Conformational arm-wrestling: battles for stereochemical control in benzamides bearing matched and mismatched chiral 2- and 6-substituents

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The orientation of a tertiary amide group adjacent to an aromatic ring may be governed by the stereochemistry of an adjacent chiral substituent. With a chiral substituent in both *ortho* positions, matched/mismatched pairs of isomers result. Evidence for matched stereochemistry is provided by the clean NMR spectra of single conformers, while mismatching gives poor or unexpected selectivities in the formation of chiral substituents, or mixtures of amide conformers. Attempts to use the match–mismatch effect to select for racemic pairs of enantiomeric substituents, and hence develop a "racemate-sequestering" reagent, are described, along with the use of "matching" to scavenge a single enantiomer of a diamine from material of incomplete enantiomeric purity.

Introduction

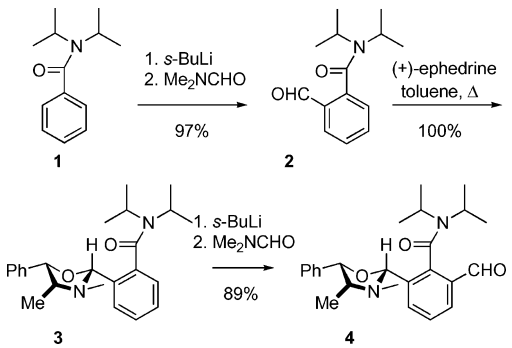
In the previous paper,[1] we showed that a chiral 2-substituent can exert powerful control over the conformational preference of the Ar–CO axis of a tertiary benzamide. We now describe molecules in which two chiral substituents are placed *ortho* to an amide axis.† Both have the opportunity to influence the orientation of the axis, and instances can be envisaged either in which both centres exert a reinforcing influence on the conformation—the "matched" case—or in which they compete for control of the amide axis—the "mismatched" case. For "mismatched" steregenic centres, the axial conformation which results might be considered a measure of the relative power of the two centres to influence conformation. In the event, we found that molecules carrying truly mismatched chiral centres are generally difficult to synthesise, and that the favourability of "matching" stereochemistry led to some unusual diastereoselectivities in the condensation reactions by which the stereogenic centres are formed. Pairs of identical groups displaying "matched" control will have opposite absolute configuration, and we also attempted to exploit this fact in developing a racemate-selective sequestering agent as a means of enhancing enantiomeric excess.

We present this work as a series of "competition/cooperation" experiments (thus, "A *vs.* B") between pairs of stereogenic centres of various types, all of which were introduced in the previous paper.[1]

Results and discussion

1. Ephedrine-derived oxazolidines *vs.* ephedrine-derived oxazolidines

Among the simplest to construct of the stereogenic centres which are known to exert a high degree of control over conformational preference are ephedrine-derived oxazolidines such as that in **3**.[3–6] The aldehyde **4** was available by lithiation[7] and formylation[8] of **1**, followed by condensation of the resulting aldehyde **2** with (+)-ephedrine to give oxazolidine **3**, and then a second lithiation and formylation to yield **4** (Scheme 1).



Scheme 1 Synthesis of aldehyde **4**.

Condensation of aldehyde **4** with a second equivalent of ephedrine should allow the synthesis of either a matched or mismatched bis(oxazolidinyl)benzamide, according to which an enantiomer of ephedrine is used. Because the two faces of the amide group are enantiotopic, the stereochemically-matched compound must carry enantiomeric ephedrine molecules, and indeed condensation of **4** with (−)-ephedrine gave a good yield of the *meso*-compound **5**. The X-ray crystal structure (Fig. 1) of **5** confirmed the stereochemistry of the two oxazolidine rings and the orientation of the amide group, which adopts the conformation observed in all related compounds, with the amide C=O and oxazolidine C–O bonds lying *anti*, probably for electronic reasons.[1]

The slow reaction of **4** with a second equivalent of (+)-ephedrine in the presence of catalytic toluenesulfonic acid gave an unstable unsymmetrical compound which we initially assumed to be **7**, in which the orientation of the pseudoasymmetric Ar–CO axis would make the oxazolidine rings diastereotopic. However, the product's NMR spectrum (Fig. 2c) contained a distinctive 1H doublet (J = 5.0 Hz) and 1H singlets at δ = 5.71 and 5.39 ppm,

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† A small part of this work has been communicated in preliminary form: see ref 2.

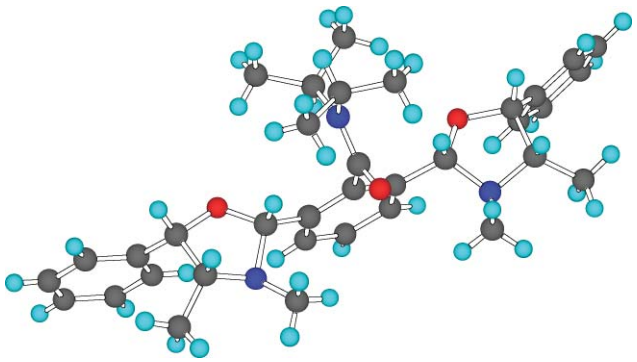


Fig. 1 X-ray crystal structure of **5**.

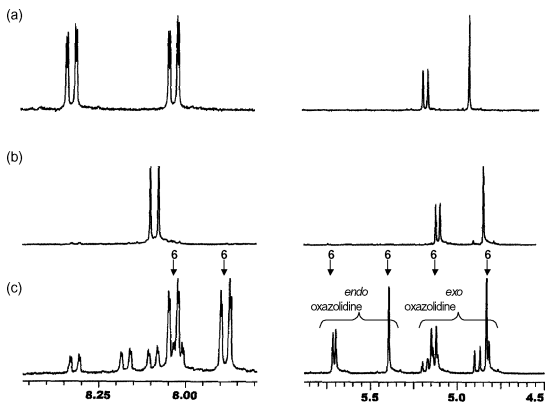
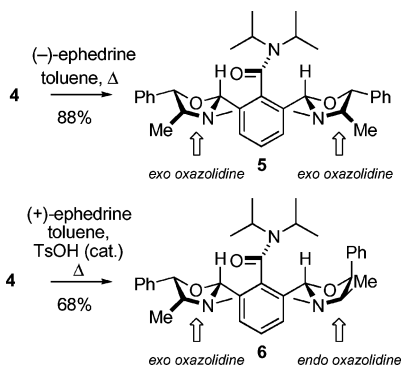


Fig. 2 Portions of the NMR spectra of (a) **4**; (b) **5**; (c) **6**, contaminated with isomers/hydrolysis products. Major peaks corresponding to **6** are labelled, including the distinctive *endo*-oxazolidine signals at $\delta = 5.71$ and 5.39 ppm.

further downfield than the typical signals for H2 and H5 in, for example, unsymmetrical mono-oxazolidine **4** (Fig. 2a) or symmetrical bis-oxazolidine **5** (Fig. 2b). We have established from the NMR spectrum of crystalline **8**[1] that such signals can be assigned to an *endo* oxazolidine, in which the C-2 aryl substituent is *anti* rather than *syn* to the two substituents at C-4 and C-5, and we therefore assign the structure **6** (Scheme 2) to this product. The inequivalence of the two downfield aromatic 1H doublets furthermore confirms that the product lacks symmetry. Rapid hydrolysis or incomplete oxazolidine formation meant that quantities of other isomers or hydrolysis products were also observed in the NMR spectrum of **6**, as seen in Fig. 2c.



Scheme 2 Bis-oxazolidinyl benzamides.

Endo oxazolidines may be formed as the major kinetic product during the condensation of ephedrine with aromatic aldehydes,[1,6] but inversion at C2 by equilibration, especially in non-polar solvents, typically leads quickly to the more stable *exo* oxazolines. In **6**, however, the usual thermodynamic driving force for inversion at C2, which would form **7**, is overcome by the fact that while the probable‡ most stable conformer of **6** has two favourable *anti* alignments between the C–O and C=O dipoles, **7** will have only one, and in addition incurs steric hindrance between the N*i*–Pr_2 groups and one of the NMe groups (Fig. 3).

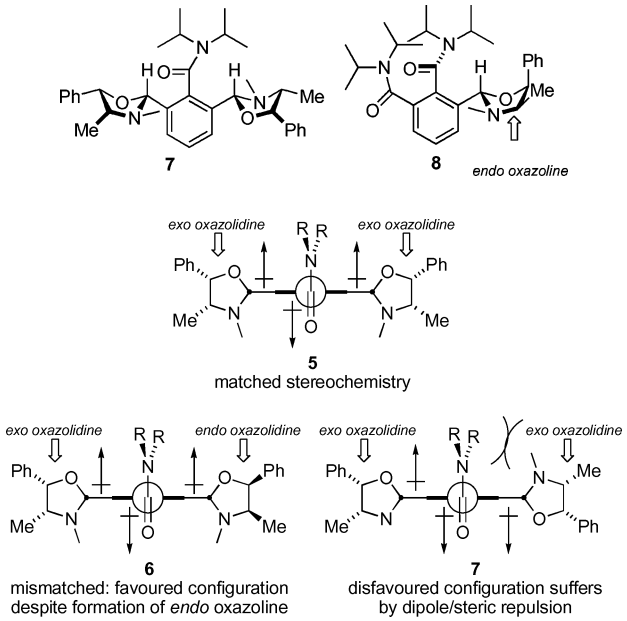
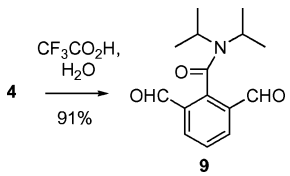


Fig. 3 Dipole orientation in **6** and **7**.

2. Attempts to develop a racemate-sequestering agent

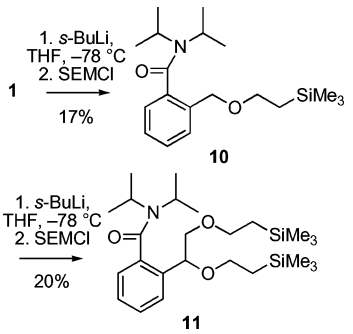
Bis-oxazolidines **5** and **6** can alternatively be viewed as products of the condensation of dialdehyde **9** with two equivalents of either racemic ephedrine (for **5**) or enantiomerically pure ephedrine (for **6**). Dialdehyde **9** was readily made simple by hydrolysis of **4** (Scheme 3). An attempt to form dialdehyde **9** without protection *via* successive double lithiation and quenching with SEMCl failed, giving instead a poor yield of **11** by lateral, rather than *ortho*, lithiation of the ether **10** (Scheme 4).§



Scheme 3 Synthesis of dialdehyde **9**.

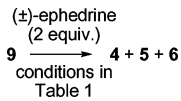
‡ In previous work we have shown that the conformer in which the C–H bond at the stereogenic centre eclipses the amide is the most stable. See ref 1.

§ The route to **9** *via* **4** illustrates the utility of (–)-ephedrine-derived oxazolidines as protecting groups for aldehydes during ortholithiation reactions. For a discussion of the favourability of lateral over ortho lithiation, which leads to selective formation of **11**, see ref. 9, pp. 90–96.



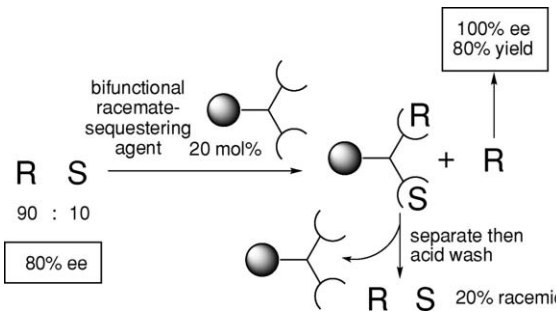
Scheme 4 Failed double ortholithiation route to **4**.

Condensation of dialdehyde **9** with (±)-ephedrine is complicated by the fact that both **5** and **6** are possible products depending on the "enantioelectivity"¶ (*i.e.*, whether the second molecule of ephedrine to be incorporated is homochiral or enantiomeric with the first) of the second condensation reaction. Dialdehyde **9** was treated with (±)-ephedrine and the mixture was heated to reflux in toluene for 3 d (Scheme 5). Comparison of the NMR spectrum of the crude product mixture with those in Fig. 2 indicated that the reaction had formed a 1.65 : 1 mixture of stereoisomers **5** and **6**.



Scheme 5 Condensation with racemic ephedrine.

We expected **5** (derived from condensation of **9** with one molecule of (+)- and one molecule of (−)-ephedrine), because it carries two *exo* oxazolidines in a matched arrangement with the amide axis, to be more stable than **6** (Fig. 2). The possibility that the product of condensing enantiomeric pairs of (+)- and (−)-ephedrine with dialdehyde **9** might be more favourable than condensing mismatched homochiral pairs offered the intriguing possibility that **9** might be considered as a racemate-sequestering agent, selectively trapping racemic pairs from solution, and therefore offering a method for the improvement of enantiomeric excess in samples of moderate ee.‖ Scheme 6 illustrates the idea: if



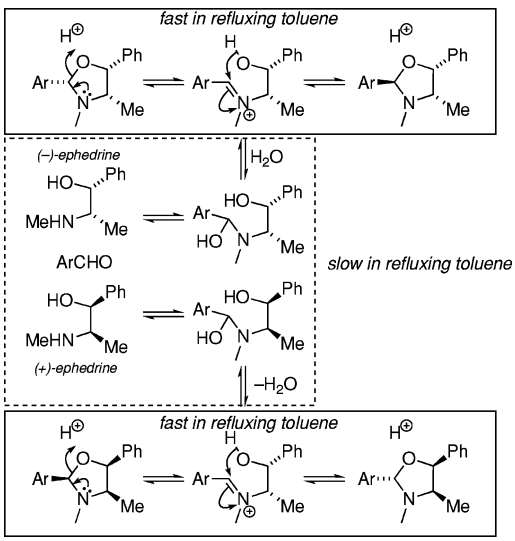
Scheme 6 A racemate-sequestering agent for improvement of ee.

¶A useful term which could be employed here, where the selectivity results not purely from choice in the *formation* of a new stereogenic centre, but from choice in the *incorporation* of alternative stereoisomers. Enantio*electivity* describes the propensity of chiral polymerising systems to incorporate one enantiomer from a racemic mixture. See ref. 10.

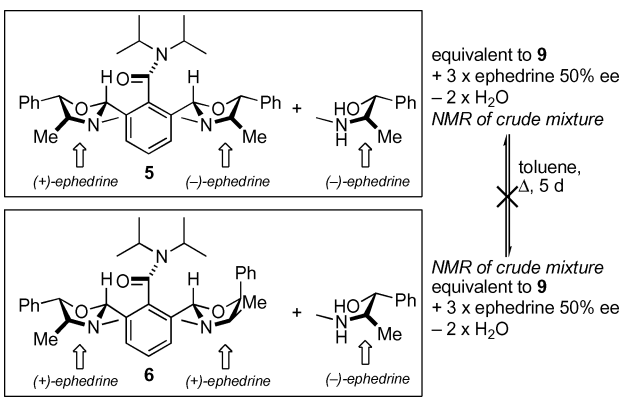
‖For related methods, relying not on racemate sequestration, but instead on a form of asymmetric amplification, see ref 11.

an appropriate amount of a racemate-sequestering agent were added to an enantiomerically enriched, but impure, sample, then an increase in ee in the remaining unreacted substrate can be expected.

Since *exo* oxazolines are favoured products only under thermodynamic control,[6] it seemed possible that the persistence of *endo* oxazolines in the reaction mixture was due to incomplete equilibration between the possible product stereoisomers. Equilibration between *exo* and *endo* oxazolines, shown in the solid box in Scheme 7, is known to be fast in refluxing toluene,[1,3,5] However, this is insufficient to interconvert **5** and **6**: for this the exchange of (+)- and (−)-ephedrine shown in the dotted box of Scheme 7 also needs to be rapid. To estimate the rate of this interconversion, we mixed each of **5** and **6** separately with one equivalent of (−)-ephedrine (so that the two mixtures contain the same, though enantiomeric, 1 : 3 ratio of amide to ephedrine of 50% ee) and heated them in refluxing toluene (Scheme 8). Even after 5 d, NMR showed that the product mixtures from the two experiments were different, indicating that the ephedrine exchange shown in the dotted box of Scheme 7 is slow, and confirming this as a possible reason for our inability to convert **9** + (±)-ephedrine entirely to **5**.



Scheme 7 Interconversions between stereoisomers of ephedrine-derived oxazolines.



Scheme 8 Attempted ephedrine exchange.

Table 1 Reaction of **9** with (±)-ephedrine

Entry	Solvent	*exo* : *endo* 25 °C, 24 h	*exo* : *endo* 45 °C, 24 h	*exo* : *endo* 70 °C, 3 d	*exo* : *endo* 67 °C + $Sc(OTf)_3$, 7 d
1	Toluene	0.40	0.62	4.3	6
2	$CHCl_3$	0.33	0.53	5.8	6
3	Dioxane	0	0.52	4.6	—
4	Dioxane–H_2O	0	0.31	—	7
5	MeCN	0.29	0.45	4.0	5
6	MeCN–H_2O	0	0.45	2.6	—
7	EtOAc	0	0.42	4.1	—
8	EtOH	0	0.42	3.2	5
9	EtOH-H_2O	—	—	—	6

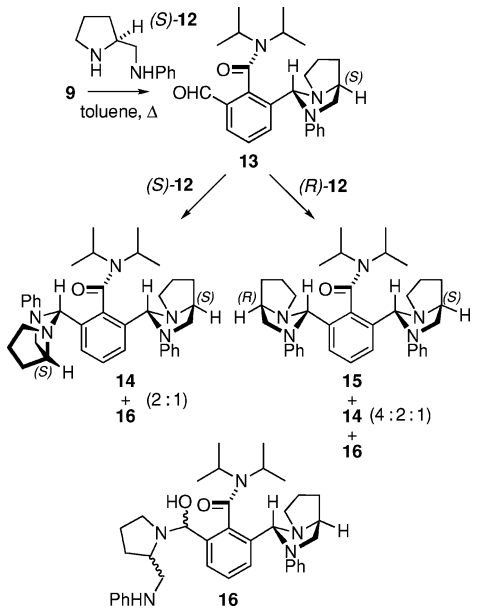
We made extensive attempts to increase the rate of the ephedrine exchange reaction by changing the solvent, or adding water, protic acids or Lewis acids. In each case, a mixture of **9**, (±)-ephedrine and the additive were heated together (Scheme 5) and the outcome of the reaction assessed by determining the overall ratio of *exo* to *endo* oxazolines in the mixture by integration of the NMR spectrum in the regions of $\delta = 5.75$–5.25 and 5.25–4.75 (see Fig. 2): the more successful the reaction, the greater the ratio. Results are shown in Table 1. At lower temperatures (25 and 45 °C), even epimerisation is slow, and *endo* oxazolines are the major products in every case, particularly in polar solvents, in agreement with the literature.[6] At higher temperatures, epimerisation is fast, and the *exo* : *endo* ratio increases to a maximum of around 5. Only the addition of scandium triflate allowed any advance to be made beyond this figure, but even then the proportion of *endo* oxazoline never decreases below about 12%, the figure expected from a still disappointing 3 : 1 ratio of **5** : **6**.

3. Proline-derived imidazolidine *vs.* proline-derived imidazolidine

The lack of rapid exchange between the enantiomers of ephedrine led us to abandon attempts to synthesise **5** under thermodynamic control in favour of trial condensations with the proline-derived diamine **12**, a compound whose imidazolidine derivatives[12,13] are powerful controllers of amide conformation,[3,14] just like the ephedrine-derived oxazolidines. Aminals derived from **12** or other 1,2-diamines are both formed and hydrolysed readily,[15] and we hoped that this increased lability would give the thermodynamic control we were seeking. In addition, the bicyclic structure of the imidazolines derived from **12**—**13**, for example—makes the formation of *endo* epimers highly unlikely, increasing the chance of a stereoselective condensation.

Dialdehyde **9** was treated with one equivalent of the diamine (*S*)-**12**** to yield the imidazolidine **13** in good yield as a single stereoisomer.[3] This compound was condensed with a second equivalent of diamine, either (*S*)-**12** or (*R*)-**12**, and the results obtained are shown in Scheme 9. With a second equivalent of (*S*)-**12** only one diastereoisomer of the bis-imidazolidine, **14**, is possible. However a second, unstable, compound was obtained in addition, to which we tentatively assign, on the basis of its NMR spectrum, the hemiaminal (carbinolamine) structure **16**.

Diamine **12 is commercially available but can be made in four steps by the method of Mukaiyama (ref. 12) or two steps by the method of Iriuchijima (ref. 16). In the context of the present work the latter method has the "advantage" of producing either enantiomerically enriched or partially (or even fully) racemised diamine according to reaction conditions.



Scheme 9 Imidazolidines from proline-derived diamine **12**.

Condensation of **13** with (*R*)-**12** was suprisingly unselective. In addition to the expected symmetrical *meso* bis-imidazolidine **15**, we obtained significant amount of the unsymmetrical bis-aminal (±)-**14** along with further hemiaminal products again tentatively assigned as diastereoisomers of **16**, the three components being present in a 4 : 2 : 1 ratio

The formation of (±)-**14** from **13** plus (*R*)-**12** is only possible if the (*S*)- and (*R*)-diamines **12** can exchange under the conditions of the reaction, something we failed to achieve with (+)- and (−)-ephedrine. This suggests that the condensation of **13** with **12** is indeed not under kinetic but under thermodynamic control, as we had hoped. However, the fact that both **15** and (±)-**14** are present also suggests that the thermodynamic preference for **15** is relatively weak. We had expected **15** to be favoured for steric reasons[1] (Fig. 4), since it can avoid any interaction between N–Ph

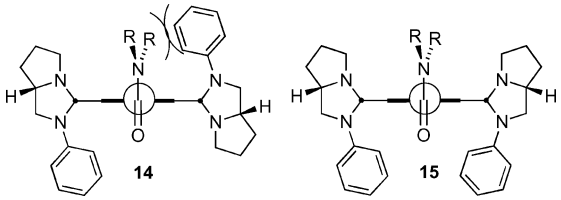
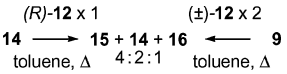


Fig. 4 Expected favourability of **15** over **14**.

and the amide N*i*–Pr$_2$ groups which we believe to be at the root of the conformational selectivity exhibited by the related amidomonoimidazolidines. The reason for the weakness of the selectivity here relative to the naphthamides may lie in the fact that these amides have relatively little flexibility: the energy minimum for amide Ar–CO bond rotation in the congested **14** and **15** is likely to be a steeper sided well than for the related naphthamides[3] and benzamides,[1] which show excellent control.

To confirm that equilibration between imidazolidines derived from enantiomeric diamines is possible, we treated **14** with one equivalent of (*R*)-**12** (Scheme 10). Over 50% of the product mixture was the *meso* compound **15**, which can be formed only if (*R*)-**12** has displaced some of (*S*)-**12** from **14**.

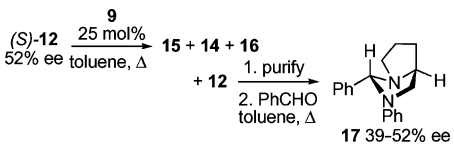


Scheme 10 Confirming thermodynamic control.

Treatment of dialdehyde **9** with two equivalents of racemic **12**, the constitutional equivalent of the reaction in Scheme 10 between **13** and (*R*)-**12** gave as expected the same thermodynamically controlled 4 : 2 : 1 ratio of **15** : **14** : **16** (Scheme 10)

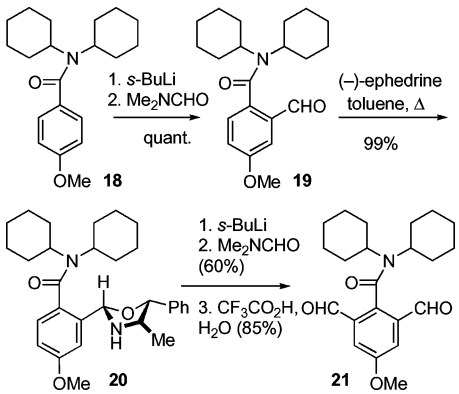
4. Racemate sequestration with diamines

Although the selectivity for the *meso* over chiral bis-imidazolidine **15** over **14** is weak, at 2 : 1 it is better than statistical (which would give a 1 : 1 ratio of chiral : meso bisimidazolidines), though the presence of the hemiaminal **16** complicates the analysis. Aiming to investigate possible improvements to ee by racemate sequestration, we treated diamine **12** of 50% ee with a deficit of the dialdehyde **9** (25 mol%, *i.e.* a molar ratio of 2 diamines to each formyl group). Purification returned unreacted the diamine **12** whose ee we determined by ^{1}H NMR in the presence of Pirkle's chiral solvating agent TFAE[17] of its imidazolidine condensation product with benzaldehyde **17**[13] (Scheme 11). The reaction was repeated in a wide range of solvents, but in no case was the ee of **12** improved.



Scheme 11 Attempted improvement of ee by racemate sequestration.

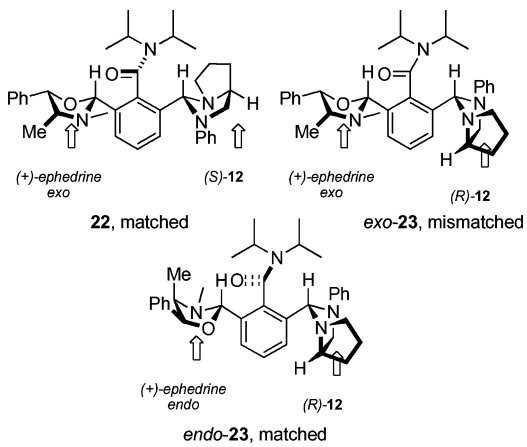
In all these reactions, the selectivity for *meso* bis-imidazolidine **15** over chiral imidazolidine **14** was low—often little better than 1 : 1—contrary to our expection, detailed in Fig. 4, that **14** would be disfavoured for steric reasons. Aiming to exacerbate steric crowding in the chiral bis-imidazolidine, we made the *N*,*N*-dicyclohexyl dialdehyde **21** by sequential ortholithiation of **18** as shown in Scheme 12, using ephedrine to protect the aldehyde during the second lithiation and described above. Repeating the reaction in Scheme 11 using **21** in the place of **9** gave a small, though probably insignificant, ee increase of around 3%. The synthesis of an even more hindered dialdehyde based on *N*-benzoyltetramethylpiperidine ran into difficulties because of a competing, though interesting, dearomatising addition of *s*-BuLi to the aromatic ring.[18]



Scheme 12 A more hindered dialdehyde.

5. Ephedrine-derived oxazolidine *vs.* diamine-derived imidazolidine

Both the ephedrine-derived oxazolidines and the diamine-derived imidazolidines have an Achilles' heel: the oxazolidines act brave, exert consistently high thermodynamic control over the adjacent axis, but turn coward in mismatched cases, being readily epimerised to the *endo* isomers. The imidazolidines on the other hand look weaker, but at least stand their ground. Pitting the two groups against one another in a battle for control over the axis would reveal whether it might be possible to use one to resolve the other. We took monooxazolidine **4** and treated it with a mixture of (*R*) and (*S*) diamine **12** in two experiments: firstly with (*R*)-**12** of 50% ee; secondly (*S*)-**12** of 38% ee. We expect (*S*)-**12** to condense to form a "matched" derivative with **4**; (*R*)-**12** would form a "mismatched" derivative with **4** but, on the basis of the discussion above, this mismatched derivative could be transformed into a matched derivative by epimerisation of the *exo* oxazolidine to an *endo* oxazolidine (Scheme 13).



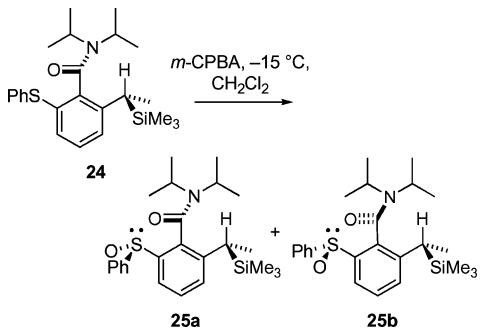
Scheme 13 Matched and mismatched imidazolidinyloxazolidines.

Both reactions proceeded to completion, and the products contained a mixture of at least two unstable compounds which we were unable to characterise but which contained both *exo*- or *endo*-oxazolidines by NMR. The ratio of *exo* : *endo* depended on the ratio of (*R*)- to (*S*)-**12** used in the reaction. 4 : 1 (*S*) to (*R*) (*i.e.* 50% ee *S*) gave 13 : 1 *exo* : *endo*; 1 : 2.2 (*S*) to (*R*) (*i.e.* 38% ee *R*) gave 2 : 1 *exo* : *endo*. Since the amount of *endo* product is dependent at least to some degree on the ee of the diamine, it

is clear that the diamine is able to influence, *via* the amide, the preferred stereochemistry of the oxazolidine. That said, however, even with mainly (*R*)-**12**, the major product is still *exo*, suggesting that there is a significant amount of *exo*-**23** present and therefore that the mismatched isomer is not heavily disfavoured. However, no quantitative conclusions can be made regarding the relative degree of control exerted by the competing influences.

6. Sulfoxide *vs.* 1-(trimethylsilyl)ethyl

Of all of the groups we have shown to exert an influence over the amide's orientation, a 2-sulfinyl group has been the most powerful.[1,2,19] We therefore made three compounds (**24**, **25** and **26**) in which we pitted the sulfinyl group against three other groups of slightly lower rank[1] in terms of conformational control: a 1-(trimethylsilyl)ethyl group,[20] an ephedrine-derived oxazolidine and a diamine-derived imidazolidine. Low temperature NMR experiments had shown that despite the high thermodynamic selectivity for a single amide conformer, the kinetic selectivity in the oxidation of an amido sulfide to an amido sulfoxide is low.[19] We reasoned therefore that the oxidations of the corresponding sulfides to sulfoxides should proceed with poor stereoselectivity, and give a mixture of two diastereoisomers, one matched and one mismatched with regard to control over the amide



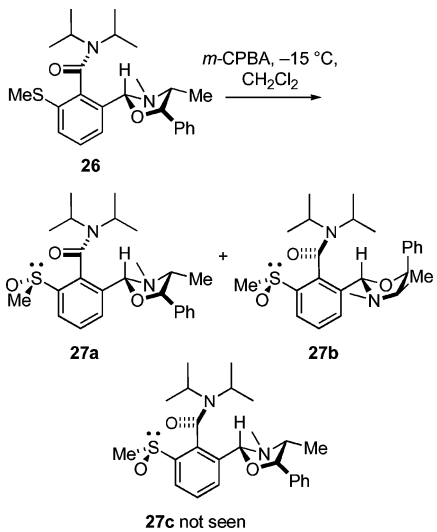
Scheme 14 Matched and mismatched sulfinylsilanes.

The known sulfide **24**[20] was oxidised with *m*-CPBA to yield two separable diastereoisomers **25a** and **25b** in a 2 : 1 ratio (Scheme 14).‡‡ While we were unable to assign unequivocally the stereochemistry or conformation of the two compounds, we propose that the major product is **25a** using the precedent that kinetic control has previously generated the analogous amide–sulfoxide relative stereochemistry with comparable stereoselectivity. Sulfoxide **25a** is the matched diastereoisomer; in **25b** the stereogenic centres are mismatched, but still the ^{1}H NMR spectrum consists of a single set of peaks at ambient temperature, suggesting that the amide adopts a single Ar–CO conformation. Since, individually, the sulfoxide group is able to exert conformational control at the 200 : 1 level,[19] while the silylethyl group usually achieves control of around 90 : 10,[1,20] we assume that the sulfoxide wins the battle hands down in this case, and the conformation of the product is as shown.

‡‡ The fact that this chiral compound and the related **26** oxidised with much lower selectivity than that apparent in the room temperature oxidation of simple achiral alkylthionapthamides gave us our first indication that the stereochemistry of such oxidations, when there are no other chiral centres in the molecule, are under thermodynamic and not kinetic control. See ref. 2.

7. Sulfoxide *vs.* ephedrine-derived oxazolidine

The silyl-bearing centre in **25b** has no choice but to capitulate to the sulfoxide. However, as shown above, ephedrine-derived oxazolidines are more fickle: forcing them into a situation where their stereochemistry is mismatched with that of a more powerful stereogenic centre, and by epimerising to *endo* stereochemistry they are able to defect to an alternative "matched" arrangement. Known sulfide **26**[1] was therefore treated with *m*-CPBA and gave two diastereoisomeric sulfoxides **27**, again in a 2 : 1 ratio. The major has the distinctive signals of an *exo* oxazolidine, and we assign the stereochemistry **27a** to this diastereoisomer (Scheme 15). The second is however clearly an *endo* oxazolidine by NMR, presumably **27b**. We can account for the formation of this diastereoisomer by assuming that the initial oxidation of the sulfide yields a mixture of **27a** (matched) and **27c** (mismatched), but that epimerisation of **27c** takes place rapidly under the reaction conditions, allowing the formation of a "quasi-matched" diastereoisomer **27b**.



Scheme 15 Matched and mismatched sulfinyloxazolidines.

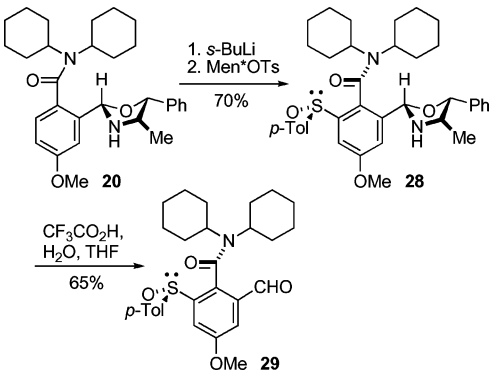
This result appears to suggest again that sulfoxide is much more powerful than the oxazolidine in its ability to control the amide axis, but it is important not to read too much into these results, since the mismatched **27c** can become more stable only by epimerisation of the oxazolidine and not of the sulfinyl group, whatever the relative controlling power of the two centres in the absence of epimerisation.

8. Sulfoxide *vs.* diamine derived imidazolidine

Given that the sulfoxide of **27** can enforce preferred stereochemistry on the benzylic centre of the oxazolidine ring, it seemed posssible that by pairing an imidazolidine with a sulfoxide it might be possible to achieve a reaction in which the stereochemistry of the diamine precursor to the imidazolidine determines whether or not the imidazolidine forms. In other words, by using an enantiomerically pure sulfoxide, we hoped to develop a reagent which would selectively scavenge a single enantiomer of the diamine.§§

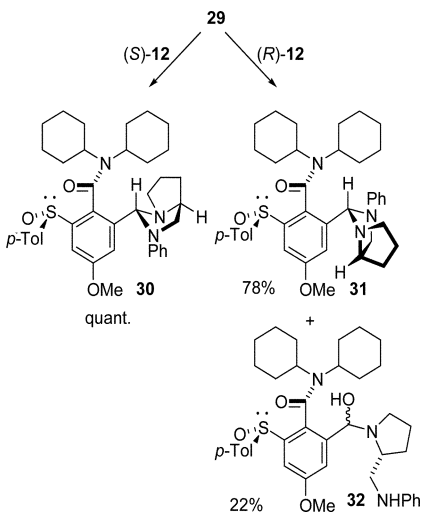
§§ Scavengers of single enantiomers have been described—see for example ref. 21.

We therefore made formyl sulfoxide **29** (Scheme 16), mindful of the fact that the dicyclohexylamides had given very slightly higher stereoselectivities than diisopropylamides in earlier reactions. Lithiation of **20** and addition of (1*R*,2*S*,5*R*,S_S)-(−)-menthyl *p*-toluenesulfinate (the method of Andersen[22,23]) gave sulfoxide **28** in good yield. **28** is, as it happens, the matched compound, though this is incidental in this case–as indicated before, ephedrine is simply a useful protecting group during lithiation reactions. However the fact that **28** is a single diastereoisomer confirmed that the new sulfur stereogenic centre is enantiomerically pure. Deprotection of **28** with TFA gave aldehyde **29**.



Scheme 16 Synthesis of a potential stereoselective diamine scavenger.

To establish the reactivity of **29** towards enantiomeric diamines **12**, we treated it separately with 1 equiv. (*R*) and 1 equiv. (*S*) diamine (Scheme 17). As expected, the (*S*) sulfoxide and (*S*) diamine are a matched pair, and the sulfinylimidazolidine **30** formed as a single diastereoisomer and conformer in quantitative yield. By contrast, the mismatched (*R*) diamine formed the imidazolidine **31** in lower yields and the crude NMR specctrum, contained significant amounts of what we assume to be the hemiaminal **32**.



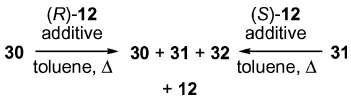
Scheme 17 Matched and mismatched sulfinylimidazolidines.

In order for **29** to be an effective scavenger of (*R*)-12, imidazolidine formation needs to take place principally under thermodynamic control. The time taken for a mixture of **30** plus (*R*)-**12** or **31** + (*S*)-**12** (constitutionally equivalent to a mixture of **29** with two equiv. (±)-**12**) to reach an equilibrium mixture of **30**, **31** and **32** (Scheme 18) was investigated by NMR, and the results are shown in Table 2. In the absence of additives, both mixtures reach an apparent equilibrium ration of about 75 : 7 : 18 **30** : **31** : **32** in 58–72 h, though the time taken to reach this equilibrium drops to under 20 h in the presence of toluenesulfonic acid or scandium triflate. The equilibrium ratio represents a selectivity of 10 : 1 in favour of formation of the desired aminal, but only 3 : 1 in favour of reaction of (*S*) *vs.* (*R*)-**12**, since it is likely that all of **32** arises from addition of (*R*)-**12**.

Table 2 Equilibration of sulfinylimidazolidines

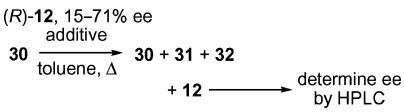
Entry	Starting material	Additive	Time/h	**30**[a]	**31**[a]	**32**[a]
1	**30** + (*S*)-**12**	—	24	90	1	9
2			48	78	5	17
3	**31** + (*R*)-**12**	—	24	38	16	46
4			48	61	12	27
5			72	72	6	22
6	**31** + (*R*)-**12**	TsOH	20	72	10	17
7	**31** + (*R*)-**12**	$Sc(OTf)_3$	20	75	7	17

[a] % in NMR spectrum of crude mixture.



Scheme 18 Equilibrating matched and mismatched sulfinylimidazolidines.

Aldehyde **29** was condensed with an two equivalents of (*R*)-diamine of varying enantiomeric enrichment (Scheme 19) and the ratio of **30** : **31** : **32** was determined by NMR. After filtration, the ee of the remaining diamine was determined by HPLC on a chiral stationary phase (Chiracel OD-H) and the results are shown in Table 3.



Scheme 19 Scavenging (*S*)-**12**.

The best increases in ee—an enhancement of 20–23%—were observed with diamine close to racemic. As the ee of the starting diamine is increased there is a corresponding drop in the extent to which ee is enhanced, though the ratio of **30** : **31** : **32** appears to be linked to ee in a more complex way that we had imagined. The ee enhancement, though the best we obtained by any method, is nonetheless moderate, and although we still believe there is merit

Table 3 Enhancement of ee by scavenging (S)-**12**

Entry	Ee **12**	Additive	**30**[a]	**31**[a]	**32**[a]	Ee enhancement
1	15	—	46	12	42	+23
2	15	$Sc(OTf)_3$	59	12	29	+20
3	60	—	65	6	29	+12
4	60	$Sc(OTf)_3$	47	12	40	+17
5	71	—	39	11	50	+8

[a] % in crude reaction mixture by NMR.

in the idea we have now abandoned efforts to develop scavenging or sequestering agents based on these structures. The ability of tertiary amide groups to relay information under kinetic control is much more powerful than these thermodynamic effects, and future publications will report our results in this area in detail.

X-Ray crystallography¶¶

5: Crystal data $C_{33}H_{45}N_3O_3$; $M = 555.74$; monoclinic P21/n; $a = 14.361(3)$ Å; $b = 7.2093(13)$ Å; $c = 31.922(5)$ Å; $\beta = 92.459(14)°$; $V = 3301.9(10)$ Å^3; $T = 296.2$ K; $Z = 4$; $\mu = 0.558$ mm^{-1}; 6543 reflections; $R_f = 0.0486$; $R_{int} = 0.0213$; CCDC reference number 286090.

Experimental

General methods have been described before.[3] Flash chromatography refers to chromatography carried out on silica by the method of Still, Kahn and Mitra.[24] Experimental data for **24** and **27** has been reported previously.[2]

N,*N*-Diisopropyl-2-[(2*R*,4*R*,5*S*)-3,4-dimethyl-5-phenyloxazolidin-2-yl]-6-formylbenzamide (4)

sec-Butyllithium (0.9 mL, 1.4 M, 1.1 equiv.) was added to a solution of oxazolidine **3**[3,25](420 mg) in THF (50 mL) at −78 °C under nitrogen. The reaction mixture became purple. After stirring at −78 °C for 1 h, dry DMF (0.2 mL) was added, and the reaction was allowed to warm to room temperature. Aqueous ammonium chloride (saturated, excess) was added, and the resulting mixture was extracted into EtOAc. The organic layer was separated, washed with water, and then dried over magnesium sulfate. Purification by flash chromatography (silica gel, petrol–EtOAc 2 : 1) gave the aldehyde **4** (401 mg, 89%) as a powdery white solid, mp 167–168 °C, R_f 0.26 (petrol–EtOAc 2 : 1), $[a]_D^{24} = +111.2$ [$c = 1.0$, $CHCl_3$), ν_{max} (chloroform film)/cm^{-1} 2980, 2877, 2846, 2792, 1706, 1621; δ_H (300 MHz, $CDCl_3$) 0.81 (3 H, d, *J* 6.5), 1.02 (3 H, d, *J* 6.5), 1.13 (3 H, d, *J* 6.5), 1.66 (3 H, d, *J* 6.5), 1.67 (3 H, d, *J* 6.5), 2.19 (3 H, s), 2.96 (1 H, dq, *J* 6.5, 8.5), 3.60 (2 H, sept, *J* 6.5), 4.87 (1 H, s), 5.12 (1 H, d, *J* 8.5), 7.30–7.45 (5 H, m), 7.63 (1 H, t, *J* 7.5), 7.99 (1 H, dd, *J* 1.0, 7.5), 8.28 (1 H, dd, *J* 1.0, 7.5), 10.12 (1 H, s); δ_C (75 MHz, $CDCl_3$) 15.1, 20.0, 20.2, 20.2, 20.4, 35.7, 46.5, 51.4, 63.9, 82.5, 93.4, 127.8, 128.0, 128.9, 130.1, 131.7, 134.8, 135.4, 139.3, 141.7, 166.5, 190.4; *m*/*z* (CI) 409 (MH^+, 100%) [Found (MH^+) 409.2490, $C_{25}H_{33}N_2O_3$ (MH^+) requires 409.2491 (0.2 ppm)].

On a 6 g scale, this reaction gives a crude product which can be purified by recrystallisation to yield amide **4** in 81% yield.

N,*N*-Diisopropyl-2-[(2*R*,4*R*,5*S*)-3,4-dimethyl-5-phenyloxazolidin-2-yl]-6-[(2*S*,4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidin-2-yl]benzamide (5)

A solution of oxazolidine **4** (408 mg, 1 mmol) and (1*R*,2*S*)-(−)-ephedrine (164 mg, 1 mmol, 1 equiv.) in toluene (100 mL) was heated at reflux using a Dean–Stark apparatus. After 3 d, the solvent was removed *in vacuo* to leave a clear oil, which was purified by flash chromatography (silica gel, petrol–EtOAc 4 : 1) to give the meso bisoxazolidine **5** (489 mg, 88%) as a white, crystalline solid, mp 141–142 °C, R_f 0.27 (petrol–EtOAc 4 : 1), ν_{max} (film)/cm^{-1} 2966, 2932, 2878, 2791, 1627; δ_H (300 MHz, $CDCl_3$) 0.80 (6 H, d, *J* 6.5), 1.09 (6 H, d, *J* 6.5), 1.66 (6 H, d, *J* 6.5), 2.20 (6 H, s), 2.92 (2 H, dq, *J* 6.5, 8.5), 3.59 (1 H, sept, *J* 6.5), 3.74 (1 H, sept, *J* 6.5), 4.81 (2 H, s), 5.11 (2 H, d, *J* 8.5), 7.30–7.49 (10 H, m), 7.61 (1 H, t, *J* 7.5), 8.04 (2 H, d, *J* 8.0); δ_C (75 MHz, $CDCl_3$) 15.3, 20.2, 20.4, 36.0, 46.2, 51.3, 64.1, 82.2, 94.4, 127.6, 127.9, 127.9, 128.9, 129.4, 133.7, 139.7, 140.5, 167.9; *m*/*z* (CI) 556 (MH^+, 100%), 407 (30%), 148 (70%) [Found (MH^+) 556.3535, $C_{35}H_{46}N_3O_3$ requires 556.3539 (0.7 ppm)].

N,*N*-Diisopropyl-2,6-bis[(2*R*,4*R*,5*S*)-3,4-dimethyl-5-phenyloxazolidin-2-yl]benzamide (6)

A solution of oxazolidine **4** (204 mg, 0.5 mmol), (1*S*,2*R*)-(+)-ephedrine monohydrate (174 mg, 1 mmol, 2 equiv.) and *p*-toluenesulfonic acid (one crystal) in toluene (100 mL) was heated at reflux using a Dean–Stark apparatus. After 7 d, the solvent was removed *in vacuo* to leave a clear oil, which was purified by flash chromatography (silica gel, petrol–EtOAc 4 : 1) to give the unstable bisoxazolidine **6** (188 mg, 68%) as a white, crystalline solid, mp 197–200 °C (dec), R_f 0.16 (petrol–EtOAc 4 : 1), ν_{max} (chloroform film)/cm^{-1} 2968, 2881, 2794, 1631; δ_H (300 MHz, $CDCl_3$) signals for **6**: 0.69 (3 H, d, *J* 6.5), 0.82 (3 H, d, *J* 6.5), 1.17 (3 H, d, *J* 6.5), 1.29 (3 H, d, *J* 6.5), 1.69 (3 H, d, *J* 6.5), 1.70 (3 H, d, *J* 6.5), 2.21 (6 H, s), 2.89–3.01 (2 H, m), 3.65 (1 H, sept, *J* 6.73) 3.77–3.86 (1 H, m), 4.83 (1 H, s), 5.14 (1 H, d, *J* 8.4), 5.39 (1 H, s), 5.71 (1 H, d, *J* 5.0), 7.27–7.61 (11 H, m), 7.88 (1 H, d, *J* 8.0), 8.04 (1 H, d, *J* 7.5); *m*/*z* (CI) 556 (MH^+, 55%), 409 (32%) 148 (100%) [Found (MH^+) 556.3550, $C_{35}H_{46}N_3O_3$ requires 556.3539 (2.0 ppm)].

N,*N*-Diisopropyl-2,6-diformyl benzamide (9)

A solution of oxazolidine **4** (4.08 g, 10 mmol) in THF (100 mL) was treated with water (3.6 mL, 20 equiv.) and TFA (22.8 g, 15.4 mL, 20 equiv.) at room temperature. The reaction mixture was stirred for 4 h, and then concentrated *in vacuo*. The crude mixture was then passed through a short column of silica gel (eluting with petrol–EtOAc 1 : 1) (this step is essential to prevent partial re-formation of the oxazolidines during work-up), concentrated and redissolved in EtOAc. After washing with saturated aqueous sodium bicarbonate, drying over magnesium sulfate, and concentration *in vacuo*, the product was further purified by flash chromatography (silica gel, petrol–EtOAc 2 : 1) to give the dialdehyde **9** (2.38 g, 91%) as an off-white solid, mp 110–111 °C, R_f 0.15 (petrol–EtOAc 2 : 1), ν_{max} (chloroform film)/cm^{-1} 2980, 2930, 2874, 2749, 1693, 1622; δ_H (300 MHz, $CDCl_3$) 1.08 (6 H, d, *J* 6.5), 1.67 (6 H, d, *J* 7.0), 3.47 (1 H, sept, *J* 6.5), 3.63 (1 H, sept, *J* 7.0), 7.68 (1 H, t, *J* 7.5), 8.19 (2 H, d, *J* 7.5); δ_C (75 MHz, $CDCl_3$) 20.1, 20.4, 46.9, 51.6, 129.0, 132.6, 134.6, 142.4, 165.2, 189.5; *m*/*z* (CI) 262 (MH^+, 100%). [Found (MH^+) 262.1438, $C_{15}H_{20}NO_3$ requires 262.1443 (1.9 ppm)].

N,*N*-Diisopropyl-2-(2-trimethylsilylethoxymethyl)benzamide (10)

sec-Butyllithium (1.57 mL, 1.4 M, 1.1 equiv.) was added to a stirred solution of *N*,*N*-diisopropylbenzamide **1** (410 mg, 1 equiv.) in THF (20 mL) at −78 °C. The reaction mixture was stirred for 30 min, and SEM-Cl (0.39 mL, 1.1 equiv.) was added. After warming to room temperature, the reaction mixture was

¶¶ CCDC reference numbers 286090. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b514558a

poured into saturated aqueous ammonium chloride and extracted into EtOAc. The combined organic fractions were then washed with water, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (petrol–EtOAc 19 : 1) gave the amide **10** (112 mg, 17%) as a viscous clear oil, δ_H (300 MHz, $CDCl_3$) 0.01 (9 H, s), 1.00 (2 H, ddd, *J* 1.0, 7.5, 9.5), 1.09 (3 H, d, *J* 6.5), 1.10 (3 H, d, *J* 6.5), 1.55 (3 H, d, *J* 6.5), 1.58 (3 H, d, *J* 6.5), 3.52 (1 H, sept, *J* 6.5), 3.56 (2 H, dt, *J* 1.0, 9.5), 3.72 (1 H, sept, *J* 6.5), 4.45 (1 H, d, *J* 11.5), 4.54 (1 H, d, *J* 11.5), 7.11 (1 H, dd, *J* 1.5, 7.5), 7.26 (1 H, dt, *J* 1.5, 7.5), 7.32 (1 H, dt, *J* 1.5, 7.5), 7.46 (1 H, d, *J* 7.5).

2-[1,2-Bis-(2-trimethylsilylethoxy)ethyl]-*N*,*N*-diisopropylbenzamide (11)

sec-Butyllithium (0.26 mL, 1.4 M, 1.1 equiv.) was added to a stirred solution of benzamide **10** (112 mg, 1 equiv.) in THF (20 mL) at −78 °C. The reaction mixture was stirred for 30 min, and SEM-Cl (0.09 mL, 1.5 equiv.) was added. After warming to room temperature, the reaction mixture was poured into aqueous ammonium chloride (saturated, excess), and extracted into EtOAc. The combined organic fractions were then washed with water, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (petrol–EtOAc 19 : 1) gave the *amide* **11** (25 mg) as a viscous clear oil, δ_H (300 MHz, $CDCl_3$) (mixture of conformers[1]) −0.04 (9 H, s), −0.01 (9 H, s), 0.86–1.01 (4 H, m), 1.13 (3 H, d *J* 6.5), 1.15 (3 H, d, *J* 6.5), 1.56 (3 H, d, *J* 6.5), 1.59 (3 H, d, *J* 6.5), 3.33–3.80 (8 H, m), 4.53 and 4.74 (1 H, 2 signals, one for each conformer, dd, *J* 2.0, 8.5 and dd, *J* 3.5, 8.0), 7.11 (1 H, d, *J* 7.5), 7.27 (1 H, t, *J* 7.5), 7.36 (1 H, t, *J* 7.5), 7.57 (1 H, d, 7.5).

(*S*)-2-(Anilinomethyl)pyrrolidine ((*S*)-12)

A modification of the method of Iriuchijima[16] was used. A mixture of L-glutamic acid (3.300 g, 22.4 mmol) and aniline (25 mL) was heated at 195–200 °C under Dean–Stark condenser. After 40 min, the reaction mixture was cooled to room temperature and the aniline was removed by distillation under reduced pressure. (Further heating leads to racemisation of the product.) The residue was dissolved in acetone and the resulting solution was cooled with ice/water bath to afford yellow crystals. After filtration, yellow crystals were dissolved in hot methanol and cooled to −15 °C to yield the pyroglutanilide as white crystals (2.142, 47% yield). $[\alpha]_D^{21} = +19.8$ (*c* = 1.17, methanol). δ_H (300 MHz, $CDCl_3$). *m*/*z* 205 (MH^+, 100%), 101 (18), 84 (52). Found 204.0897; $C_{11}H_{12}N_2O_2$ requires 204.0898.

$LiAlH_4$ (0.787 g, 20.70 mmol) was added to a solution of the pyroglutanilide (1.695 g, 8.30 mmol) in THF (25 mL). The solution was heated at reflux for 2 h and was cooled with an ice bath. Water (5 mL) was slowly added with stirring followed by 2.5M aqueous sodium hydroxide (20 mL). The solution was extracted with CH_2Cl_2 (3 × 50 mL) and combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was distilled under reduced pressure to give the (*S*)-anilinomethylpyrrolidine **12** as yellow oil (1.090 g, 75% yield). $[\alpha]_D^{21} = +14.8$ (*c* = 0.225, methanol). ν_{max}/cm^{-1} 3367, 2961, 1603, 1503. δ_H (300 MHz, $CDCl_3$) 1.50 (1H, m, $CH_2CH_2CH_2$), 1.70–2.02 (3H, m, $CH_2CH_2CH_2$), 2.97 (3H, m, NCH_2CH_2, CH_2NHPh), 3.20 (1H, dd, *J* 4.7, 12, CH_2NHPh), 3.42 (1H, m, $NCHCH_2N$), 6.68 (2H, dd, *J* 1.0, 8.6), 6.74 (1H, t, *J* 0.8, 7.3), 7.21 (1H, ddd, *J* 1.7, 6.6, 7.3). δ_C (75 MHz, $CDCl_3$) 25.7, 29.5, 46.4, 48.6, 57.6, 112.9, 117.2, 129.1, 148.5. *m*/*z* (EI) 176 (M, 56%), 106 (100), 70 (99). Found 176.1318; $C_{11}H_{16}N_2$ requires 176.1313.

N,*N*-Diisopropyl-2-formyl-6-[(2′*R*,4′*S*)-2-phenylperhydropyrrolo-(1,2*c*)-imidazol-3-yl]benzamide (13)

A solution of dialdehyde **9** (0.319 g, 1.22 mmol) and (*S*)-diamine **12** (0.215 g, 1.22 mmol) in toluene (20 mL) was heated at reflux for 20 h. After cooling to room temperature, the mixture was poured onto a column of neutral alumina and eluted (5–20% EtOAc–petroleum ether solvent gradient) to produce the imidazolidine **13** as waxy yellow solid (0.353 g, 69% yield). ν_{max}/cm^{-1} 2971, 1697, 1624, 1503. δ_H (300 MHz, C_6D_6) 0.41 (3H, d, *J* 6.6 Hz), 0.55 (3H, d, *J* 6.6 Hz), 1.15–1.50 (10H, m), 1.98 (1H, q, *J* 8.9 Hz), 2.58 (1H, t, *J* 8.9 Hz), 2.75–2.96 (3H, m), 3.18 (2H, m), 5.78 (1H, s), 6.38 (3H, m), 6.58 (1H, t, *J* 7.7 Hz), 6.83–6.96 (3H, m), 7.49 (1H, dd, J 1.1, 7.7 Hz), 10.08 (1H, s). δ_C (75 MHz, $CDCl_3$) 19.4, 19.6, 20.8, 23.3, 27.4, 46.1, 50.8, 51.9, 52.6, 60.4, 78.9, 112.2, 116.6, 126.7, 128.0, 129.2, 131.9, 132.8, 139.6, 140.6, 145.9, 167.2, 189.7. *m*/*z* (EI) 420 (MH^+, 100%). Found 419.2571; $C_{26}H_{33}N_3O_2$ requires 419.2573.

N,*N*-Dicyclohexyl-*p*-anisamide (18)

4-Methoxybenzoyl chloride (1.8 mL, 13.29 mmol) was added slowly to a solution of dicyclohexylamine (5.8 mL, 29.25 mmol) and DMAP (1 crystal) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was stirred for 1 h and allowed to warm to room temperature. After 1 h of stirring, water (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic fractions were washed 1 M hydrochloric acid (20 mL), water (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization from petrol ether to gave the amide **18** as white crystals (4.035 g, 96% yield). ν_{max}/cm^{-1} 2928, 1611, 1511, 1433. δ_H (300 MHz, $CDCl_3$) 1.12 (8H, br), 1.50–1.79 (12H, br), 3.76 (3H, OCH_3), 6.84 (2H, d, *J* 8.6 Hz), 7.22 (2H, d, *J* 8.6 Hz). δ_C (75 MHz, $CDCl_3$) 25.2, 26.1, 30.7, 55.1, 113.4, 127.2, 131.3, 159.7, 171.0. *m*/*z* (CI) 315 (M, 38%), 232 (47), 135 (100). Found 315.2198; $C_{20}H_{29}NO_2$ requires 315.2198.

N,*N*-Dicyclohexyl-2-formyl-*p*-anisamide (19)

sec-BuLi (0.905 mL, 1.24 mmol) was added to a solution of amide **18** (0.325 g, 1.03 mmol) in dry THF (10 mL) at −78 °C and the solution was stirred for 1 h. DMF (0.11 mL, 1.44 mmol) was slowly added at −78 °C. After 30 min the solution was allowed to warm to room temperature. After 1 h, saturated ammonium chloride (10 mL) was added and the resulting mixture was extracted with EtOAc. The combined organic phases were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to produce the pure aldehyde **19** as colourless oil (0.356 g, quantitative yield). ν_{max}/cm^{-1} 2927, 2853, 1695, 1631, 1452, 1435, 1366, 1315, 1273, 1250, 732. δ_H (300 MHz, $CDCl_3$) 0.92 (3H, br m), 1.23 (3H, br m), 1.45 (3H, br m), 1.60 (7H, br m), 1.79 (2H, br), 2.62 (2H, br), 3.08 (2H, br), 3.82 (3H, s, OCH_3), 7.09 (1H, dd, *J* 2.6, 8.4 Hz, H-5), 7.17 (1H, d, *J* 8.4 Hz, H-6), 7.38 (1H, d, *J* 2.6 Hz, H-3), 10.02 (1H, s, *CHO*). δ_C (75 MHz, $CDCl_3$) 24.8, 25.2, 25.4, 26.4, 29.7, 30.9, 55.4, 56.2, 60.0, 111.4, 120.9, 127.0, 133.5, 134.8, 159.4, 159.4, 168.3, 190.1. *m*/*z* (CI) 344 (MH^+, 100%). Found 343.2145; $C_{21}H_{29}NO_3$ requires 343.2147.

N,*N*-Dicyclohexyl-2-[(2*S*,4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidin-2-yl]-6-formyl-*p*-anisamide (20)

A solution of aldehyde **19** (2.469 g, 7.19 mmol) and (1*R*,2*S*)-(−)-ephedrine (2.376 g, 14.38 mmol) in toluene (90 mL) was heated at reflux for 20 h. After cooling to room temperature, the mixture was poured on a column of neutral alumina and eluted (5–20% EtOAc–petroleum ether solvent gradient) to yield the oxazolidine **20** as yellow oil (3.502 g, 99%). δ_H (300 MHz, C_6D_6) 0.35 (3H, d, *J* 6.3 Hz, NCHCH_3), 0.48 (3H, br m), 1.02 (8H, br m), 1.30 (2H, br), 1.44 (1H, br d, *J* 12.1 Hz), 1.59 (3H, br), 1.72 (1H, br d, *J* 11.3 Hz), 1.88 (3H, s, NCH_3), 2.39 (1H, q, *J* 6.5 Hz, NC*H*CH$_3$), 2.74 (1H, br m), 2.94 (2H, br m), 3.09 (3H, s, OCH_3), 3.18 (1H, br m), 4.68 (1H, d, *J* 8.1 Hz, OC*H*Ph), 4.94 (1H, s, C*H*(O)N), 6.53 (1H, dd, *J* 2.6, 8.4 Hz, H-5), 6.83 (4H, m, 3 × H_{ar}, H-6), 7.12 (2H, d, *J* 6.9 Hz), 7.55 (1H, d, *J* 2.5 Hz, H-3). δ_C (75 MHz, C_6D_6) 14.9, 24.9, 25.1, 25.4, 25.5, 26.7, 29.9, 30.0, 30.8, 31.2, 35.7, 54.3, 55.7, 59.3, 63.7, 82.3, 94.4, 112.8, 114.8, 126.0, 133.8, 136.4, 140.2, 159.6, 169.5.

N,*N*-Dicyclohexyl-2,6-diformyl-*p*-anisamide (21)

sec-BuLi (1.08 mL, 1.40 mmol) was added to a solution of oxazolidine **20** (0.577 g, 1.17 mmol) in dry THF (11 mL) at −78 °C and the solution was stirred for 1 h. DMF (0.127 mL, 1.64 mmol) was slowly added at −78 °C. After 1 h, water (10 mL) was added and the mixture was extracted with EtOAc. The combined organic phases were washed with water (20 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc–petroleum ether) gave the oxazolidinoaldehyde as a yellow oil (0.362 g, 60%) as a mixture of *endo* and *exo* oxazolidines δ_H (300 MHz, C_6D_6) 0.33 (6H, m, 3 × $H_{cyclohex}$, NCHCH_3), 0.95 (9H, br m), 1.30 (3H, br), 1.54 (4H, br), 1.84 (1H, br), 1.85 (3H, s, *exo* NCH_3), 1.88 (3H, s, *endo* NCH_3), 2.34 (1H, q, *J* 6.4, NC*H*CH$_3$), 2.76 (2H, br), 2.92 (3H, s, OCH_3), 4.64 (1H, d, *J* 8.2, *exo* OC*H*Ph), 4.68 (1H, d, *J* 8.2, *exo* OC*H*Ph), 4.84 (1H, s, *endo* C*H*(O)N), 4.94 (1H, s, *endo* C*H*(O)N), 6.84 (3H, m, 3 × H_{ar}), 7.09 (2H, d, *J* 7.0), 7.31 (1H, d, *J* 2.7 Hz, H-3), 7.79 (1H, d, *J* 2.7, H-5), 10.08 (1H, s, *endo* C*H*O), 10.17 (1H, s, *exo* C*H*O). δ_C (75 MHz, C_6D_6) 14.9, 24.7, 25.0, 25.2, 25.4, 26.6, 26.6, 26.7, 29.4, 29.8, 30.7, 30.9, 35.5, 54.5, 56.4, 59.9, 63.7, 82.4, 93.6, 112.2, 120.9, 127.0, 133.6, 136.2, 137.5, 139.6, 159.7, 166.5, 189.3.

Trifluoroacetic acid (0.732 mL, 9.5 mmol) and water (0.171 mL, 9.5 mmol) were added to a solution of this oxazolidinoaldehyde (0.246 g, 0.47 mmol) in THF (5 mL). The reaction mixture was stirred for 2 h and concentrated under reduced pressure. The residue was quickly purified by flash chromatography (EtOAc–petroleum ether 1 : 1) to remove the ephedrine. The resulting residue was dissolved in EtOAc and the solution was washed saturated sodium carbonate, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc–petroleum ether) gave the dialdehyde **21** as colourless oil (0.148 g, 85% yield). ν_{max}/cm^{-1} 2931, 2856, 1700, 1629, 1436, 1364, 1317, 1285, 732. δ_H (300 MHz, $CDCl_3$) 0.83 (3H, m), 1.22 (3H, br m), 1.46 (5H, br m), 1.61 (5H, br m), 1.80 (2H, br m), 2.65 (2H, br m), 2.93 (1H, m), 3.08 (1H, br m), 3.87 (3H, s, OCH_3), 7.61 (2H, s, H-3 and H-5), 10.08 (2H, s, C*H*O). δ_C (75 MHz, $CDCl_3$) 24.8, 25.1, 25.4, 26.4, 29.5, 30.7, 55.9, 56.9, 60.6, 118.8, 133.9, 135.9, 159.6, 165.5 (C, *C*ON(cHex)$_2$), 189.1 (C, 2 × *C*HO). *m*/*z* (CI) 372 (MH$^+$, 100%).

N,*N*-Dicyclohexyl-2-[(2*S*,4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidin-2-yl]-6-[(*S*)-*p*-toluenesulfinyl]-*p*-anisamide (28)

sec-BuLi (1.00 mL, 1.30 mmol) was added to a solution of oxazolidine **20** (0.531 g, 1.08 mmol) in dry THF (11 mL) at −78 °C and the solution was stirred for 1 h. (−)-Menthyl *p*-toluenesulfinate[23] (0.636 g, 2.16 mmol) was slowly added at −78 °C. After 1 h, water (10 mL) was added and the mixture was extracted with EtOAc. The combined organic fractions were washed with water (20 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc–petroleum ether) gave the sulfoxide **28** as a colourless oil (0.476 g, 70% yield). δ_H (300 MHz, C_6D_6) 0.33 (3H, d, *J* 6.5 Hz, NCHCH_3), 0.47 (3H, br m), 1.04 (9H, br m), 1.30 (3H, br), 1.52 (4H, br), 1.62 (3H, s, ArCH_3), 1.80 (3H, s, NCH_3), 1.83 (1H, br), 2.03 (1H, br), 2.37 (1H, q, *J* 6.4 Hz, NC*H*CH$_3$), 2.88 (4H, s, $H_{cyclohex}$ and OCH_3), 3.37 (1H, br m), 4.67 (2H, d, *J* 8.1 Hz, OC*H*Ph), 4.81 (1H, s, C*H*(O)N), 6.65 (1H, d, *J* 8.1), 6.83 (3H, m, 3 × H_{ar}), 7.10 (2H, d, *J* 6.9), 7.42 (1H, d, *J* 2.6, H-3), 7.58 (1H, d, *J* 2.6), 7.92 (2H, d, *J* 8.2). δ_C (75 MHz, C_6D_6) 13.8, 14.9, 20.6, 24.9, 25.1, 25.4, 25.5, 26.5, 26.6, 29.4, 30.0, 30.9, 31.4, 35.5, 54.4, 56.5, 59.6, 60.3, 63.6, 82.4, 93.9, 109.8, 118.0, 124.3, 129.6, 131.4 136.9, 139.6, 139.9, 143.8, 146.1, 160.5, 166.5.

N,*N*-Dicyclohexyl-2-formyl-6-[(*S*)-*p*-toluenesulfinyl]-*p*-anisamide (29)

Trifluoroacetic acid (0.770 mL, 10.00 mmol) and water (0.180 mL, 10.00 mmol) were added to a solution of oxazolidine **28** (0.318 g, 0.50 mmol) in THF (5 mL). The mixture was stirred for 2 h and concentrated under reduced pressure. Rapid filtration thrrough silica (EtOAc–petroleum ether 1 : 1) removed the ephedrine. The residue was dissolved in EtOAc and the solution was washed with saturated sodium carbonate, dried over $MgSO_4$ and concentrated under reduced pressure. Purifiation by flash chromatography (20% EtOAc–petroleum ether) gave the aldehyde **29** as pale yellow oil (0.156 g, 65%). δ_H (300 MHz, $CDCl_3$) 0.91 (3H, br m), 1.21 (3H, br m), 1.53 (8H, br m), 1.75 (3H, br m), 1.97 (1H, br m), 2.25 (3H, s, ArCH_3), 2.63 (2H, br m), 3.12 (2H, br m), 3.74 (3H, s, OCH_3), 7.11 (3H, m), 7.41 (1H, d, *J* 2.7 Hz, H-3), 7.52 (1H, d, *J* 2.7 Hz, H-5), 7.60 (1H, d, *J* 8.2 Hz), 9.97 (1H, s, C*H*O).

N,*N*-Dicyclohexyl-2–[(2′*R*,4′*S*)-2-phenylperhydropyrrolo-(1,2*c*)-imidazol-3-yl]-6-[(*S*)-*p*-toluenesulfinyl]-*p*-anisamide (30)

A solution of aldehyde **29** (0.120 g, 0.28 mmol) and (*S*)-diamine **12** (0.070 g, 0.4 mmol) in toluene (3 mL) was heated at reflux for 20 h. After cooling to room temperature, the mixture was poured onto a column of neutral alumina and eluted (5–20% EtOAc–petroleum ether solvent gradient) to produce the imidazolidine **30** as waxy yellow solid (0.172 g, quantitative yield). δ_H (300 MHz, C_6D_6) 0.62 (3H, br m), 0.80–1.48 (20H, m), 1.55 (3H, s, ArCH_3), 1.72 (2H, m), 2.00 (1H, q, *J* 8.9 Hz), 2.33 (1H, br m), 2.58 (1H, t, *J* 8.9 Hz), 2.65 (3H, s, OCH_3), 2.86 (2H, br m), 3.26 (2H, br m), 5.75 (1H, s), 6.37 (2H, d, *J* 8.2 Hz), 6.66 (1H, d, *J* 2.6 Hz, H-3), 6.87 (5H, br m), 7.23 (1H, d, *J* 2.6 Hz, H-5), 7.89 (2H, d, *J* 8.2). δ_C (75 MHz, $CDCl_3$) 20.5, 23.4, 25.2, 25.5, 25.7, 25.8, 26.6, 27.4, 29.0, 30.8, 30.9,

31.0, 51.9, 52.7, 54.1, 56.4, 60.5, 60.6, 79.2, 105.5, 112.1, 116.5, 117.8, 124.0, 129.1, 129.7, 140.0, 141.1, 144.1, 146.1, 146.3, 160.2, 167.8.

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