{31}H_{45}N_3O_3$; $M = 507.70$; monoclinic $P2_1$; $a = 10.547(8)$ Å; $b = 12.605(5)$ Å; $c = 12.023(4)$ Å; $b = 96.44(4)°$; $V = 1588.3(15)$ Å^3; $T = 296.2$ K; $Z = 2$; $m = 0.535$ mm^{-1}; 3456 reflections; $R_{int} = 0.0540$; $R(F) = 0.0500$. CCDC reference number 286006

‡‡ CCDC reference numbers 286005–286006. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b514557k

Experimental

General methods have been published previously.[14] Flash chromatography was performed by the method of Still, Kahn and Mitra.[66]

Published elsewhere

The synthesis of the naphthamides detailed in Table 1, along with benzamides **4a**,[7] **4b**[31] **17**,[14] **22**,[14] and **23**[14] have been published previously. Benzamide **14** is published in the following paper,[49] and diamide **25**[67] will be published in the context of related research shortly.

2-(1-Methylpropyl)-*N*,*N*-diisopropylbenzenecarboxamide (8). *sec*-Butyllithium (1.1 equiv., 1.3 M solution in hexane) was added dropwise to a stirred solution of 2-ethyl-*N*,*N*-diisopropylbenzenecarboxamide **7**[7] (0.2 g, 0.857 mmol) in THF under nitrogen at −78 °C. The burgundy solution was allowed to stir at this temperature for an hour and ethyl iodide (0.1 ml, 1.286 mmol) was added. The solution became colourless. The reaction mixture was allowed to warm to ambient temperature. Saturated aqueous ammonium chloride solution was added, the precipitate dissolved with a small amount of water, and the majority of the THF removed under reduced pressure. The aqueous suspension was extracted into dichloromethane (×3), and the combined organic extracts were washed with distilled water, dried ($MgSO_4$), and evaporated under reduced pressure to yield the pale yellow crude product. Purification by flash chromatography (7.5% ethyl acetate in light petroleum) afforded the pure amide **8** as white solid. (0.0202 g, 9%), R_f (10% ethyl acetate–light petroleum) 0.36, (plus a mixture of **7** and **8**); δ_H (300 MHz; $CDCl_3$) Signals for major conformer: 6.98–7.27 (4H, m, Ar–H), 3.65 (1H, sept, J 6.5, NC*H*(Me)$_2$), 3.40 (1H, m, NC*H*(Me)$_2$), 2.65 (1H, m, C*H*CH$_2$), 1.65 (2H, m, C*H*$_2$), 1.56 (3H, d, J 7.0, NCH*Me*$_A$Me$_B$), 1.55 (3H, d, J 7.0, NCHMe$_A$*Me*$_B$), 1.19 (3H, d, J 7.0, *Me*CH), 1.05 (6H, m, NCH*Me*$_2$), 0.8 (3H, m, *Me*CH$_2$); δ_C (75 MHz; $CDCl_3$) 175.0, 128.5, 128.1, 125.6, 124.7 (Ar–*C*); 50.6 (–N*C*(Me)$_2$), 45.6 (N*C*(Me)$_2$), 25.6 (*C*H$_2$CH$_3$), 20.7, 20.6, 20.5, 20.4 (2xNC(*Me*)$_2$), 15.0 (–CH$_2$*C*H$_3$); m/z CI 262 (6%, M + H$^+$), 234 (100%, $C_{15}H_{23}NO$ + H$^+$), EI 234 (2%). Found M$^+$ 261.2101. $C_{17}H_{27}NO$ requires M 261.20925.

2-(1-Hydroxy-1-methylethyl)-*N*,*N*-diisopropylbenzamide (10b). *sec*-Butyllithium (1.41 ml, 1.3 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of *N*,*N*-diisopropylbenzamide **9**[37] (0.25 g, 1.22 mmol) in dry THF (5 ml) under nitrogen at −78 °C. After 20 min at −78 °C, butanone (0.218 ml, 2.44 mmol) was added and the mixture was allowed to reach room temperature, quenched with saturated ammonium chloride solution, and extracted with ether (10 ml). The combined ether extracts were washed with aqueous ammonium chloride

(3 × 25 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The compound was purified by flash chromatography (petroleum ether–ethyl acetate, 90 : 10) to give the alcohol **10b** (0.200 g, 59%) as a yellow oil; R_f (ether–ethyl acetate, 90 : 10) 0.26; ν_{max} (film)/cm^{-1} 1633 (C=O), 2970 (CH), 3420 (OH); δ_H (300 MHz; $CDCl_3$), 7.6–7.2 (4H, m), 3.72 (1H, sept, *J* 7), 3.40 (1H, sept, *J* 7), 1.80 (3H, s, Me), 1.5–1.3 (2H, m, CH_2), 1.2–0.9 (15 H, 5 × d, *J* 7, Me × 5) and 0.70 (3 H, t, *J* 7); *m*/*z* CI 276 (10%, M$^+$), 147 (98%), 105 (85%).

2-(1-Hydroxy-1-methylbenzyl)-*N*,*N*-diisopropylbenzamide (10c). In a similar way, *N*,*N*-diisopropylbenzamide **9**[37] and acetophenone gave the alcohol **10c** (0.240 g. 60%) as a yellow oil; R_f (ether–ethyl acetate, 90 : 10) 0.39; ν_{max} (film)/cm^{-1} 1604 (C=O), 2977 (C–H), 3270 (O–H); δ_H (300 MHz; $CDCl_3$) 7.8–6.9 (9H, m, Ar), 3.9 (1H minor, sept, *J* 7), 3.5 (1H minor, sept, *J* 7), 3.3 (1H major, sept, *J* 7) 3.15 (1H major, sept, *J* 7), 2.03 (3H minor, s), 1.79 (3H major, s), 1.6–1.4 (12H minor, 4 × d, *J* 7), 1.39, 1.10, 1.02, 0.30 (4 × 3H major, 4 × 4, *J* 7); *m*/*z* 325 (10%, M$^+$), 105 (50%), 77 (45%).

2-(2-Hydroxy-bicyclo[2.2.1]hept-2-yl)-*N*,*N*-diisopropyl-benzamide (10d). *sec*-Butyllithium (1.5 equiv., 2.9 mL, 3.73 mmol, 1.3 M solution in cyclohexane), was added to a stirred solution of *N*,*N*-diisopropylbenzamide **9**[37] (0.51 g, 2.49 mmol) in THF (40 ml) under a nitrogen atmosphere at −78 °C. The resultant orange solution was left to stir for 1.5 h at −78 °C. 2-Norbornanone (1.6 equiv., 0.44 g, 3.98 mmol) in THF (10 ml) was added at −78 °C and stirred for 10 min. The mixture was allowed to warm to room temperature and the solution became colourless. Water was added and the mixture was extracted with dichloromethane. The organic fractions were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the crude product as a white solid. Purification by flash chromatography eluting with [4 : 1 petrol (bp 40–60 °C)–EtOAc] afforded a single diastereoisomer of the product **12d** as a white solid (0.46 g, 59%), mp 110.3–111.9 °C; R_f [4 : 1 petrol (bp 40–60 °C)–EtOAc] 0.46; ν_{max} (film)/cm^{-1} 3341, 2964, 1606, 1442, 1341, 1031, 762; δ_H (300 MHz; $CDCl_3$) (mixture of major and minor conformers) 7.66–7.60 (1H, d, *J* 7.8, major & minor ArH), 7.42–7.19 (3H, m, major & minor ArH), 6.09 (1H, s, major C*H*OH), 5.01 (1H, s, minor C*H*OH), 4.06–3.85 (1H, m, major & minor NC*H*Me$_2$), 3.58 (1H, sept, *J* 6.7, major & minor NC*H*Me$_2$), 2.04–1.96 (1H, m, major & minor COHC*H*), 1.71(1H, d, *J* 3.0, major & minor COHCH_2), 1.67 (1H, d, *J* 3.0, major & minor COHCH_2), 1.63 (3H, d, *J* 6.7, major & minor NCH*Me*$_2$), 1.59 (3H, d, *J* 6.7, minor NCH*Me*$_2$), 1.57 (3H, d, *J* 6.7, major NCH*Me*$_2$), 1.54–1.50 (1H, m, major & minor COHCH$_2$C*H*), 1.50–1.43 (4H, m, major & minor COHCHCH_2), 1.42–1.34 (2H, m, major & minor COHCHCH_2), 1.28 (3H, d, *J* 6.6, major & minor NCH*Me*$_2$), 1.19 (3H, d, *J* 6.6, major NCH*Me*$_2$), 1.18 (3H, d, *J* 6.7, minor NCH*Me*$_2$); δ_C (75 MHz; $CDCl_3$) 173.9 (C=O), 147.7, 136.1, 128.8, 127.1, 125.9, 124.8 (aromatic) 79.4 (*C*OH), 51.1, COH*C*H), 48.2 (COH*C*H$_2$), 46.1, 43.9 (N*C*H(CH$_3$)$_2$), 38.2 (COHCH*C*H$_2$), 29.0 (COHCH*C*H$_2$), 27.1 (COHCH$_2$*C*H), 21.71 (COHCH*C*H$_2$), 20.57, 20.312, 20.16, 20.05 (NCH*Me*$_2$); *m*/*z* (CI) 316 (100%, M + H$^+$) (Found (EI): M$^+$, 315.2200. $C_{20}H_{29}NO_2$ requires M, 315.2198).

2-(1-Hydroxy-2-isopropyl-5-methylcyclohexyl)-*N*,*N*-diisopropyl-benzamide (10e). *sec*-Butyllithium (1.5 equiv., 1.4 mL, 1.83 mmol, 1.3 M solution in cyclohexane), was added to a stirred solution of *N*,*N*-diisopropylbenzamide **9**[37] (0.25 g, 1.22 mmol) in THF (20 ml) under a nitrogen atmosphere at −78 °C. The resultant orange solution was left to stir for 90 min at −78 °C. Menthone (1.6 equiv., 0.34 mL, 1.952 mmol) was added at −78 °C and stirred for 10 min. The mixture was then allowed to warm to room temperature and the solution became colourless. Water was added and the mixture was extracted with dichloromethane. The organic fractions were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford a white crude solid. Purification by flash chromatography using 3 : 1 petrol (bp 40–60 °C)–EtOAc as eluent afforded a single diastereoisomer of the product **10e** as a colourless oil (0.26 g, 59%) (1 : 1 mixture of conformers), ν_{max} (film)/cm^{-1} 2952, 2927, 1765, 1612, 1447, 1342, 1033, 757; δ_H (300 MHz; $CDCl_3$) 7.38–7.18 (6H, m, ArH), 7.12–7.02 (2H, m, ArH), 3.88 (1H, sept, *J* 6.7, NC*H*Me$_2$), 3.73 (1H, sept, *J* 6.7, NC*H*Me$_2$), 3.51 (2H, sept, *J* 6.7, NC*H*Me$_2$), 2.88 (1H, d, *J* 2.8, COH), 2.70 (1H, s, COH), 2.41–2.30 (2H, m, C*H*CHMe$_2$), 1.88–1.82 (2H, m, CHC*H*Me$_2$), 1.78–1.70 (4H, m, CCH$_2$), 1.61–1.52 (8H, m, CCH$_2$), 1.38–1.32 (2H, m, C*H*Me), 1.29 (6H, s, CHC*H*$_3$), 1.02 (6H, d, *J* 6.7, NCH*Me*$_2$), 0.90–0.86 (12H, m, menthone CHCH*Me*$_2$), 0.96 (6H, d, *J* 6.7, NCH*Me*$_2$), 0.82 (6H, d, *J* 6.9, NCH*Me*$_2$), 0.76 (6H, d, *J* 6.9, NCH*Me*$_2$); *m*/*z* CI 360 (100%, M + H$^+$) (Found (EI) M$^+$, 359.2831. $C_{23}H_{36}NO_2$ requires M, 359.2824).

***N*,*N*-Diisopropylnicotinamide (11)[68].** Nicotinic acid (1.0 g, 8.1 mmol) was heated to reflux in thionyl chloride (5 ml) for 30 min until all of the solid had dissolved. The mixture was cooled to room temperature and excess thionyl chloride removed under vacuum. The resulting yellow solid was dissolved in dichloromethane (25 ml) and diisopropylamine (1.4 ml, 10.0 mmol) added. After stirring for 3 h the mixture was diluted with dichloromethane (25 ml), washed with saturated ammonium chloride solution (3 × 20 ml) and solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc) to give the amide (1.44 g, 90%) as a orange crystals; R_f (70 : 30 petrol–EtOAc) 0.09; δ_H (300 MHz; $CDCl_3$) 1.44 (6H, m (broad), CH_3), 1.33 (6H, m (broad), CH_3), 3.60 (2H, m (broad), CH_3), 7.17 (1H, m, ArH), 7.55 (1H, m, ArH), 8.42–8.54 (2H, m, ArH). Spectroscopic data were in agreement with the literature.[68]

4-(1-Hydroxybenzyl)-*N*,*N*-diisopropylnicotinamide (12a). *N*,*N*-Diisopropylnicotinamide **11** (312 mg, 1.0 mmol) was dissolved in dry THF (3 ml) and added dropwise to a solution of LiTMP (3.0 mmol in 3 ml THF) at −78 °C under nitrogen giving a bright red solution. After stirring for 3 h, distilled benzaldehyde (3.5 mmol, 0.36 ml) was added dropwise at −78 °C and the mixture was left to warm to room temperature and quenched with saturated ammonium chloride solution (1 ml). The THF was removed under reduced pressure and the mixture dissolved in dichloromethane (30 ml) and washed with saturated ammonium chloride solution (3 × 15 ml), dried ($MgSO_4$) and solvents evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc) to give the alcohol **12a** (325 mg, 67%) as yellow prisms, mp 38–40 °C; R_f (EtOAc) 0.33; ν_{max}/cm^{-1} 3307 (O–H), 2972 and 2933 (C–H), 1627 (C=O); δ_H

(300 MHz; $CDCl_3$) (1 : 1 mixture of conformers), 0.51 (3H, d, *J* 7, CH_3), 0.66 (3H, d, *J* 7, CH_3), 1.16 (3H, d, *J* 7, CH_3), 1.18 (3H, d, *J* 7, CH_3), 1.33 (3H, d, *J* 7, CH_3), 1.46 (3H, d, *J* 7, CH_3), 1.53 (3H, d, *J* 7, CH_3), 1.55 (3H, d, *J* 7, CH_3), 3.34 (1H, sept, *J* 7, CH), 3.45–3.60 (3H, m, CH), 5.76 (1H, s, CH), 6.10 (1H, s, CH), 7.25–7.38 (10H, m, ArH), 7.46 (2H, d, *J* 5, ArH), 8.39 (1H, s, ArH), 8.45 (1H, s, ArH), 8.59 (1H, d, *J* 5, ArH), 8.64 (1H, d, *J* 5, ArH); δ_C (75 MHz; $CDCl_3$) 20.4, 20.4, 20.6, 20.6, 20.8, 20.9, 21.0, 46.7, 46.8, 51.7, 51.7, 72.1, 76.1, 76.9, 122.4, 125.4, 126.3, 127.5, 128.0, 128.5, 128.7, 129.0, 132.3, 132.5, 141.0, 142.7, 145.8, 147.7, 150.2, 150.9, 151.1, 151.4, 168.5, 169.6; *m/z* (CI) 313 (100%, MH^+); Found (M^+) 312.1832. $C_{19}H_{24}N_2O_2$ requires (M) 312.1832.

4-(2-Hydroxybut-2-yl)-*N*,*N*-diisopropylnicotinamide (12b). In the same way, *N*,*N*-diisopropylnicotinamide **11** (312 mg, 1.0 mmol) and butan-2-one (3.5 mmol, 0.31 ml) gave the alcohol **12b** (349 mg, 83%) as a colourless oil, R_f (6 : 4 EtOAc–petrol) 0.15; ν_{max}/cm^{-1} 3367 (O–H), 2971, 2934 and 2878 (C–H), 1620 (C=O); δ_H (300 MHz; $CDCl_3$) (1 : 1 mixture of conformers), 0.80 (3H, t, *J* 7, CH_3), 0.89 (3H, t, *J* 7, CH_3), 1.17–1.22 (12H, m, CH_3), 1.50 (3H, s, CH_3), 1.56–1.60 (15H, m, CH_3), 1.82–2.02 (4H, m, CH_2), 3.19 (1H, s (broad), OH), 3.42 (1H, s (broad), OH), 3.54 (1H, sept, *J* 7,CH), 3.54 (1H, sept, *J* 7, CH), 3.71 (1H, sept, *J* 7, CH), 3.77 (1H, sept, *J* 7, CH), 7.14 (1H, d, *J* 5, ArH), 7.18 (1H, d, *J* 7, ArH), 8.33 (1H, s, ArH), 8.36 (1H, s, ArH), 8.51 (1H, d, *J* 6, ArH), 8.52 (1H, d, *J* 6, ArH); *m/z* (CI) 278 (100%, MH^+); Found (M^+) 277.1905. $C_{16}H_{26}N_2O_2$ requires (M) 277.1911.

4-(1-Hydroxy-1-methylbenzyl)-*N*,*N*-diisopropylnicotinamide (12c). In the same way, *N*,*N*-diisoproylnicotinamide **11** (312 mg, 1.0 mmol) and distilled acetophenone (3.5 mmol, 0.41 ml) gave the alcohol **12c** (301 mg, 61%) as a colourless oil, R_f (6 : 4 EtOAc–petrol) 0.30; ν_{max}/cm^{-1} 3261 (O–H), 2978 (C–H), 1604 (C=O); δ_H (300 MHz; $CDCl_3$) (9 : 1 mixture of conformers : signals for major conformer), 0.44 (3H, d, *J* 7, CH_3), 1.15 (3H, d, *J* 7, CH_3), 1.19 (3H, d, *J* 7, CH_3), 1.42 (3H, d, *J* 7, CH_3), 1.84 (3H, s, CH_3), 3.26 (1H, sept, *J* 7, CH), 3.38 (1H, sept, *J* 7, CH), 6.76 (1H, s (broad), OH), 7.20–7.41 (5H, m, ArH), 7.66 (1H, d, *J* 5, ArH), 8.43 (1H, s, ArH), 8.69 (1H, d, *J* 5, ArH); δ_C (75 MHz; $CDCl_3$) 20.2, 20.5, 20.6, 20.9, 31.6, 46,8, 51.5 122.0, 126.0, 127.0, 128.6, 148.0, 151.0, 154.9, 170.7; *m/z* (CI) 327 (100%, MH^+); Found (M^+) 326.1986: $C_{20}H_{26}N_2O_2$ requires (M) 326.1989.

4-(1-Methoxy-1-methylbenzyl)-*N*,*N*-diisopropylnicotinamide (13). Alcohol **12c** (105 mg, 0.32 mmol) in THF (1 ml) was added to a solution of 60% NaH (26 mg, 0.64 mmol) in THF (3 ml) at 0 °C. After 5 min, the solution was raised to 45 °C, stirred for 10 h and quenched with saturated ammonium chloride (1 ml). The THF was removed under reduced pressure and the mixture dissolved in ether (30 ml) and washed with saturated ammonium chloride solution (3 × 15 ml), dried ($MgSO_4$) and solvents evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc) to give the methyl ether **13** (93 mg, 85%) as a clear oil, R_f (EtOAc) 0.54; ν_{max}/cm^{-1} 2976, 2933 (C–H), 1632 (C=O); δ_H (300 MHz; $CDCl_3$) 3 : 1 mixture of conformers, 1.16 (3H, d, *J* 7, CH_3), 1.25 (3H, d, *J* 7, CH_3), 1.60 (3H, d, *J* 7, CH_3), 1.62 (3H, d, *J* 7, CH_3), 1.98 (3H, s, CH_3), 3.09 (3H, s, CH), 3.54 (1H, sept, *J* 7, CH), 3.81 (1H, sept, *J* 7, CH), 6.47 (1H, d, *J* 5, ArH), 7.29–7.41 (5H, m, ArH), 8.26 (1H, d, *J* 5, ArH), 8.35 (1H, s, ArH), 8.41 (1H, d, *J* 5, ArH); *m/z* (CI) 341 (100%, MH^+); Found (M^+) 341.2222 ($C_{21}H_{18}N_2O_2$ requires (M) 341.2224).

(*R*a,2′*S*,4′*S*,5′*S*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]benzamide (24). (1*S*,2*S*)-(+)-Pseudoephedrine (1.75 equiv., 1.24 g, 7.51 mmol) in toluene (80 ml) was added to aldehyde **21**[69] (1.0 g, 4.29 mmol) and heated at reflux using a Dean–Stark apparatus. The solution was then allowed to cool to room temperature. Toluene was removed under reduced pressure. The reaction mixture was extracted with dichloromethane, organic fractions washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product as a white solid. Purification by flash chromatography eluted with [3 : 1 petrol (bp 40–60 °C)–EtOAc] afforded the product **24** as a yellow oil (1.21 g, 75%), $[a]_D^{19} = +14.4$ (c = 1.37, CH_2Cl_2); R_f [3 : 1 petrol (bp 40–60 °C)–EtOAc] 0.31; ν_{max} (film)/cm^{-1} 2968, 1632, 1440, 1374, 1338, 1036, 755; δ_H (300 MHz; $CDCl_3$) 7.78 (1H, dd, *J* 7.7 and 1.1, Ar–H), 7.38–7.12 (7H, m, Ar–H (2H), Ph (5H)), 7.05 (1H, dd, *J* 7.6 and 1.2, Ar–H), 5.10 (1H, s, C*H*Ph), 4.63 (1H, d, *J* 8.7, OC*H*), 3.61 (1H, sept, *J* 6.7, NC*H*Me_2), 3.45 (1H, sept, *J* 6.7, NC*H*Me_2), 2.43 (1H, dq, *J* 8.7 and 5.9, NC*H*Me) 2.17 (3H, s, NMe), 1.58 (3H, d, *J* 6.7, NCHMe_2), 1.52 (3H, d, *J* 6.7, NCHMe_2), 1.14 (3H, d, *J* 6.0, NCH*Me*), 1.00 (3H, d, *J* 6.9, NCHMe_2), 0.97 (3H, d, *J* 6.7, NCHMe_2); δ_C (75 MHz; $CDCl_3$), 169.6 (C=O), 140.4, 139.5, 135.5, 128.8, 128.5, 128.2, 128.1, 127.7, 126.6, 124.2 (aromatics), 95.1 (NCO), 86.8 (NMe), 68.9 (O*C*HPh), 51.0, 45.7 (N*C*HMe_2), 35.3 (N*C*HMe), 20.5, 20.4, 20.1 (NCHMe_2), 14.2 (NCH*Me*); *m/z* (CI) 381 (100%, M + H^+) (Found (EI) M + H^+, 381.2543. $C_{24}H_{32}N_2O_2$ requires M + H, 381.2542).

***N*,*N*,*N*′,*N*′-Tetraisopropyl-4-formylisophthalamide (26).** *sec*-Butyllithium (2 equiv., 43.0 mL, 60.2 mmol, 1.4 M solution in cyclohexane) was added to a solution of **25**[69] (10.0 g, 30.1 mmol) in THF (100 ml) at −78 °C under a nitrogen atmosphere. The resultant yellow solution was stirred at −78 °C for 1 h and quenched with *N*,*N*-dimethylformamide (4 equiv., 9.3 mL, 120.4 mmol) and allowed to warm to room temperature. Water (50 ml) was added and the mixture was extracted with dichloromethane, organic fractions washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product as a white solid. Purification by flash chromatography eluted with [1 : 1 petroleum ether (bp 40–60 °C)–EtOAc] gave the aldehyde **26** as a white solid (8.45 g, 78%), mp 137.1–139.3 °C; R_f [3 : 1 petrol (bp 40–60 °C)–EtOAc] 0.31; ν_{max} (film)/cm^{-1} 2969, 2934, 1701, 1627, 1440, 1340, 1211, 1034, 778; δ_H (300 MHz; $CDCl_3$), 10.17 (1H, s, CHO), 7.97 (1H, dd, *J* 7.7 and 1.4, ArH) 7.55 (1H, t, *J* 7.7, ArH), 7.45 (1H, dd, *J* 7.6 and 1.4, ArH), 3.72 (2H, sept, *J* 6.7, NC*H*Me_2), 3.56 (2H, sept, *J* 6.7, NC*H*Me_2), 1.63 (3H, d, *J* 6.9, NCHMe_2), 1.55–1.60 (9H, m, NCHMe_2), 1.31 (3H, d, *J* 6.6, NCHMe_2), 1.26 (3H, d, *J* 6.6, NCHMe_2), 1.10 (3H, d, *J* 6.7, NCHMe_2), 1.04 (3H, d, *J* 6.6, NCHMe_2); δ_C (75 MHz; $CDCl_3$), 190.1 (CHO), 167.8, 166.0 (C=O), 137.5, 136.8, 131.8, 130.7, 128.4, 127.9 (aromatics) 51.5, 51.2, 46.3, 45.8 (4 × N*C*HMe_2), 20.4, 20.4, 20.3, 20.3, 20.1, 20.0, 19.9, 19.7 (4 × NCHMe_2); *m/z* (CI) 361 (100%, M + H^+) (Found (EI): M + H^+, 361.2486. $C_{21}H_{32}N_2O_3$ requires M + sH, 361.2491).

(*R*a,*S*a,2′*S*,4′*S*,5′*R*)-*N*,*N*,*N*′,*N*′-Tetraiisopropyl-3-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]phthalamide (*exo*-27) and (*R*a,*S*a,2′*R*,

4′*S*,5′*R*)-*N*,*N*,*N*′,*N*′-Tetraisopropyl-3-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]phthalamide (*endo*-27). (1*R*,2*S*)-(−)-Ephedrine (1.5 equiv., 2.35 g, 14.4 mmol) in toluene (100 ml) was added to **26** (3.45 g, 9.6 mmol) and heated at reflux using a Dean–Stark apparatus for 2 d under nitrogen (until no starting material was present on TLC). The solution was then allowed to cool to room temperature. Toluene removed under reduced pressure. The reaction mixture was extracted with dichloromethane, organic fractions washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product as a white solid. NMR of the crude product showed that the 2 diastereoisomers were present. Purification by flash chromatography eluting with [4 : 1 petrol (bp 40–60 °C)–EtOAc] afforded the oxazolidine *exo*-**27** as a white powder (2.53 g, 64%), $[\alpha]_D^{24} = -74.5$ ($c = 1.02$, CH_2Cl_2); mp 147.6–149.2 °C; R_f [4 : 1 petrol (bp 40–60 °C)–EtOAc] 0.58; ν_{max} (film)/cm^{-1} 2965, 2931, 1618, 626, 1440, 1341, 1049; δ_H (300 MHz; $CDCl_3$) 8.00 (1H, dd, *J* 7.8 and 1.0, Ar–H), 7.54–7.28 (7H, m, Ar–H (2H), Ph (5H)), 7.22 (1H, dd, *J* 7.4 and 1.1, Ar–H), 5.14 (1H, d, *J* 8.4, CHPh), 4.83 (1H, s, OCH), 3.82–3.65 (2H, m, NCHMe$_2$), 3.61–3.44 (2H, m, NCHMe$_2$), 2.94 (1H, dq, *J* 8.4 and 6.5, NCHCH$_3$) 2.21 (3H, s, NMe), 1.63 (3H, d, *J* 6.7, NCHMe$_2$), 1.50–1.58 (9H, m, NCHMe$_2$), 1.28 (3H, d, *J* 6.6, NCHMe$_2$), 1.24 (3H, d, *J* 6.6, NCHMe$_2$), 1.16 (3H, d, *J* 6.6, NCHMe$_2$), 1.08 (3H, d, *J* 6.7, NCHMe$_2$), 0.83 (3H, d, *J* 6.5, NCHMe); δ_C (75 MHz; $CDCl_3$), 168.9, 167.2 (C=O), 139.3, 135.8, 135.3, 134.5, 128.2, 128.0, 127.9, 127.9, 127.7, 125.7 (Ar) 94.1 (NCO), 82.2 (NMe) 64.2 (OCHPh) 51.3, 50.9, 45.8, 45.5 (NCHMe$_2$), 36.2 (NCHMe) 20.5, 20.4, 20.3, 20.3, 20.2, 20.1, 20.2 (NCHMe$_2$), 15.4 (NCHMe); *m*/*z* (CI) 508 (100%, M + H$^+$) (Found (EI): M + H$^+$, 508.3538. $C_{31}H_{45}N_3O_3$ requires M + H, 508.3539).

The aminal *endo*-**27** was also isolated as a white solid (1.22 g, 25%), $[\alpha]_D^{24} = -39.6$ ($c = 1.02$, CH_2Cl_2); mp 159.9–161.3 °C; R_f [4 : 1 petrol (bp 40–60 °C)–EtOAc] 0.47; δ_H (300 MHz; $CDCl_3$) 7.81 (1H, dd, *J* 7.8 and 1.1, Ar–H), 7.47–7.28 (7H, m, Ar–H (2H), Ph (5H)), 7.18 (1H, dd, *J* 7.6 and 1.2, Ar–H), 5.73 (1H, d, *J* 4.8, C*H*Ph), 5.39 (1H, s, OC*H*), 3.90–3.42 (5H, m, NC*H*Me$_2$ and NC*H*Me), 2.28 (3H, s, NMe), 1.63 (3H, d, *J* 6.7, NCH*Me*$_2$), 1.57 (3H, d, *J* 6.9, NCH*Me*$_2$), 1.53 (6H, d, *J* 6.7, NCH*Me*$_2$), 1.33 (3H, d, *J* 6.5, NCH*Me*$_2$), 1.35 (3H, d, *J* 6.5, NCH*Me*$_2$), 1.24 (3H, d, *J* 6.6, NCH*Me*$_2$), 1.09 (3H, d, *J* 6.6, NCH*Me*$_2$), 0.68 (3H, d, *J* 6.7, NCH*Me*); δ_C (75 MHz; $CDCl_3$), 168.9, 167.3 (C=O), 138.8, 136.7, 135.2, 134.9, 128.0, 128.0, 127.9, 127.7, 125.9, 125.3 (aromatics) 90.4 (NCO), 83.0 (NMe) 61.6 (O*C*HPh) 51.2, 50.8, 45.8, 45.5 (N*C*HMe$_2$), 32.8 (N*C*HMe) 20.4, 20.4, 20.2, 20.2, 20.1, 20.0, (NCH*Me*$_2$), 7.3 (oxazolidine NCHMe).

***N*,*N*-Diisopropyl-2-(toluene-4-sulfinyl)benzamide (28).** Amide **9** (2.00 g, 9.25 mmol) in THF (50 ml) at −78 °C was treated with *sec*-butyllithium (1.5 equiv., 10.67 mL, 13.8 mmol, 1.3 M solution in cyclohexane). After 30 min, (1*R*,2*S*,5*R*)-(−)-menthyl *p*-toluenesulfinate **29**[51] (2 equiv., 5.74 g, 18.5 mmol) in THF (10 ml) was added. The solution was stirred for a further 30 min, warmed to room temperature and quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted with dichloromethane (×3) and the combined organic extracts were dried using magnesium sulfate, filtered and concentrated under reduced pressure to afford the crude product. Purification by recrystallisation from petrol (bp 40–60 °C) and a few drops of EtOAc gave the sulfoxide **28** as colourless crystals (2.57 g, 81%), mp 89.3–92.5 °C; R_f [2 : 1 petrol (bp 40–60 °C)–EtOAc] 0.12; $[\alpha]_D^{20} = -85.2$ ($c = 1.00$, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2962, 2361, 1628, 1440, 1340, 1042; δ_H (300 MHz; $CDCl_3$) 7.86 (1H, d, *J* 7.6, ArH), 7.72 (2H, d, *J* 8.0, sulfoxide ArH), 7.52–7.42 (2H, m, sulfoxide ArH), 7.30–7.22 (3H, m, ArH), 3.86–3.72 (1H, m, NC*H*Me$_2$), 3.66–3.52 (1H, m, NC*H*Me$_2$), 2.37 (3H, s, ArCH$_3$), 1.63 (3H, d, *J* 6.9, NCH*Me*$_2$), 1.59 (3H, d, *J* 6.7, NCH*Me*$_2$), 1.30 (3H, d, *J* 6.3, NCH*Me*$_2$), 1.10 (3H, broad s, NCH*Me*$_2$); δ_C (75 MHz; $CDCl_3$) 167.4 (C=O), 143.4, 141.0, 140.9, 131.1, 129.8, 129.7, 125.4, 125.1, 124.8 (Ar) 51.3, 46.2 (N*C*HMe$_2$), 30.8 (Ar*Me*), 21.2, 20.7, 20.5, 20.1 (NCH*Me*$_2$); *m*/*z* (CI) 344 (100%, M + H$^+$); *m*/*z* (EI) 343 (41%, M$^+$) and 227 (100%) (Found (EI): M$^+$, 343.1611. $C_{20}H_{25}NO_2S$ requires M, 343.1606).

***N*,*N*-Diisopropyl-2-(1,3-oxathiolan-2-yl)benzamide (31a).** By the method of Kamal, 2-mercaptoethanol (0.26 cm^3, 3.86 mmol, 1.00 equiv.) was added dropwise to a stirred solution of *N*-bromosuccinimide (0.14 g, 0.77 mmol, 0.30 equiv.) and 2-formyl-*N*,*N*-diisopropylbenzamide **21** (0.60 g, 2.58 mmol, 1.50 equiv.) in dry CH_2Cl_2 (20 cm^3) at room temperature. The mixture was stirred at this temperature for 8 h. An aqueous solution of 2.0 mol dm^{-3} NaOH (10 cm^3) was added and the resulting mixture extracted with CH_2Cl_2 (2 × 15 cm^3). The combined organic phases were washed with brine (30 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, petrol–EtOAc, 8 : 1) to give the oxathioacetal **31a** (0.61 g, 81%) as a white solid, mp 93–96 °C. R_f (4 : 1 petrol–EtOAc) 0.22 & 0.10; ν_{max}(film)/cm^{-1}: 2969, 2934, 2872 (C–H), 1629 (C=O), 1438, 1338. ^{1}H-NMR (300 MHz, CD_3OD): δ = 1 : 1 mixture of conformers, 7.78 (1H, dd, $J = 7.5$ and 1.5 Hz, ArH), 7.69 (1H, dd, $J = 7.8$ and 1.5 Hz, ArH), 7.48–7.36 (4H, m, ArH), 7.19 (2H, m, ArH), 6.21 (1H, s, SC*H*O), 6.04 (1H, s, SC*H*O), 4.63–4.54 (2H, m, OC*H*$_2$), 3.95–3.81 (2H, m, OC*H*$_2$), 3.74–3.61 (4H, m, NC*H*(CH$_3$)$_2$), 3.31–3.18 (4H, m, *CH*$_2$S), 1.58 (3H, d, $J = 6.9$ Hz, NCH(*CH*$_3$)$_2$), 1.57 (6H, d, $J = 6.9$ Hz, NCH(*CH*$_3$)$_2$), 1.56 (3H, d, $J = 6.6$ Hz, NCH(*CH*$_3$)$_2$), 1.26 (3H, d, $J = 6.6$ Hz, NCH(*CH*$_3$)$_2$), 1.18 (3H, d, $J = 7.2$ Hz, NCH(*CH*$_3$)$_2$), 1.15 (6H, d, $J = 6.9$ Hz, NCH(*CH*$_3$)$_2$); ^{13}C-NMR (75 MHz, CD_3OD): δ = 170.8, 170.7, 137.3, 136.8, 136.3, 135.6, 128.9, 128.9,128.8, 128.3, 127.4, 124.9, 124.5, 83.8, 83.3, 72.3, 72.1, 51.8, 51.6, 46.2, 46.1, 33.6, 33.5, 19.6, 19.5, 19.4, 19.4, 19.3; *m*/*z* CI: 294 (100%, M$^+$ + H) *m*/*z* EI: 294 (18%, M + H). (Found: M + H, 294.1522. $C_{16}H_{24}O_2NS$, requires M + H 294.1522).

***N*,*N*-Diisopropyl-2-methoxy-6-[1,3]oxathiolan-2-yl-benzamide (31b).** 2-Mercapoethanol (0.20 ml, 2.85 mmol, 1.5 equiv.) was added to a stirred solution of indium triflate (0.053 g, 5 mol%) and 2-formyl-5-methoxy-*N*,*N*-diisopropylbenzamide **30**[70] (0.50 g, 1.90 mmol) in toluene (40 ml). The mixture was heated under a Dean–Stark condenser for 1 h. The mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. Flash chromatography yielded a mixture of two diastereoisomers of the oxathiolane **31b** (0.55 g, 90%), mp168–172 °C; R_f (petrol–EtOAc 5 : 3) 0.55 and 0.45; ν_{max} (NaCl)/cm^{-1} 2963, 2929, 1627 (s, C=O); δ_H (500 MHz; $CDCl_3$), 7.34–7.27 (4H, m), 6.82 (lH, dd, *J* 7.5, 2.0), 6.80 (lH, dd, *J* 8.0, 1.5), 6.10 (lH, s), 6.00 (lH, s), 4.60–4.52 (2H, m), 3.84 (2H, sept, *J* 6.0), 3.80 (3H, s), 3.79 (3H, s), 3.64 (lH, sept, *J* 6.5), 3.59 (lH, sept, *J* 6.5), 3.51 (2H, dt, *J* 6.5, 3.0), 3.48 (2H, dt, *J* 6.5, 3.0), 1.58

(3H, d, *J* 6.5), 1.56 (6H, d, *J* 6.5), 1.55 (3H, d, *J* 6.5), 1.17 (3H, d, *J* 6.5), 1.13 (3H, d, *J* 6.5), 1.12 (3H, d, *J* 6.5), 1.05 (3H, d, *J* 6.5); δ_C (500 MHz; $CDCl_3$) 166.9 (C=O), 137.9 (C), 136.9 (C), 129.8 (C), 120.3 (C), 111.3 (C), 110.8 (C), 56.0 (*CH), 51.5 (OCH_3), 46.5 (OCH_2), 46.3 (OCH_2), 34.7 (CH), 34.3 (CH), 22.3 (CH_3), 21.0 (CH_3), 20.8 (CH_3), 20.4 (CH_3); *m/z* 324 (MH^+); (found: MH^+, 324.1629, $C_{17}H_{25}NO_3S$. MH^+ requires 324.1629).

***N*,*N*-Diisopropyl-2-methoxy-6-[1,3]-oxathian-2-yl benzamide (31c).** Similarly, aldehyde **30**, indium triflate, and 3-mercapto-1-propanol (0.16 ml, 2.85 mmol, 1 equiv.) gave two diastereoisomers of the amide **31c** (0.57 g, 90%). Mp168–172 °C; R_f (petrol–EtOAc 5 : 3) 0.67 and 0.55; ν_{max} (NaCl)/cm^{-1} 2964, 2360, 1628 (s, C=O); δ_H (500 MHz; $CDCl_3$), 7.32–7.30 (4H, m), 6.89–6.80 (2H, m), 5.82 (lH, s), 5.77 (lH, s), 4.29–4.23 (2H, m), 3.79 (6H, s), 3.79–3.66 (2H, m), 3.64–3.55 (2H, m), 3.54–3.49 (2H, m), 3.15 (lH, dt, *J* 13.0, 2.5), 3.10 (lH, dt, *J* 13.0, 3.0),2.84–2.78 (2H, m), 2.12–2.04 (2H, m), 1.75–1.70 (2H, m), 1.61 (3H, d, *J* 6.5), 1.60 (6H, d, *J* 6.5),1.59 (3H, d, *J* 6.5), 1.16 (3H, d, *J* 6.5), 1.14 (3H, d, *J* 6.5), 1.11 (3H, d, *J* 6.5), 1.03 (3H, d, *J* 6.5); δ_C (500 MHz; $CDCl_3$), 166.9 (C=O), 137.7 (C), 129.8 (C), 120.3 (C), 120.3 (C), 111.3 (C), 110.8 (C), 55.9 (*CH), 51.5 (OCH3), 46.4 (OCH_2), 46.2 (OCH_2), 29.9 (CH), 29.5 (CH), 26.3 (CH_3), 26.1 (CH_3), 21.2 (CH_3), 20.8 (CH_3); *m/z* 338 (MH^+); (found: MH, 338.1783, $C_{18}H_{27}NO_3S + H^+$ requires M 338.1783).

***N*,*N*-Diisopropyl-2-(1,3-oxathiolan-2-yl)benzamide-*S*,*S*-dioxide (32).** The oxathioacetal **31a** (0.25 g, 0.85 mmol, 1.00 equiv.) in dry CH_2Cl_2 (3.0 cm^3) was added dropwise to a solution of 3-chloroperoxybenzoic acid (*ca.* 50%, 0.74 g, 2.13 mmol, 2.50 equiv.) in dry CH_2Cl_2 (15 cm^3) at 0 °C and the reaction was stirred at this temperature for 1 h. 10% Aqueous sodium sulfite (10 cm^3) was added and the mixture was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic phases were washed with saturated $NaHCO_3$ (30 cm^3), brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (petrol–EtOAc, 6 : 1) to yield the sulfone **32** (0.21 g, 74%) as a white solid, mp 134–137 °C. R_f (4 : 1 petrol–EtOAc) 0.34^{maj} & 0.21^{min}; ν_{max}(film)/cm^{-1}: 2968, 2930, 2880, 1624 (C=O), 1340, 1320 (S=O), 1158, 1130 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) (7.9 : 1 mixture of conformers): δ = 7.68 ($1H^{maj+min}$, m, ArH), 7.53–7.43 ($2H^{maj+min}$, m, ArH), 7.27 ($1H^{maj+min}$, m, ArH), 5.73 ($1H^{maj}$, s, S*CH*O), 5.26 ($1H^{min}$, s, S*CH*O), 4.70 ($1H^{maj+min}$, dd, *J* = 10.2 and 10.2, OCH_2), 4.45–4.35 ($1H^{maj+min}$, m, OCH_2), 3.83 ($1H^{maj+min}$, sept, *J* = 6.3 Hz, N$CH(CH_3)_2$), 3.57 ($1H^{maj+min}$, sept, *J* = 6.6 Hz, N$CH(CH_3)_2$), 3.48–3.28 ($2H^{maj+min}$, m, CH_2SO_2), 1.64 ($6H^{maj+min}$, d, *J* = 6.9 Hz, NCH(CH_3)$_2$), 1.59 ($6H^{maj+min}$, d, *J* = 6.6 Hz, NCH(CH_3)$_2$), 1.23 ($6H^{maj+min}$, d, *J* = 6.0 Hz, NCH(CH_3)$_2$), 1.21 ($6H^{maj+min}$, d, *J* = 6.0 Hz, NCH(CH_3)$_2$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 169.2, 138.4, 129.7, 129.2, 128.3, 127.2, 125.8, 90.7, 64.7, 51.7, 49.1, 46.5, 21.2, 20.7, 20.6, 20.4; *m/z* CI: 326 (20%, M^+ + H). (Found: M + H^+, 326.1420. $C_{16}H_{24}O_4NS$, M + H^+ requires 326.1420).

(2′*S*, 4′*S*, 5′*R*)-*N*,*N*-Diethyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-6-methylbenzamide (33a). A solution of oxazolidine **22** (99.7 mg) in THF (10 ml) was added dropwise to a stirred solution of *sec*-butyllithium (3.0 equiv.) and TMEDA (3.0 equiv.) in dry THF (40 ml) at −78 °C under an atmosphere of nitrogen. After 60 min at −78 °C, methyl iodide (12.0 equiv.) was added. The mixture was warmed to ambient temperature (colour change from dark yellow/orange to colourless solution) and was stirred overnight. Water was added and the organic layer was separated. The reaction mixture was reduced pressure at room temperature to half of its origin volume. It was extracted with diethylether (3 × 30 ml). The organic fractions were combined and washed with brine (50 ml), water (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography, eluting with petroleum ether bp (40–60°)–EtOAc (11 : 1) to afford amide **33a** as an oil (60 mg, 57.7%). δ_H (400 MHz; $CDCl_3$) 7.81 (1H, d, *J* 8, Ar*H*), 7.49 (2H, d, *J* 8, Ar*H*), 7.35–7.21 5H, m, Ar*H*), 5.07 (1H, d, C*H*OCHPh), 4.75 (1H, s, CHO), 3.68 (2H, m, NCH_2CH_3), 2.91–2.84 (1H, dqn, *J* 2 and 7, CHPhC*H*CH_3), 2.43–2.23 (2H, m, NCH_2CH_3), 2.33 (3H, s, NCH_3), 2.15 (3H, s, ArCH_3), 1.62 (3H, dt, *J* 2 and 7, NCH_2CH_3), 0.72 (3H, t, *J* 7, NCH_2CH_3), 0.71 (3H, d, *J* 7, CHPhCHCH_3); δ_C (75MHz, $CDCl_3$) 169.1 (C=O), 139.8, 139.0, 137.9, 133.9 (Cq), 128.7–125.1 (aromatics), 94.8 (*C*HOCHPh), 82.3 (O*C*HPh), 63.7 (CHPh*C*CH_3), 51.0 (Benz–*C*H_3), 43.0 (N*C*H_2), 35.7 (N*C*H_2), 14.7, 13.4 (2 × NCH_2CH_3), 12.6 (CH*C*H_3). ν_{max}(thin film)/cm^{-1} 1620 (C=O); (found; *M* 366.5124; $C_{25}H_{34}N_2O_2$ requires M 366.5078); *m/z* (CI) 367 (100%, M + H^+); *m/z* (EI) 367 (15.4%, M + H^+), 366 (100%, *M*); $[\alpha]_D^{25}$ − 14.9 (*c* = 0.99, $CHCl_3$).

General method for the preparation of oxazolidines 33b–g from 23

sec-Butyllithium (1.3 equiv.) was added dropwise to a stirred solution of amide **23** (1.0 equiv.; 3.92 mmol) in dry THF (40 ml) at −78 °C under an atmosphere of nitrogen. After 60 min at −78 °C, the electrophile (2.0 equiv.) in THF (10 ml) was added dropwise to the reaction mixture. The mixture was warmed to ambient temperature and water was added. Most of the THF was removed under reduced pressure at room temperature and the mixture extracted with diethyl ether (3 × 30 ml). The organic fractions were combined and washed with brine (50 ml) and water (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product.

(2′*S*,4′*S*,5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-6-methylbenzamide (33b). In this way, benzamide **23** (250 mg) and methyl iodide (2.0 equiv.) gave a crude oil. Purification by flash chromatography, eluting with petroleum ether (40–60°)–EtOAc (11 : 1) gave a single diastereoisomer **33b** as crystalline white solid (142.5 mg, 55%), mp 153.4–155.3 °C. δ_H (400 MHz; $CDCl_3$) 7.81 (1H, d, *J* 7, Ar*H*), 7.49 (2H, d, *J* 7, Ph*H*), 7.35 (3H, m, Ar*H* and Ph*H*), 7.30–7.24 (1H, m, Ph*H*), 7.21 (1H, d, *J* 7, benz-*H*), 5.07 (1H, d, *J* 8, OC*H*Ph), 4.72 (1H, s, C*H*OCHPh), 3.68 (1H, septet, *J* 7, NC*H*CH_3CH_3), 3.54 (1H, septet, *J* 7, NC*H*CH_3CH_3), 2.91–2.84 (1H, m, CHPhC*H*CH_3), 2.33 (3H, s, NCH_3), 2.15 (3H, s, ArCH_3), 1.62 (6H, d, *J* 7, NCHCH_3CH_3), 1.11 (3H, d, *J* 7, NCHCH_3CH_3), 1.07 (3H, d, *J* 7, $NCHCH_3CH_3$), 0.78 (3H, d, *J* 7, CHPhCHCH_3); δ_C (100 MHz, $CDCl_3$), 169.3 (C=O), 140.0, 139.3, 133.9, 134.3, 133.9, 130.9, 128.3, 128.0, 127.7, 125.7 (Ar), 94.8 (*C*HOCHPh), 82.3 (O*C*HPh), 64.1 (CHPh*C*CH_3), 51.0 (Ar*C*H_3), 46.0 (N*C*HMe_2), 35.8 (CHN*C*H_3), 20.9, 20.6, 20.4, 18.9 (4 × NCH*C*H_3CH_3), 15.2 (CH*C*H_3); ν_{max}(thin film)/cm^{-1} 1626 (C=O); Found: M + H^+ 395.2714; $C_{25}H_{34}N_2O_2$ requires M + H^+ 395.2699); *m/z* (CI) 395 (100%, M + H^+), 176 (11%); *m/z* (EI) 395 (15%, M + H^+), 176

(55%); $C_{35}H_{34}N_2O_2$ requires C, 76.2; H, 8.78; N, 6.86. Found: C, 76.10, H, 8.69, N, 7.10; $[a]_D^{25}$ − 47.9 ($c = 0.31$, chloroform).

(2′*S*, 4′*S*, 5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-6-ethylbenzamide (33c). In the same way, amide **23** (250 mg) and ethyl iodide (2.0 equiv.) gave a crude oil. Purified by flash chromatography on silica, eluting with petroleum ether (40–60°)–EtOAc (11 : 1) gave the corresponding oxazolidine **33c** as a waxy oil (251.2 mg, 69%). δ_H (300 MHz; $CDCl_3$) 7.82 (1H, d, *J* 7, Ar*H*), 7.47 (2H, d, *J* 7, Ph*H*), 7.40 (1H, t, *J* 7, Ar*H*), 7.37–7.33 (2H, m, Ar*H* and Ph*H*), 7.30–7.26 (2H, m, Ar*H* and Ph*H*), 5.70 (1H, d, *J* 8, OC*H*Ph), 4.72 (1H, s, C*H*OCHPh), 3.67 (1H, septet, *J* 7, NC*H*Me$_2$), 3.54 (1H, septet, *J* 7, NC*H*Me$_2$), 2.91–2.84 (1H, m, CHPhC*H*CH$_3$), 2.70 (1H, dq, *J* 14 and 7, C*H*$_2$CH$_3$), 2.58 (1H, dq, *J* 14 and 7, C*H*$_2$CH$_3$), 2.15 (3H, s, NC*H*$_3$), 1.62 (3H, d, *J* 7, NCH*Me*), 1.61 (3H, d, *J* 7, NCH*Me*), 1.26 (3H, t, *J* 7, CH$_2$*Me*), 1.11 (3H, d, *J* 7, NCHC*H*$_3$CH$_3$), 1.05 (3H, d, *J* 7, NCHCH$_3$C*H*$_3$), 0.77 (3H, d, *J* 7, CHC*H*$_3$). δ_C (100 MHz, $CDCl_3$), 168.9 (C=O), 139.8, 139.1, 139.0, 133.9, 128.9, 128.5, 128.0, 127.7, 125.8 (Ar), 94.8 (*C*HOCHPh), 82.3 (O*C*HPh), 64.1 (CHPh*C*CH$_3$), 50.9 and 46.0 (N*C*H), 35.9 (N*C*H$_3$), 25.5 (*C*H$_2$CH$_3$), 20.9–20.3 (NCH*C*H$_3$), 15.2 (CH*C*H$_3$), 15.0 (CH$_2$C*H*$_3$). ν_{max}(thin film)/cm^{-1} 1627 (C=O); (found; M + H$^+$ 409.5901; $C_{26}H_{36}N_2O_2$ requires M + H$^+$ 409.5969); *m*/*z* (CI) 409 (100%, M + H$^+$), 190 (11%); *m*/*z* (EI) 409 (12%, M + H$^+$), 190 (100%); $[a]_D^{25}$ − 56.7 ($c = 0.04$, chloroform).

(2′*S*, 4′*S*, 5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-6-(1-hydroxyl-1-methylethyl)benzamide (33e). In the same way, benzamide **23** (250 mg) and dry acetone (2.0 equiv.) gave a crude oil. Purification by flash chromatography on silica, eluting with petroleum ether (40–60°)–EtOAc (11 : 1), gave the oxazolidine **33e** as a waxy oil (197.9 mg, 69%). δ_H (300 MHz; $CDCl_3$) 7.94 (1H, d, *J* 8, ArH), 7.55–7.28 (7H, m, Ar*H* and Ph*H*), 5.13 (1H, d, *J* 9, OC*H*Ph), 4.87 (1H, s, C*H*OCHPh), 3.74 (1H, septet, *J* 7, NC*H*CH$_3$), 3.59 (1H, septet, *J* 7, NC*H*CH$_3$), 2.29–2.86 (2H, m, CHPhC*H*CH$_3$ and OH), 2.15 (3H, s, NCH$_3$), 1.64 (12H, m, CCH(C*H*$_3$)$_2$ and NCHC*H*$_3$C*H*$_3$), 1.09 (3H, d, *J* 7, NCHC*H*$_3$), 1.08 (3H, d, *J* 7, NCHC*H*$_3$), 0.80 (3H, d, *J* 7, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$), 171.9 (C=O), 145.0, 139.5, 135.1, 134.6, 128.1, 128.0, 127.9, 127.9, 127.6, 127.0 (Ar), 93.5 (*C*HOCHPh), 82.1 (O*C*HPh), 74.5 [*C*OH(CH$_3$)$_2$], 64.1 (CHPHh*C*CH$_3$), 51.3 and 46.0 (N*C*H), 35.8 (N*C*H$_3$), 34.6 and 31.298 [COHC(*C*H$_3$)$_2$], 20.1 [*C*OH(CH$_3$)$_2$], 19.8 and 19.3 (NCH*Me*$_2$), 15.3 (CH*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3421 (OH), 1621 (C=O); (found; M + H$^+$ 439.2963; $C_{27}H_{38}N_2O_3$ requires M + H$^+$ 439.2961,) *m*/*z* (CI) 439 (100%, M + H$^+$); *m*/*z* (EI) 439 (45%, M + H$^+$), 381 (100%), 263 (57%); $[a]_D^{21}$ − 21.3 ($c = 0.14$, chloroform).

(2′*S*, 4′*S*, 5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-6-(methylsulfanyl)benzamide (33f). In the same way, benzamide **23** (250 mg) and methyl disulfide (2.0 equiv.) gave a yellow oil. Flash chromatography on silica, eluting with petroleum ether (40–60°)–EtOAc (12 : 1), gave the oxazolidine **33f** as a white crystalline solid (109.3 mg, 69%) mp 135.1–136.6 °C. δ_H (400 MHz; $CDCl_3$) 7.81 (1H, dd, *J* 8 and 1, Ar*H*), 7.47–7.25 (7H, m, Ar*H*), 5.07 (1H, d, *J* 8, OC*H*Ph), 4.74 (1H, s, C*H*OCHPh), 3.63 (1H, septet, *J* 7, NC*H*CH$_3$CH$_3$), 3.55 (1H, septet, *J* 7, NC*H*CH$_3$CH$_3$), 2.93–2.85 (1H, m, CHPhC*H*CH$_3$), 2.47 (3H, s, SC*H*$_3$), 2.17 (3H, s, NC*H*$_3$), 1.63 (3H, d, *J* 8, NCHC*H*$_3$), 1.62 (3H, d, *J* 8, NCHC*H*$_3$), 1.19 (3H, d, *J* 7, NCHC*H*$_3$), 1.09 (3H, d, *J* 7.0, NCHC*H*$_3$), 0.77 (3H, *J* 7, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$), 167.3 (C=O), 140.0, 139.7, 135.3, 134.3, 128.8, 128.5, 128.0, 127.7, 125.9 (aromatics), 94.4 (*C*HOCHPh), 82.4 (O*C*HPh), 64.1 (CHPh*C*CH$_3$), 51.4, 46.2 (N*C*H), 35.9 (N*C*H$_3$), 20.8, 20.6, 20.4, 20.1 (NCH*C*H$_3$), 17.1 (S*C*H$_3$), 15.2 (CH*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1627 (C=O). (Found; M + H$^+$ 427.2412; $C_{27}H_{38}N_2O_3$ requires M + H$^+$ 427.2387) *m*/*z* (CI) 427 (100%, M + H$^+$); *m*/*z* (EI) 427 (100%, M + sH$^+$); $C_{25}H_{34}N_2O_2S$ requires C, 70.10; H, 8.11; N, 6.41; S, 6.41. Found: C, 70.38; H, 8.03; N, 6.41; S, 6.57. $[a]_D^{24}$ − 104.4 ($c = 0.228$, chloroform).

(2′*S*, 4′*S*, 5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-6-(phenylsulfanyl)benzamide (33g). In the same way, benzamide **23** (250 mg) and phenyl disulfide (2.0 equiv.) gave a yellow oil. Purification by flash chromatography on silica, eluting with petroleum ether (40–60°)–EtOAc (9 : 1), gave oxazolidine **33g** as a crystalline pale yellow solid (170.2 mg, 53%) mp 147–149.1 °C. δ_H (400 MHz; $CDCl_3$) 7.88 (1H, dd, *J* 8 and 1, Ar*H*), 7.73–7.42 (2H, m, Ar*H*), 7.2–7.4 (10H, m, Ph × 2), 5.09 (1H, d, *J* 8, OC*H*Ph), 4.78 (1H, s, C*H*OCHPh), 3.76 (1H, septet, *J* 7, NC*H*CH$_3$CH$_3$), 3.56 (1H, septet, *J* 7, NC*H*CH$_3$CH$_3$), 2.95–2.87 (1H, m, CHPhC*H*CH$_3$), 2.19 (3H, s, NC*H*$_3$), 1.63 (3H, d, *J* 7, NCHC*H*$_3$CH$_3$), 1.18 (3H, d, *J* 7, NCHC*H*$_3$CH$_3$), 1.13 (3H, d, *J* 7, NCHCHC*H*$_3$), 0.78 (3H, *J* 7, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$), 167.0 (C=O), 141.3, 139.3, 135.4, 127.9, 132.7, 131.5, 129.2, 129.0, 128.0, 127.7, 127.3, 127.2 (aromatics), 94.4 (*C*HOCHPh), 82.4 (O*C*HPh), 64.0 (CHPHh*C*CH$_3$), 51.4 and 46.2 (N*C*H), 35.9 (N*C*H$_3$), 20.8, 20.6, 20.4, 20.1 (NCH*C*H$_3$), 15.2 (CH*C*H$_3$). ν_{max}(thin film)/cm^{-1} 1620 (C=O); (found; M + H$^+$ 489.6987; $C_{30}H_{36}N_2O_2S$ requires M + H$^+$ 489.7055) *m*/*z* (CI) 489(100%, M + H$^+$); *m*/*z* (EI) 489 (20%, M + H$^+$), 488 (100%, *M*); $[a]_D^{21}$ − 123.4 ($c = 0.421$, chloroform).

General procedure for the deprotection-reduction of oxazolidines 33

A solution of trifluoroacetic acid (20.0 equiv.) and water (2.0 equiv.) was added dropwise to a solution of oxazolidine (1.51 mmol) dissolved in THF (30 ml) at 0 °C (ice-bath). After 60 min, small batches of sodium methoxide (33 equiv.) were added slowly until pH 6 was attained, followed by a slurry of sodium borohydride (10 equiv.) in ethanol (20 ml) at 0 °C. The mxture was allowed to warm to room temperature. Evaporation under reduced pressure without external heating reduced the solution to half its original volume. It was extracted with diethyl ether (3 × 30 ml), washed with brine (2 × 30 ml), dried ($MgSO_4$) and filtered. Evaporation under reduced pressure without external heating afforded the crude alcohol **34**.

(R_a)-*N*,*N*-Diisopropyl-2-methyl-6-(hydroxymethyl)benzamide (34b). In this way oxazolidine **33b** (157 mg) was reduced to give the crude alcohol. Purification by flash column chromatography eluting with petroleum ether–EtOAc (5 : 1) gave enantiomerically enriched alcohol **34b** as an oil (81.2 mg, 82%). Integration of the ^{1}H NMR spectrum of this material in the presence of Pirkle's chiral shift reagent[71] indicated an enantiomeric excess of 8%. δ_H (300 MHz; $CDCl_3$), 7.41–7.08 (2H, m, Ar–*H*), 7.04 (1H, d, *J* 7, Ar–*H*), 4.55 (1H, d, *J* 13, C*H*$_A$H$_B$OH), 4.30 (1H, d, *J* 13, CH$_A$*H*$_B$OH), 3.54 (1H, sept, *J* 7, NC*H*), 3.47 (1H, sept, *J* 7, NC*H*), 2.22 (3H, s, ArC*H*$_3$), 1.54 (3H, d, *J* 7, NCHC*H*$_3$), 1.50 (3H, d, *J* 7, NCHC*H*$_3$), 1.09 (3H, d, *J* 7, NCHC*H*$_3$), 0.87 (3H, d,

J 7, NCHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.3 (C=O), 139.3, 137.0, 136.6, 128.5, 127.4, 126.6 (Ar), 63.5 (*C*H_2OH), 50.9 (N*C*H_2), 46.2 (Ar*C*H_3), 46.0 (N*C*H_2), 20.9, 20.6, 20.4, 20.3 (NCH*C*H_3); ν_{max}(thin film)/cm^{-1} 3510 (br, OH), 1617 (C=O). (Found: M + H^+ 250.3567; $C_{15}H_{23}NO_2$ requires M + H^+ 250.3601); *m*/*z* (CI) 250 (100%, M + H^+), 235 (11%); *m*/*z* (EI) 250 (22%, M + H^+), 235 (100%), 104 (15%).

(*R*$_a$)-*N*,*N*-Diisopropyl-2-ethyl-6-(hydroxymethyl)benzamide (34c). In the same way, oxazolidine **33c** (259 mg) was reduced to give a crude alcohol. This was purified by flash column chromatography eluting with petroleum ether (40–60°)–EtOAc (5 : 1) to afford enantiomerically enriched alcohol **34c** as white powder (145.2 mg, 87%). Integration of the ^{1}H NMR spectrum of this material in the presence of Pirkle's chiral shift reagent[71] indicated an enantiomeric excess of 28%. δ_H (300 MHz; $CDCl_3$), 7.39–7.26 (2H, m, Ar*H*), 7.23 (1H, d, *J* 7, Ar*H*), 4.69 (1H, d, *J* 13 and 3, CH_AH$_B$OH), 4.42 (1H, d, *J* 13 and 2, CH$_A$*H*$_B$OH), 3.65 (1H, sept, *J* 7, NC*H*),3.22 (1H, sept, *J* 7, NC*H*), 2.70 (1H, dq, *J* 14 and 7, CH_AH$_B$CH$_3$), 2.60 (3H, dq, *J* 14 and 7, CH$_A$*H*$_B$CH$_3$), 1.66 (3H, d, *J* 7, NCHC*H*$_3$), 1.62 (3H, d, *J* 7, NCHC*H*$_3$), 1.28 (3H, t, *J* 8, CH$_2$C*H*$_3$), 1.19 (3H, d, *J* 7, NCHC*H*$_3$), 0.08 (3H, d, *J* 7, NCHC*H*$_3$); δ_C (75MHz, $CDCl_3$) 170.3 (C=O), 139.3, 137.0, 136.6, 128.5, 127.4, 126.6 (aromatics), 63.5 (*C*H_2OH), 50.9, 46.0 (N*C*H_2), 25.5 (*C*H_2CH$_3$), 20.9, 20.6, 20.4, 20.3 (NCH*C*H_3), 14.9 (CH$_2$*C*H_3); ν_{max}(thin film)/cm^{-1} 3488 (br, OH), 1613 (C=O); (found; M + H^+ 264.1967; $C_{16}H_{25}NO_2$ requires M + H^+ 264.1964); *m*/*z* (CI) 264 (100%, M + H^+), 234 (5%); *m*/*z* (EI) 264 (100%, M + H^+), 234 (31%), 133 (13%).

(*S*$_a$)-*N*,*N*-Diisopropyl-2-hydroxymethyl-6-(methylsulfanyl)-benzamide (34f). In the same way, oxazolidine **33f** (78 mg) was reduced to give a crude alcohol. This was purified by flash column chromatography eluting with petroleum ether (40–60°)–EtOAc (5 : 1) as to afford enantiomerically enriched alcohol **34f** as an oil (10.9 mg, 20%). Integration of the ^{1}H NMR spectrum of this material in the presence of Pirkle's chiral shift reagent[71] indicated an enantiomeric excess of <1%. δ_H (300 MHz; $CDCl_3$), 7.43 (2H, m, Ar*H*), 7.26 (1H, dd, *J* 7 and 3, Ar*H*), 5.8 (1H, d, *J* 13, CH_AH$_B$OH), 5.06 (1H, d, *J* 13, CH$_A$*H*$_B$OH), 3.54 (2H, septet, *J* 7, NCH), 2.49 (3H, s, S–C*H*$_3$), 1.65 (3H, d, *J* 7, NCHC*H*$_3$), 1.61 (3H, d, *J* 7, NCHC*H*$_3$), 1.29 (3H, d, *J* 7, NCHC*H*$_3$), 1.13 (3H, d, *J* 7, NCHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.0 (C=O), 139.0, 137.1, 136.6, 129.0, 128.3, 127.1 (aromatics), 64.1 (*C*H_2OH), 50.7 (N*C*H_2), 47.1 (S*C*H_3), 46.0 (N*C*H_2), 20.9, 20.6, 20.4, 20.3 (NCH$_2$*C*H_3).

***N*,*N*-Diisoproyl-2-ethyl-6-(1-trimethylsilyl)ethylbenzamide (35).** *sec*-Butyllithium (0.83 ml, 1.3 M solution in cyclohexane, 1.08 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-2-(1-trimethylsilyl)ethylbenzamide (300 mg, 0.982 mmol) in THF (80 ml) cooled to −78 °C under an atmosphere of nitrogen. The resultant orange-pink solution was stirred for 1 h at −78 °C before the addition of ethyl iodide (0.16 ml, 1.96 mmol). The solution was allowed to warm to 0 °C, water (40 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 40 ml) and the combined organic extracts were washed with water (40 ml), dried over magnesium sulfate and filtered. The solvent evaporated and the residue was purified by column chromatography (3% ethyl acetate in light petroleum, R_f 0.31) to give the silane **35** as a colourless oil which crystallised on standing in the freezer (171 mg, 52%). M$^+$ 333.2488 ($C_{20}H_{35}NOSi$ requires 333.2488); ν_{max} (thin film) 1632 cm^{-1}; δ_H (300 MHz; $CDCl_3$), 7.23 (1H, t, *J* 7.7, *p*-ArH), 7.02 (1H, d, *J* 7.7, *m*-ArH), 6.97 (1H, d, *J* 7.7, *m*-ArH), 3.67 (1H, sept, *J* 6.7, NCH), 3.52 (1H, sept, *J* 6.7, NCH), 2.77–2.45 (2H, m, ArCH$_2$CH$_3$), 2.16 (1H, q, *J* 7.4, ArCH), 1.63 (3H, d, *J* 6.7, NCH*Me*), 1.61 (3H, d, *J* = 6.7 Hz, NCH*Me*), 1.36 (3H, d, *J* 7.4, ArCH*Me*), 1.26 (3H, t, *J* 7.6, ArCH$_2$*Me*), 1.14 (3H, d, *J* 6.7, NCH*Me*), 1.08 (3H, d, *J* 6.7, NCH*Me*), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (75 MHz; $CDCl_3$), 169.8 (s, CO), 142.3 (s, Ar), 139.6 (s, Ar), 135.9 (s, Ar), 127.4 (d, Ar), 123.9 (d, Ar), 123.3 (d, Ar), 50.0 (d, NCH), 45.6 (d, NCH), 25.8 (d, ArCH), 25.3 (t, ArCH$_2$), 20.9 (q, NCH*Me*), 20.8 (q, NCH*Me*), 20.3 (q, NCH*Me*), 20.2 (q, NCH*Me*), 16.3 (q, CH$_3$), 15.0 (q, CH$_3$), −2.9 (q, Si(CH$_3$)$_3$); *m*/*z* CI + 336 (6%), 335 (23%), 334 (100%), 304 (8%), 290 (4%), 233 (4%), 161 (10%), 90 (5%), 73 (4%).

(1*RS*,1′*SR*)-*N*,*N*-Diisopropyl-2,6-bis-{(1-trimethylsilyl)ethyl}-benzamide (36). *sec*-Butyllithium (0.25 ml, 1.3M solution in cyclohexane, 0.323 mmol) was added dropwise to a solution of benzamide **35** (92 mg, 0.276 mmol) in dry THF (30 ml) at −78 °C, under an atmosphere of nitrogen. The resultant orange solution was stirred at −78 °C for 1.5 h and trimethylsilyl chloride (56 µl, 0.441 mmol) was added. The solution was then allowed to warm to 0 °C, water (30 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 30 ml), the combined extracts were washed with water (40 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. The symmetrical amide was obtained pure following column chromatography (2% ethyl acetate in light petroleum, R_f 0.48) as a white crystalline solid (67 mg, 60%) in addition to starting material, R_f 0.24 (25 mg, 27%). Mp 113.5–114 °C; M 405.2889 ($C_{23}H_{43}NOSi_2$ requires 405.2883); ν_{max} 1619 cm^{-1}; δ_H (300 MHz; $CDCl_3$), 7.20 (1H, t, *J* 7.7, *p*-ArH), 6.89 (2H, d, *J* 7.7, 2 × *m*-ArH), 3.73 (1H, sept, *J* 6.7, NCH), 3.52 (1H, sept, *J* 6.7, NCH), 2.15 (2H, q, *J* 7.4, 2 × CHSi), 1.61 (6H, d, *J* 6.7, NCH*Me*$_2$), 1.36 (6H, d, *J* 7.4, 2 × ArCH*Me*), 1.11 (6H, d, *J* 6.7, NCHMe$_2$), 0.00 (18H, s, 2 × Si(CH$_3$)$_3$); δ_C (75 MHz; $CDCl_3$), 170.1 (s, CO), 142.8 (s, 2 × *o*-Ar), 134.7 (s, *C*CON, 127.3 (d, *p*-ArH), 122.1 (d, 2 × *m*-ArH), 49.5 (d, NCH), 45.5 (d, NCH), 25.5 (d, 2 × ArCH), 20.9 (q, NCH*Me*$_2$), 20.2 (q, NCH*Me*$_2$), 16.4 (q, 2 × ArCH*Me*), 2.8 (q, 2 × Si(CH$_3$)$_3$); *m*/*z* CI+ 407 (33%), 406 (100%). HPLC analysis of the crude product (Phenosphere 80 Å 100 × 8.00 mm 5 µm silica column, Merck–Hitachi system, eluent 1% ethanol in hexane, flow rate 2 ml min^{-1}, showed **36** room temperature 1.65 min (64.5%), **35** 2.13 min plus further peaks of 6 and 4% intensity.

(2′*S*, 4′*S*, 5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-6-(1-trimethylsilylethyl)benzamide (37). In a similar way, amide **33b** (150 mg, 0.37 mmol) was lithiated with *sec*-BuLi and quenched with ethyl iodide. Chromatography (SiO_2; EtOAc) gave the alcohol **37** (77 mg, 50%) as a yellow oil, R_f (9 : 1 : 0.1 petrol–EtOAc–NEt_3) 0.30; $[\alpha]_D$ = − 132.0° (*c* = 2.0, acetone); ν_{max}/cm^{-1} 2963, 2930 and 2873 (CH), 1628 (C=O); δ_H (300 MHz; $CDCl_3$, 0.81 (3H, d, *J* 7, CH$_3$), 0.90 (3H, t, *J* 7, CH$_3$), 1.12 (3H, d, *J* 7, CH$_3$), 1.17 (3H, d, *J* 7, CH$_3$), 1.29 (3H, d, *J* 7, CH$_3$), 1.65 (3H, d, *J* 7, CH$_3$), 1.69 (3H, d, *J* 7, CH$_3$), 2.21 (3H, s, NMe), 2.72 (2H, m, CH), 2.92 (1H, m, CH), 3.56 (1H, sept, *J* 7, CH), 3.76 (1H, sept, *J* 7, CH), 4.78 (1H, s, CH), 5.11 (1H, d, *J* 8, CH), 7.30–7.53

(7H, m, ArH), 7.87 (1H, dd, *J* 7 and 1, ArH); δ_C (75MHz; $CDCl_3$) 12.5, 15.6, 20.5, 20.6, 20.7, 21.1, 32.9, 36.3, 37.5, 46.3, 51.0, 64.4, 82.5, 95.1, 126.3, 126.8, 127.9, 128.2, 128.3, 128.8, 134.1, 138.9, 140.1, 143.6, 169.1; *m/z* (CI) 437 (20%, MH^+); 218 (60%); Found (M^+) 436.2988; $C_{28}H_{40}N_2O_2$ requires (M) 436.3090.

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