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Dynamic resolution of atropisomeric amides using proline-derived imidazolines and ephedrine-derived oxazolidines

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Abstract—Condensation of atropisomeric tertiary 2-formyl naphthamides or 2-formyl benzamides with some chiral diamines and amino alcohols leads, via a dynamic resolution process, to single atropisomers of tertiary amides bearing chiral imidazolidines or oxazolidines. Hydrolysis of the new heterocycle competes a dynamic thermodynamic resolution of the starting aldehyde, and rapid reduction allows the isolation of atropisomeric amides bearing 2-hydroxymethyl substituents in enantiomerically enriched form. Evidence that the reactions are under thermodynamic control is presented.

1. Introduction

Tertiary aromatic amides are now well known to have the potential for atropisomerism: We,[1] and others,[2–4] have demonstrated that they are resolvable[5] by chromatography on a chiral stationary phase. Given the wide utility of other more well known classes of atropisomers such as the biphenyls and binaphthyls in asymmetric catalysis[6,7] (principally because of the flexibility inherent in a stereogenic axis as opposed to a stereogenic centre[8]), we set out to develop a method for the resolution of tertiary aromatic amides on a practical scale which would open up the opportunity for their development as a new family of chiral ligands based on the aromatic amide structure. A small number of enantiomerically pure atropisomeric amides have already been used as effective chiral ligands, being made in enantiomerically pure form either by classical resolution[9] or by asymmetric synthesis.[10,11] Dynamic kinetic resolution[12,13] and enantioselective lithiation[14–17] have also been used to synthesise atropisomeric amides in enantiomerically form, and some of these compounds have also been used as chiral reagents[4] and auxiliaries[18] or are of biological interest.[19–25] Our studies into the resolution of aromatic amides via the condensation of amidoaldehydes with 1,2-diamines and 1,2-amino-alcohols to form imidazolidines and oxazolidines are described in full in this paper.[26–28] During the course of this work, we discovered a remarkable propensity of the atropisomers being resolved to equilibrate and thus facilitate a dynamic resolution, a reaction which appears to be a member of the relatively small class of dynamic thermodynamic resolutions.[29]

2. Results and discussion

2.1. Starting materials

The known[30,31] 2-formyl naphthamides **1** were made in good yield from the parent amides by a modification of the ortholithiation conditions described by Beak and Brown,[32,33] quenching with DMF as electrophile (Scheme 1). The benzamides **2a**-**d** were also made by ortholithiation, though the ethyl group of **2c** was protected as its 1-silyl derivative to prevent competing lateral lithiation.[34] Ortholithiation and formylation of **3**[35] gave **4** which was desilylated to yield **2c**. **2d** was made from benzamide **5** by two successive ortholithiation reactions. **2e** was made from the mesitamide **7**[17] by lateral lithiation and hydroxylation to yield **8** which was oxidised with the Dess Martin periodinane[36,37] to the aldehyde.

2.2. Condensation with a proline-derived diamine

The documented easy formation and cleavage of aminals derived from 1,2-diamines[38] prompted us to try, initially, the proline-derived diamine **9**[39] as a resolving agent for these aldehydes. We heated **9**, which is available in two[40] or four[39] steps from pyroglutamate or proline respectively, with aldehydes **1a** and **1b** in toluene at reflux for 24 h. The NMR spectrum of the crude reaction mixture showed, surprisingly, only a single diastereoisomer (>90:10 diastereoselectivity) of the imidazolines **10a** and **10b**, and purification by chromatography on neutral alumina (the

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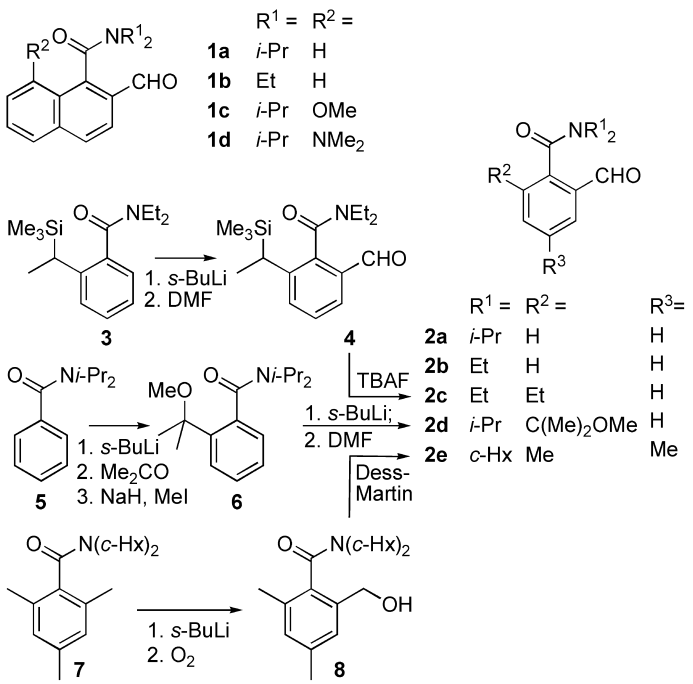
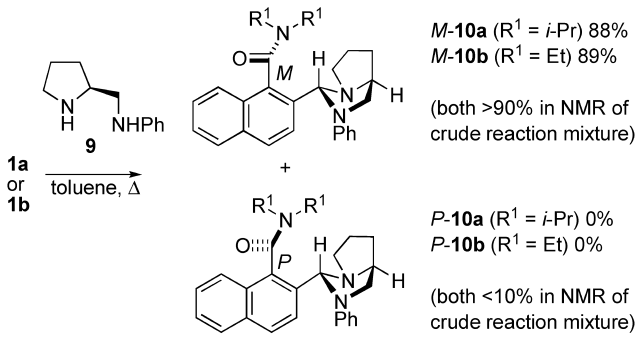


Scheme 1. The starting 2-formylnaphthamides.



Scheme 2. Synthesis of naphthamide-derived imidazolidines.

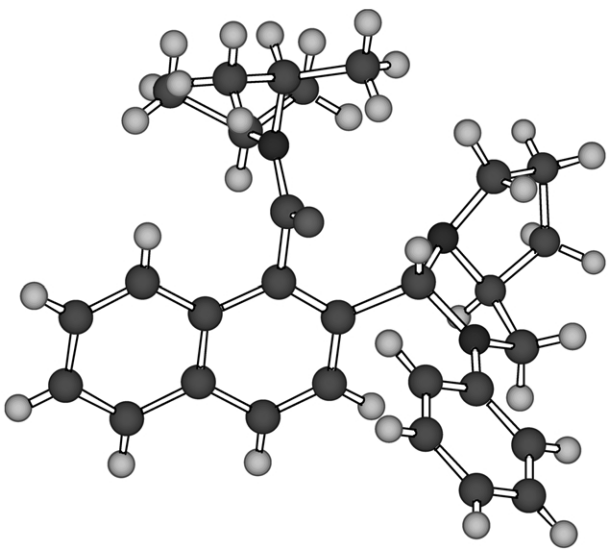
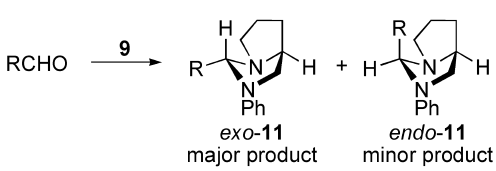


Figure 1. X-ray crystal structure of *M*-**10a**.

imidazolines are somewhat sensitive to chromatography on silica) allowed us to isolate these compounds in 88–89% yield (Scheme 2). X-ray crystallography (Fig. 1) proved the stereochemistry of *M*-**10a**.

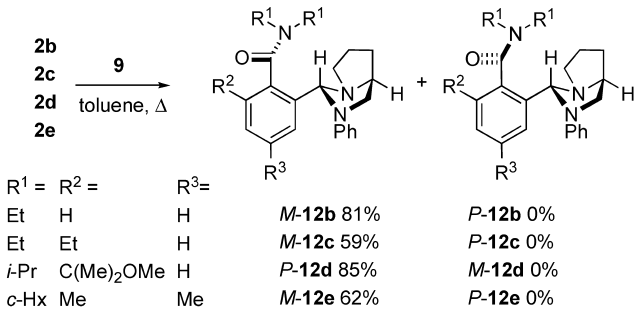
The formation of the imidazolines creates a new stereogenic centre at the aminal carbon, but based on previous results published by Mukaiyama[41] we expected this aspect of the reaction to be highly stereoselective: aldehydes RCHO tend to form imidazolidines *exo*-**11** rather than *endo*-**11**, which places R on the *endo* face of the bicyclic system (Scheme 3). However, the aldehydes **2** are chiral racemic compounds, so our initial expectation was that we would see the formation of *M*- and *P*-**10** in approximately equal quantities. The formation of a single isomer of **10a** and **10b** must indicate that rotation about the Ar–CO axis takes place under the conditions of the reaction, either before the formation of the imidazolidines, or both before and after their formation. In common with other atropisomers in which bond rotation is blocked by a trigonal carbon substituent,[42–44] the barrier to racemisation of aldehydes **1** and **2** is expected to be low relative to those bearing, say, a methyl group in the place of the formyl substituent: **1a** has a half-life of racemisation of only ca. 12 min at 20 °C,[43] which extrapolates to ca. 0.1 s at 110 °C, the temperature of the condensation. Naphthamides bearing branched substituents with a steric demand similar to the imidazolines of **10** have barriers to Ar–CO rotation of the order of 110 kJ mol^{-1},[43] which would suggest



Scheme 3. Typical stereoselectivity in the formation of proline-derived imidazolidines.

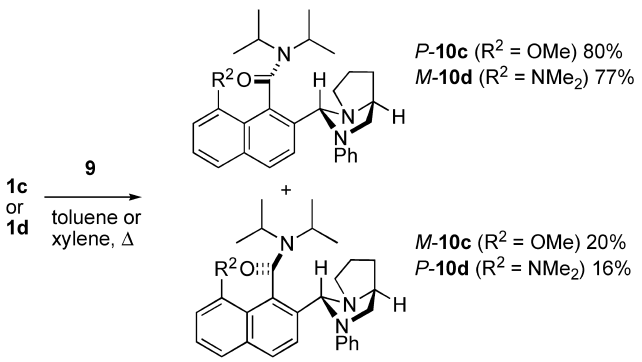
epimerisation of **10** should take place over a period of only minutes at 110 °C, easily within the timescale of the reaction. We shall return to the likely mechanism of the stereoselectivity later.

The same diamine **9** was condensed with 2-formyl benzamides **2b-e** and the reactions were similarly diastereoselective: ^{1}H NMR analysis of the crude reaction mixture indicated that the products were formed with at least >95% stereochemical purity (Scheme 4). Chromatography on alumina yielded pure imidazolines **12b-e** in good yield.



Scheme 4. Synthesis of benzamide-derived imidazolidines.

However, as previously reported,[18,45] diastereoselectivity in the condensation of the *peri*-substituted naphthamides **1c** and **1d** was rather poorer, with 20–25% of a minor epimer being evident in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 5).



Scheme 5. Lower selectivity in more hindered *peri*-substituted naphthamides.

2.3. Condensation with chiral amino alcohols

Although condensation with the diamine **9** is a simple and versatile way of introducing chirality into the atropisomeric amides, **9** is rather expensive commercially and its synthesis, though not difficult, poses some practical problems on scale-up.[46] Moreover, we found that the imidazolidines were unstable to further lithiation reactions: attempted ortholithiation[33] of **12b** or lateral lithiation[47] of **12c** gave complex mixtures of products. We, therefore, sought a more readily available 'resolving agent', especially one which would be stable to lithiation conditions.

We chose readily available aminoalcohols (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine as likely candidates. Both are known to condense with aldehydes to yield stable imidazolidines **15** with good, though not perfect, stereocontrol at the new stereogenic centre (Scheme 6).[48–51] Condensation of **1a** with ephedrine and with pseudoephedrine, and **1b** with ephedrine, gave essentially single diastereoisomers of the product imidazolines **16** and **17**, which were isolated after chromatography on silica (the oxazolidines are more stable to silica than the imidazolines) in good yield (Scheme 7). The stereochemistry of **16a** was proved by an X-ray crystal structure (Fig. 2), and is consistent with the expected 'all-*syn*' stereochemistry[51,50] which allows the four oxazolidine substituents in **16** to lie pseudoequatorial on the new five-membered ring.

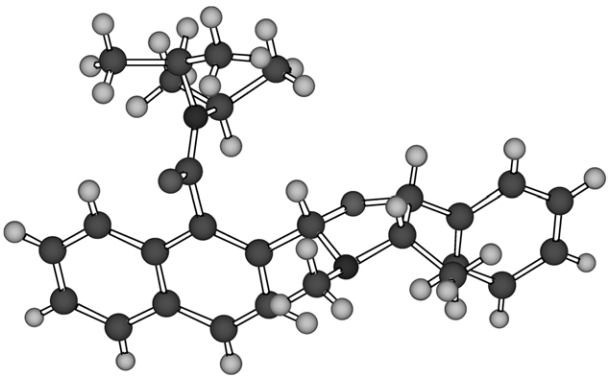
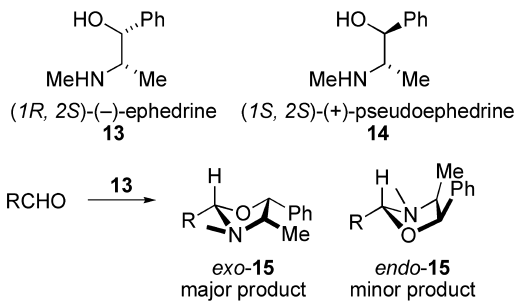
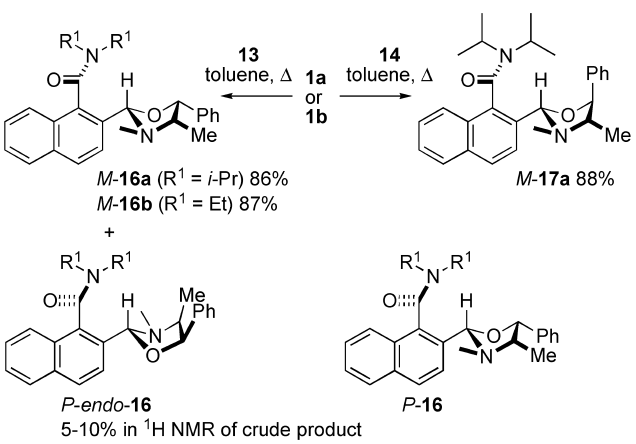


Figure 2. X-ray crystal structure of *M*-**16a**.

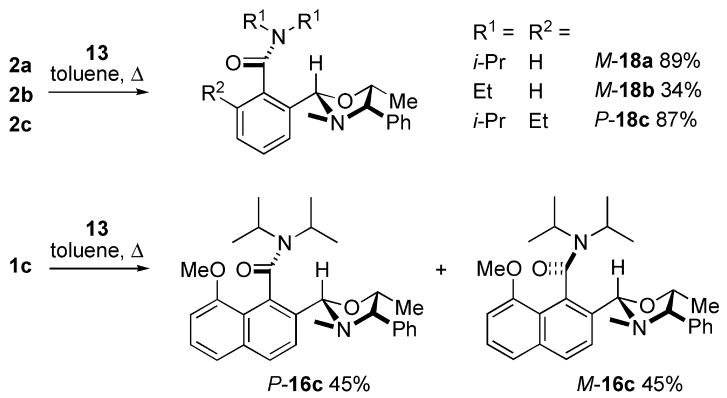
The ^{1}H NMR spectra of the crude products **16** showed consistently 5–10% of a minor diastereoisomer, unlike those of the crude products **10** which were essentially free of diastereoisomeric impurities. Although we were unable to isolate and fully characterise this diastereoisomer, it had a distinctive pattern of signals in the region of 5–6 ppm



Scheme 6. Oxazolidines from ephedrine.



Scheme 7. Synthesis of naphthamide-derived oxazolidines.



Scheme 8. Oxazolidines from benzamides and a *peri*-substituted naphthamide.

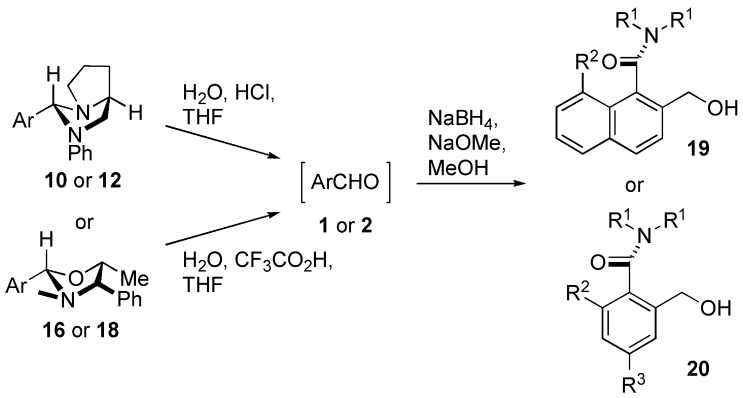
which we have found in other work[52] to be characteristic of ephedrine-derived oxazolidines with *endo* relative stereochemistry (Scheme 6). Indeed, condensations of aldehydes with ephedrine typically give varying amounts of the *endo* product, according to solvent and conditions,[51,50] and for this reason we assume this minor diastereoisomer is *P*-*endo*-**16** rather than the alternative *P*-**16**, of which we saw no sign (<5% by NMR). Nonetheless, it was a straightforward matter to remove this minor impurity during purification.

Condensation of the aldehydes **2a**-**2c** with (−)-ephedrine was similarly diastereoselective, with the oxazolidines **18a**-**18c** being formed with high diastereoselectivity, even if instability towards hydrolysis led to a low yield after purification in one case (Scheme 8). As with the diamine **9**, condensation of a hindered *peri*-substituted naphthamide with (−)-ephedrine gave much poorer selectivities, and **1c** gave a 1:1 mixture of the two diastereoisomers of **16c** in 90% yield.[45]

2.4. Completion of the resolution: hydrolysis of the imidazolidines and oxazolidines

Hydrolysis of the imidazolidines and oxazolidines back to the aldehydes **1** and **2** should complete a method for the dynamic resolution of **1** and **2**. However, as noted before, atropisomeric 2-formyl amides have low barriers to racemisation relative to structurally similar amides bearing tetrahedral 2-substituents.[43,53] The products of hydrolysis are, therefore, likely to racemise too fast for it to be possible to isolate them in enantiomerically enriched form. We, therefore, sought conditions which would allow us to remove the resolving agent (the diamine or aminoalcohol), preferably by hydrolysis at low temperature, and then rapidly reduce the formyl group to a methyl or hydroxymethyl substituent.

After a series of trial hydrolyses, we found that the imidazolidine **10a** was completely hydrolysed by 1 M aqueous HCl in THF at 0 °C over a period of 30 min.



Scheme 9. Deprotection and recovery of enantiomerically enriched amides.

Table 1. Completion of the resolution

Entry	S.M.	Conditions	Product	Yield	ee	Overall yield from **1** or **2**[a]
1	**10a**	1 M HCl	(−)-**19a**	94	89	83
2	**10b**	1 M HCl	(−)-**19b**	84	97	75
3	**12d**	1 M HCl	(−)-**20d**	90	77	77
4	**12e**	1 M HCl	(−)-**20e**=(−)-**8**	93	53	58
5	**16a**	CF_3CO_2H	(−)-**19a**	85	74	73
6	**16b**	CF_3CO_2H	(−)-**19b**	85	74	74

[a] Representing the efficiency of the resolution.

Hydrolysis of the ephedrine-derived oxazolidines was much slower, and remaining starting material was evident even after treatment with 6 M HCl in THF at 0 °C for 30 min. However, stirring with a excess of trifluoroacetic acid in wet THF at 0 °C for 30 min promoted complete hydrolysis of the oxazolidine to the aldehyde.

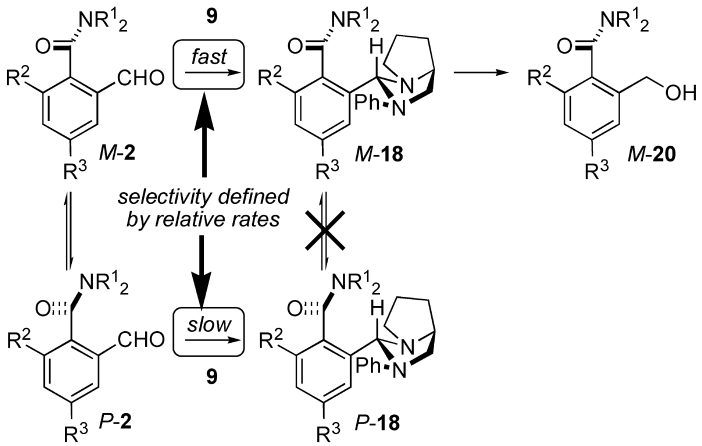
Reduction of the aldehyde to the alcohol was achieved by adding a large excess of sodium borohydride to the acidic solution containing the crude aldehydes. Because of the low pH, the borohydride rapidly decomposed somewhat exothermically under these conditions, and for reduction of the imidazolidine-derived aldehydes we added the sodium borohydride as a cold slurry in a solution of sodium methoxide in ethanol. A later improvement, which was used for reduction of the oxazolidine-derived aldehydes, was to add first an excess of methoxide to neutralise the trifluoroacetic acid and then to add the borohydride. Scheme 9 and Table 1 detail the application of these conditions for hydrolysis and reduction to the imidazolidines **10** and **12** and oxazolidines **16**. For determination of ee, where necessary, racemic alcohols **19** and **20** were also made by sodium borohydride reduction of the racemic aldehydes **1** and **2**.

In many cases, excellent enantiomeric excesses were observed in the atropisomeric hydroxymethyl amide products, and overall yields for the condensation–hydrolysis–reduction sequence which results in resolution of racemic aldehyde to enantiomerically pure alcohol were in most cases well over 50% (final column), demonstrating the very practical nature of this dynamic resolution process. In general, the ees obtained from the oxazolidines were lower, reflecting the harsher conditions necessary to force the hydrolysis to completion, and the imidazolidine method is to be preferred as a method for dynamic resolution.

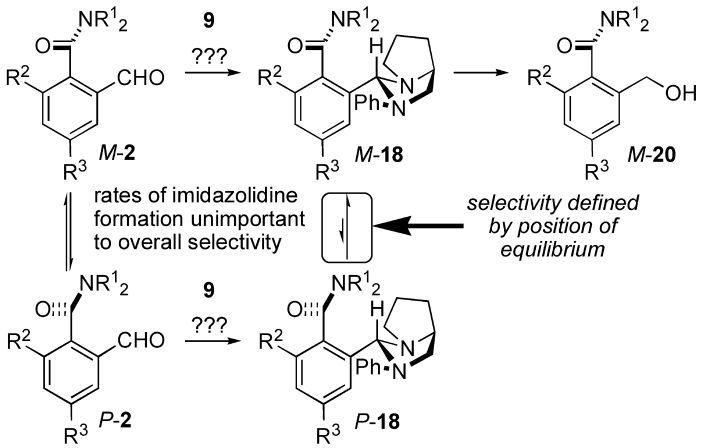
2.5. Mechanism of the resolution and origin of the stereoselectivity

When we set out to resolve racemic, atropisomeric aldehydes **1** and **2c-e**, we expected to obtain a 1:1 diastereoisomeric mixture of the imidazolidines **10** and **12** and the oxazolidines **16-18**. Formation of anything other than a 1:1 mixture of atropisomers of **10** and **12** can be explained only by dynamic resolution, involving Ar–CO bond rotation. As explained earlier, the conditions of the condensation reaction are such that for most of the aldehyde starting materials Ar–CO rotation is likely to be rapid prior to condensation and still possible over a period of minutes even after condensation.

Two distinct dynamic resolution mechanisms are possible, both of which may be operative at least to some extent. One



Scheme 10. Dynamic kinetic resolution of **2**.



Scheme 11. Dynamic Thermodynamic resolution of **2**.

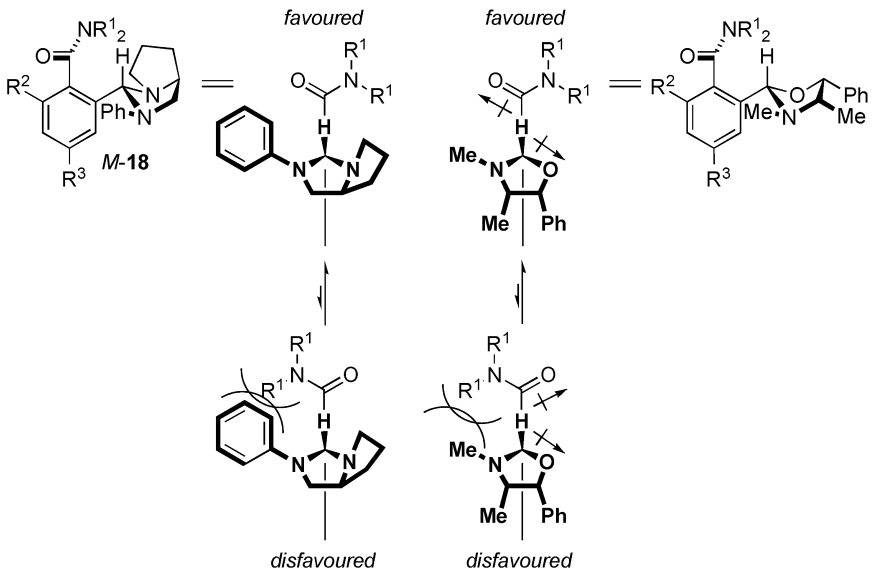
amounts to a dynamic resolution under kinetic control;[54–57] the other a dynamic resolution under thermodynamic control.[29] In the first, equilibration between stereoisomers by rotation about the Ar–CO bond occurs before formation of the imidazoline or oxazolidine; one enantiomer of the aldehyde reacts with the aldehyde faster than the other, and an excess of one product stereoisomer is formed (Scheme 10). In the second, stereochemistry is defined by equilibration after the formation of the imidazolines: whatever the initial ratio of products, the final product ratio is defined by their relative stability and not by their relative rate of formation (Scheme 11). We were unable to prove conclusively which mechanism operates, but we have strong evidence that the stereoselectivity of the reactions both with the diamine **9** and with ephedrine **13** is under thermodynamic control, that is, Scheme 11 best represents the mechanism of the resolution.

First, we repeated the condensation of **1a** with **9**, but allowed it to take place in an NMR tube in C_6D_6. NMR showed that as starting material disappeared at 20 °C, two products in a proportion of 3:1 were seen to increase in concentration. The minor product was the imidazolidine *M*-**10a** which we had previously isolated; the major product, however, appeared to be an epimer of **10a**, probably *P*-**10a**, although a structure related to *endo*-**11** cannot be ruled out. Attempts to characterise this epimer fully failed, though HPLC allowed us to obtain a small quantity which converted to *M*-**10a** on standing at ambient temperature for 20 min. Since *M*-**10a** is clearly not the kinetic product of the condensation, the stereoselectivity of the reaction must be due to control by an alternative, presumably thermodynamically controlled, mechanism. If the major epimer formed under kinetic control is indeed *P*-**10a** then interestingly a dynamic kinetic resolution appears to be operating inconsequentially in the opposite direction from the overall dynamic resolution.

Supporting evidence that a dynamic kinetic resolution is not the origin of the stereoselective formation of **10**, **12**, **16** or **18** is provided by two further observations. First, in the condensation of **1c** or **1d** with **9** or **13** (Schemes 5 and 8) to yield **10c**, **10d** and **16c**, a dynamic thermodynamic resolution is prevented by very high barriers to Ar–CO rotation in the *peri*-substituted products, though dynamic kinetic resolution should still be possible because of the lower barriers to Ar–CO rotation in the aldehydes **10c** and **10d**.[43,58] Yet selectivity is poor, suggesting that interconversion of the imidazolidine or oxazolidine products is necessary for good stereoselectivity.

Second, the imidazolidine **12a**, and the oxazolidines **18a** and **18b**, in which the Ar–CO bond is free to rotate (a typical tertiary amide bearing a single branched 2-substituent shows a half-life for Ar–CO rotation of the order of 0.01 s at 20 °C[43,35]) all exist as single conformers (>95:5 by NMR: Ar–CO rotation in such amides is slow on the NMR timescale). Evidently structures **12** and **18** display a thermodynamic preference for the stereochemistry of *M*-**18** (Scheme 11) when equilibration of the products is possible, a preference which is likely to persist in related structures **10**, **12**, **16** and **18**.

We therefore propose that the selectivity of all the condensation reactions arises because whatever the initial ratio of atropisomers formed in the condensation, interconversion of the products in refluxing toluene allows them to equilibrate to a ratio which is almost entirely the stereoisomer shown as, or analogous to, *M*-**18** in Scheme 11. Our proposed rationale for the favourability of this isomer, both for the imidazolidines and the oxazolidines, is illustrated in Scheme 12. In both series, we presume the benzylic stereogenic centre must arrange itself such that its smallest substituent, the C–H bond, more or less eclipses the amide group. For the imidazolidines, the favoured isomer allows the bulky *N*,*N*-dialkyl group of the amide to lie *anti* to the *N*-phenyl substituent. For the oxazolidines, the *N*,*N*-dialkyl group must choose between lying *syn* to N–Me or to smaller O, and presumably favours the latter, Moreover, an electronic factor presumably also favours the alignment of the amide C=O dipole and the oxazolidine C–O dipole *anti* to one another.



Scheme 12. Conformational preference in amidoimidazolidines and amidooxazolidines.

3. Conclusion

Condensation of 2-formyl benzamides and naphthamides with the proline-derived diamine **9** or with (−)-ephedrine **13** yields single atropisomers of imidazolidine or oxazolidine products by a process of dynamic thermodynamic resolution. Enantiomerically enriched products may be obtained by subsequent deprotection of these compounds by hydrolysis in aqueous acid, though for isolation of products in good ee it is necessary to 'fix' the stereochemistry of the aldehydes by immediate reduction to the corresponding alcohols.

Dynamic thermodynamic resolution protocols seem particularly well-suited for the synthesis of enantiomerically enriched atropisomers, in which epimerisation may be the result merely of thermally induced bond rotation. More recent developments of this work,[59] to be reported shortly in full, have employed sulfinyl substituents as versatile alternatives to the imidazolidinyl or oxazolidinyl groups described here.

4. Experimental

4.1. General

Aldehydes **1a**,[43] **1b**,[30] **2a**[60] and **2b**[61] were made by published methods.

X-ray crystal structures of *M*-**10a** and *M*-**16a** have been deposited with the Cambridge Crystallographic Database, Deposition numbers: *M*-**10a**: 228413; *M*-**16a**: 166016.

All commercially available solvents are distilled before use. Tetrahydrofuran (THF) was dried over sodium and distilled under dry nitrogen using benzophenone as an indicator. Dichloromethane was distilled from calcium hydride under an atmosphere of nitrogen. Toluene was distilled using a Dean–Stark apparatus and stored over 4 Å molecular sieves. 'Petrol' refers to petroleum ether (bp 40–60 °C); 'ether' refers to diethyl ether.

Thin layer chromatography (TLC) was performed using commercially available Macherey-Nagel 0.25 mm silica gel pre-coated aluminum sheets with fluorescent indicator UV_{254}. In the cases of the imidazolidines, TLC was performed on Merck neutral aluminum oxide pre-coated aluminum sheets. Flash chromatography refers to chromatography carried out on Merck silica gel 60H (40–63 m, 230–300 mesh) stationary phase by the method of Still, Kahn and Mitra.[62]

Analytical HPLC was carried out on a Chiralpak AD, 25 cm×4.6 mm ID or (*R*,*R*) Whelk-01, 25 cm×4.6 mm ID column at room temperature using a Merck Hitachi L-6200 Intelligent pump, typically eluting with 10% ethanol in hexane, flow rate 1 mL/min, 10 μL injection. Detection was carried out using a Merck L-300 Photo Diode Array System at UV absorbance at 280 nm.

^{1}H NMR spectra were recorded on a Varian XL 300 spectrometer at 300 MHz, a Bruker XC300 (300 MHz) or a Varian Unity 500 (500 MHz); ^{13}C NMR spectra were recorded on a Bruker XC300 (75 MHz) or a Varian Unity 500 (125 MHz). Chemical shifts are quoted in part per million downfield from tetramethylsilane. Coupling constants *J* are given in Hertz (Hz).

Infrared spectra were recorded on an ATI Genesis Series FTIR and only structurally significant peaks are listed. Mass spectra were recorded on a Fisons VG Trio 2000 (EI/CI and FAB) or a Concept IS (HRMS) Spectrometer.

Micronanalyses were performed using a Carlo-Erba combustion analyzer on C, H or N. Melting points are uncorrected and were carried out on a Gallenkamp melting point apparatus. Optical rotations were performed using an AA-100 polarimeter and are quoted in units of $^\circ\,g^{-1}\,mol\,dm^{-1}$.

4.1.1. *N*,*N*-Diethyl-2-formyl-6-(1-trimethylsilylethyl)-benzamide 4. *N*,*N*-Diethyl-2-(1-trimethylsilyl)ethylbenzamide **3**[35] (831 mg, 3.0 mmol) in THF (10 mL) was added dropwise to a stirred solution of *sec*-butyllithium (6 mL of a 1.5 M solution in cyclohexane, 3.0 equiv.) and TMEDA (1.35 mL, 9.0 mmol, 3.0 equiv.) in dry THF (40 mL) at −78 °C under an atmosphere of nitrogen. After 60 min, DMF (0.93 mL, 12.0 mmol, 4.0 equiv.) was added. The mixture was warmed to ambient temperature (colour change from dark yellow/orange to colourless) and stirred overnight. Water was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (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 aldehyde **4** (871 mg, 95%) as a rapidly interconverting mixture of diastereoisomeric atropisomers/conformers, which were used without further purification. δ_H (300 MHz; $CDCl_3$) (Peaks for major atropisomer/conformer) 9.99 (1H, s, C*H*O), 7.70 (1H, dd, *J*=6, 3 Hz, Ar*H*), 7.48–7.41 (3H, m, Ar*H*), 3.71 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.54 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.08 (2H, m, NCH_2), 2.15 (1H, m, C*H*SiMe$_3$), 1.38 (3H, t, *J*=8 Hz, NCH$_2$CH_3), 1.31 (3H, t, *J*=7 Hz, NCH$_2$CH_3), 0.99 (3H, t, *J*=7 Hz, CH$_2$CH_3), 0.0 [12H, s, Si(CH$_3$)$_3$]; δ_C (75 MHz, $CDCl_3$) (Peaks for major atropisomer/conformer) 191.0 (C=O), 167.7 (C=O), 144.1, 137.6, 132.3, 128.4, 126.5, 125.5 (aromatics), 42.5 (NCH$_2$), 38.7 (NCH$_2$), 25.2 (*C*H$_2$CH$_3$), 16.2, 13.7 (NCH$_2$CH_3), 12.4 (CH$_2$CH_3), 3.0 (Si*Me*$_3$).

4.1.2. *N*,*N*-2-Triethyl-6-formylbenzamide 2c. *tetra-n*-Butylammonium fluoride (4.0 equiv. of a 1 M solution in THF) was added to a stirred solution of benzamide **4** (871.8 mg, 2.85 mmol) in THF (20 mL). The crude mixture was filtered though a pad of Celite® which was washed with THF (20 mL). The solvent was evaporated to give a crude product which was purified by chromatography eluting with petrol/EtOAc (5:1) to afford benzamide **2c** (168.2 mg, 24%) as an oil. δ_H (300 MHz; $CDCl_3$) 10.05 (1H, s, C*H*O), 7.82 (1H, dd, *J*=7, 1 Hz, Ar*H*), 7.59 (1H, dd, *J*=7, 1 Hz, Ar*H*), 7.52 (1H, t, *J*=8 Hz, Ar*H*), 3.76 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.64 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.12 (2H, t, *J*=7 Hz, NCH_2), 2.68 (2H, m, CH_2CH$_3$), 1.37 (3H, t, *J*=7 Hz, NCH$_2$CH_3), 1.31 (3H, t, *J*=8 Hz, CH$_2$CH_3), 1.04 (3H, t, *J*=7 Hz, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 190.09 (C=O),

167.9 (C=O), 141.0, 138.4, 132.2, 134.3, 128.8, 127.4 (aromatics), 42.7 (NCH_2), 38.6 (NCH_2), 25.2 (CH_2CH_3), 14.8, 13.5 (NCH_2CH_3), 12.4 (CH_2CH_3); ν_{max}(thin film)/cm^{-1} 1690 (aldehyde C=O), 1628 (amide C=O); *m/z* (CI) 234 (100%, $M+H^+$); *m/z* (EI) 234 (10.3%, $M+H^+$), 204 (100%, $M-CH_2CH_3$), 161 (73%, $M+H^+-CHO$ and NCH_2CH_3). (Found: $M+H^+$ 234.1487; $C_{14}H_{19}NO_2$ requires $M+H^+$ 234.1495).

4.1.3. *N*,*N*-Diisopropyl-2-(1-methoxy-1-methylethyl)-benzamide 6. *sec*-Butyllithium (13.6 mL of a 1.4 M solution in cyclohexane, 19 mmol, 1.3 equiv.) was added dropwise to a stirred solution of *N*,*N*-diisopropylbenzamide **5**[32] (3.0 mg, 14.6 mmol) in dry THF (40 mL) at −78 °C under an atmosphere of nitrogen. After 60 min at −78 °C, dry, distilled acetone (1.88 mL, 30 mmol, 2.0 equiv.) in THF (10 mL) was added dropwise to the reaction mixture. The mixture was warmed to ambient temperature (colour change from dark cloudy brown to clear) and water was added. Most of the THF was removed by evaporation under reduced pressure and the aqueous residue was extracted with diethyl ether (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 an oil, which was purified by flash chromatography, eluting with petrol/EtOAc (85:15, R_f 0.17) to yield the adduct (1.56 g, 40.6%) as a white crystalline solid, mp 82.3–83.1 °C; δ_H (300 MHz; $CDCl_3$), 7.40–7.29 (2H, m, Ar*H*), 7.25 (1H, td, *J*=7, 2 Hz, Ar*H*), 7.15 (1H, d, *J*=7 Hz, Ar*H*), 3.87–3.84 (1H, broad s, O*H*), 3.76 (1H, septet, *J*=7 Hz, NC*H*), 3.53 (1H, septet, *J*=7 Hz, NC*H*), 1.69 (3H, s, C(OH)CH_3CH$_3$), 1.6 (3H, d, *J*=7 Hz, NCHCH_3), 1.59 (3H, s, C(OH)CH$_3$CH_3), 1.57 (3H, d, *J*=7 Hz, NCHC*H*), 1.2 (6H, d, *J*=7 Hz, NCHCH_3CH_3); δ_C (75 MHz, $CDCl_3$), 174.2 (C=O), 145.9, 135.1, 128.3, 126.9, 126.2 (aromatics), 73.3 (*C*OH), 32.5, 31.0 (C*C*H$_3$), 20.3, 20.1, 19.7 (NCHCH$_3$CH$_3$); ν_{max}(thin film)/cm^{-1} 2886, 1609 (C=O); *m/z* (CI) 264 (100%, $M+H^+$), 246 (53.8%, $M+H^+-OH$); *m/z* (EI) 264 (100%, $M+H^+$), 246 (16.6%, $M+H^+-OH$). Found: *M* 263.1888; $C_{16}H_{25}NO_2$ requires *M* 263.1885. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found C, 73.07, H, 9.38, N, 5.22.

This alcohol (500 mg, 1.9 mmol) was dissolved in dimethylformamide (15 mL). Sodium hydride (0.17 g of a 60% suspension in mineral oil) was added at 0 °C. After 95 min, methyl iodide was added (0.5 mL, excess). The mixture was allowed to room temperature and stirred overnight. Water was added, and the mixture was extracted with ether (2×30 mL). The organic extracts were washed with brine (3×50 mL), dried ($MgSO_4$), filtered and concentrated to yield an oil which was purified by flash chromatography, eluting with 7:1 petrol/EtOAc) to afford the amide **6** (357.5 mg, 68%) as a white crystalline solid, mp 84.7–85.9 °C. δ_H (300 MHz; $CDCl_3$) 7.48 (1H, d, *J*=8 Hz, Ar*H*), 7.31 (1H, t, *J*=7 Hz, Ar*H*), 7.23 (1H, t, *J*=7 Hz, Ar*H*), 7.06 (1H, d, *J*=7 Hz, Ar*H*), 3.69 (1H, septet, *J*=7 Hz, NC*H*), 3.47 (1H, septet, *J*=7 Hz, NC*H*), 3.23 (3H, s, OCH_3), 1.55–1.42 (12H, m, NCHCH_3CH_3 and COCH$_3$(CH_3)$_2$), 1.14 (3H, d, *J*=7 Hz, NCHCH$_3$CH_3), 1.09 (3H, d, *J*=7 Hz, NCHCH_3CH$_3$); δ_C (75 MHz, $CDCl_3$), 171.9 (C=O), 143.8, 136.7, 127.8, 126.6, 126.4 (aromatics), 77.6 (*C*OCH$_3$), 51.0 (N*C*H), 49.6 (O*C*H$_3$), 45.2 (N*C*H), 27.4, 26.4 (C*C*H$_3$*C*H$_3$), 20.3, 20.3, 20.1, 19.7 (NCH*C*H$_3$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 2970, 2929, 1631 (C=O); *m/z* (CI) 278 (100%, $M+H^+$), 246 (55%, $M-OCH_3$); *m/z* (EI) 278 (4%, $M+H^+$), 145 (100% $M-OCH_3$, NCH(CH$_3$)$_2$CH(CH$_3$)$_2$). Found: *M* 277.2044; $C_{17}H_{27}NO_2$ requires *M* 277.2042.

4.1.4. *N*,*N*-Diisopropyl-2-formyl-6-(1-methoxy-1-methylethyl)benzamide 2d. By the method for the lithiation of **3** in the preparation of **4**, amide **6** (500 mg, 1.80 mmol) was treated with *sec*-BuLi and quenched with DMF (2 equiv.). The crude product was purified by flash chromatography, eluting with petrol/EtOAc (85:15, R_f=0.17) to yield aldehyde **2d** (165 mg, 30%) as a white crystalline solid, mp 88.3–91.7 °C. δ_H (300 MHz; $CDCl_3$) 10.1 (1H, s, CHO), 7.8 (1H, d, *J*=8 Hz, ArH), 7.59 (1H, d, *J*=8 Hz, ArH), 7.34 (1H, t, *J*=8 Hz, ArH), 3.56–3.3 (2H, m, NCH), 3.18 (3H, s, OCH$_3$), 1.55–1.48 (12H, m, NCHCH_3CH_3 and COCH$_3$(CH_3)$_2$), 1.07 (3H, d, *J*=7 Hz, NCHCH$_3$CH_3), 0.88 (3H, d, *J*=7 Hz, NCHCH_3CH$_3$); δ_C (75 MHz, $CDCl_3$), 191.7 (C=O), 145.0, 138.9, 132.9, 132.8, 128.0, 126.1 (aromatics), 78.0 (*C*OCH$_3$), 51.0 (NCH), 49.3 (OCH$_3$), 46.2 (NCH), 27.3, 26.3 (CCH$_3$), 20.4, 20.1, 20.0, 19.5 (NCH*Me*$_2$); ν_{max}(thin film)/cm^{-1} 1690 (aldehyde C=O), 1628 (amide C=O);; *m/z* (CI) 306 (100%, $M+H^+$); *m/z* (EI) 306 (100%, $M+H^+$). Found: $M+H^+$ 306.2065; $C_{18}H_{27}NO_3$ requires $M+H^+$ 306.2071. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.61, H, 9.03, N, 4.16.

4.1.5. *N*,*N*-Dicyclohexyl-2-hydroxymethyl-4,6-dimethyl-benzamide 8. *sec*-Butylithium (1.4 mL of a 1.4 M solution in cyclohexane, 2 mmol) was added to a stirred solution of *N*,*N*-dicyclohexyl-2,4,6-trimethylbenzamide **7**[17] (500 mg, 1.53 mmol) in THF under argon at −78 °C. The resulting orange solution was stirred for 60 min. Oxygen was bubbled though the reaction solution for 20 min, when the mixture became colourless. (TLC, 1:1 petrol/EtOAc: starting material R_f 0.58, product alcohol R_f 0.39; traces of aldehyde also present at R_f 0.52). Water was added and the mixture was extracted with ether (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried ($MgSO_4$) and concentrated to an oil which was purified by flash chromatography, eluting with petrol/EtOAc (4:1) to yield the alcohol **8** (330.1 mg, 63%) as a white crystalline solid, mp 142.7–144.6 °C. δ_H (300 MHz; $CDCl_3$) 7.06 (1H, s), 6.90 (1H, s), 4.54 (1H, d, *J*=13 Hz, CH_AH_BOH), 4.29 (1H, d, *J*=13 Hz, CH_AH_BOH). 3.97–3.71 (1H, broad s, O*H*), 3.21–2.99 (2H, m, NC*H*), 2.98–2.56 (2H, m, cyclohexyl-*H*), 2.95 (3H, s, CCH_3), 2.22 (3H, s, CCH_3), 1.96–0.72 (20H, m, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 170.9 (C=O), 137.6, 136.9, 134.0, 132.6, 129.7, 126.8 (aromatics), 62.8 (*C*N), 60.0 (*C*H$_2$OH), 56.1 (*C*N), 31.3, 31.2, 29.7, 29.7, 26.5, 25.5, 25.5, 25.2, 25.0 (cyclohexyl carbons), 21.0, 18.7 (C*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3339 (OH), 1609 (CO).

4.1.6. *N*,*N*-Dicyclohexyl-2-formyl-4,6-dimethylbenzamide 2e. A solution of *N*,*N*-dicyclohexyl-2-hydroxymethyl-4,6-dimethylbenzamide **8** (476.7 mg) in CH_2Cl_2 (20 mL) was added to a stirred solution of the Dess Martin reagent[36,37] (707.9 mg, 1.2 equiv.) in CH_2Cl_2 (20 mL). After 30 min, the mixture was diluted with ether (50 mL), and 1.3 M NaOH (100 mL) was added. After stirring for 20 min, the aqueous mixture was extracted with ether

(2×20 mL), and the extracts washed with 1.3 M HCl (2×20 mL), brine (2×30 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave an oil which was purified by flash chromatography, eluting with petrol/EtOAc (9:1) to yield the aldehyde **2e** (291.9 mg, 62%) as a white crystalline solid, mp 149.9–151.2 °C; R_f=0.52 (1:1 petrol/EtOAc); δ_H (300 MHz; $CDCl_3$) 9.95 (1H, s, CHO), 7.48 (1H, s, C*H*CCH$_3$), 7.19 (1H, s, C*H*CCH$_3$), 3.08–2.88 (2H, m, NCH), 2.31 (3H, s, CH$_3$), 2.24 (3H, s, CH$_3$), 1.83–1.74 (2H, m, CH$_2$), 1.68–1.53 (8H, m, CH$_2$), 1.50–1.07 (10H, m, CH$_2$); δ_C (75 MHz, $CDCl_3$) 191.0 (*C*HO), 168.1 (C=O), 138.4, 137.9, 136.9, 134.4, 131.9, 126.5 (aromatics), 60.1 and 56.4 (N*C*H), 31.4, 30.9, 29.8, 29.6, 26.5, 25.6, 25.5, 25.2, 24.9 (cyclohexyl), 20.9 and 19.3 (*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1696 (CHO), 1625 (CO); *m/z* (CI) 342 (100%, *M*+H$^+$); *m/z* (EI) 342 (3%, *M*+H$^+$−CH(CH$_3$)$_2$ CH(CH$_3$)$_2$). Found: *M* 341.2359; $C_{22}H_{31}NO_2$ requires *M* 341.2355. Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15, N, 4.10. Found C, 77.78, H, 9.15, N, 4.08.

4.1.7. (*M*,2′*R*,4′*S*)-*N*,*N*-Diisopropyl-2-[-2-phenylperhydropyrrolo-(1,2*c*)-imidazol-3-yl]-1-naphthamide 10a. Aldehyde **1a** (250 mg, 0.882 mmol) and (*S*)-2-(anilinomethyl)-pyrrolidine **9** (155.1 mg, 0.885 mmol) were heated at reflux in dry toluene (25 mL) for 16 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on alumina eluting with petrol/EtOAc (10:1) to afford the imidazolidine **10a** (282.4 mg 88%) as a pale yellow solid, mp 210.6–212.1 °C; $[\alpha]_D^{22}$=+0.84 (*c*=0.100, ethanol); R_f=0.75 (petrol/EtOAc 10:1); δ_H (300 MHz, $CDCl_3$) 7.85 (1H, dd, *J*=8, 1 Hz, Ar*H*), 7.69 (1H, dd, *J*=7, 3 Hz, Ar*H*), 7.59 (1H, d, *J*=9 Hz, Ar*H*), 7.43–7.33 (2H, m, Ar*H*), 7.18 (2H, d, *J*=9 Hz, Ar*H*), 7.05 (2H, t, *J*=7 Hz, Ar*H*), 6.56–5.45 (3H, m, Ar*H*), 5.88 (1H, s, C*H*N), 3.92 (1H, q, *J*=7 Hz, NC*H*CH$_2$), 3.70 (1H, t, *J*=8 Hz, PhNC*H*), 3.57 (1H, septet, *J*=7 Hz, NC*H*CH$_3$), 3.45 (1H, septet, *J*=7 Hz, NC*H*CH$_3$), 3.27–3.19 (2H, m, NC*H*HCH$_2$CH$_2$ and PhNCH*H*CHN), 2.65 (1H, m, NCH*H*CH$_2$CH$_2$), 2.02–1.81 (4H, m, PhNCH$_2$CHC*H*$_2$C*H*$_2$), 1.76 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.65 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.09 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.91 (3H, d, *J*=7 Hz, NCHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.5 (CO), 145.8, 138.0, 134.5, 134.5, 132.6, 129.7, 129.1, 127.9, 127.9, 126.0, 125.9, 125.2, 124.0 115.9, 112.0 (aromatics), 79.6 (*C*HN), 60.9 (PhNCH$_2$*C*H), 53.4 (PhN*C*H$_2$), 52.5 (N*C*H$_2$CH$_2$), 51.3 (N*C*H), 46.2 (N*C*H), 27.9 (*C*H$_2$), 23.5 (*C*H$_2$), 21.1 (*C*H$_3$), 20.5 (*C*H$_3$), 20.3 (*C*H$_3$), 19.98 (*C*H$_3$); ν_{max} (thin film)/cm^{-1} 2940, 1623 (C=O); *m/z* (CI) 442 (100%, *M*+H$^+$); *m/z* (EI) 442 (12.2%, *M*+H$^+$); 441 (9%, *M*), 356 (100%, *M*+H$^+$−C$_6$H$_{14}$). Found: *M* 441.2771. $C_{29}H_{35}N_3O$ requires *M*, 441.2781. Anal. Calcd for $C_{29}H_{35}N_3O$, C, 78.88, H, 7.59, N, 9.52. Found: C, 78.86, H, 7.86, N, 9.59.

4.1.8. (*M*,2′*R*,4′*S*,)-*N*,*N*-Diethyl-2-(2-phenylperhydropyrrolo-[1,2*c*]imidazol-3-yl)-1-naphthamide 10b. In the same way, aldehyde **1b** (987.1 mg) gave, after purification by flash chromatography on alumina eluting with petrol/EtOAc (11:1, R_f=0.77), the imidazolidine **10b** (1.42 g, 89%) as a yellow solid, mp 97.2–198.7 °C; $[\alpha]_D^{22}$=+107.2 (*c*=0.218, $CHCl_3$); δ_H (300 MHz, $CDCl_3$), 7.76–7.68 (2H, m, ArH), 7.64 (1H, d, *J*=9 Hz, ArH). 7.39 (2H, m, ArH), 7.26 (1H, d, *J*=8 Hz, ArH), 7.07 (2H, t, *J*=7 Hz, ArH), 6.60–6.48 (3H, m, ArH), 5.7 (1H, s, C*H*NN), 3.9 (1H, q, *J*=8 Hz, NC*H*CH$_2$CH$_2$), 3.71 (3H, m, NC*H*$_2$CH$_3$ and NC*H*HCHN), 3.27–3.09 (3H, m, NC*H*$_2$CH$_3$ and NCH*H*CHN), 2.98 (1H, dq, *J*=14, 7 Hz, NC*H*HCH$_2$), 2.72–2.61 (1H, m, NCH*H*CH$_2$), 2.02–1.7 (4H, m, PhNCH$_2$CHC*H*$_2$C*H*$_2$), 1.37 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 0.89 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.5 (CO), 145.8, 138.0, 134.5, 134.5, 132.6, 129.7, 129.1, 127.9, 127.9, 126.0, 125.9, 125.2, 124.0 115.9, 112.0 (aromatics), 80.6 (CNN), 61.0 (PhNCH$_2$*C*H), 53.8 (PhN*C*H$_2$), 52.9 (N*C*H$_2$CH$_2$), 43.5 (N*C*H$_2$CH$_3$), 38.9 (N*C*H$_2$CH$_3$), 29.6 (N*C*HCH$_2$), 28.3 (NCH$_2$*C*H$_2$CH$_2$), 24.0 (NCH$_2$CH$_2$*C*H$_2$), 13.4 (*C*H$_3$) and 13.3 (*C*H$_3$); ν_{max} (thin film)/cm^{-1} 2907, 1632 (C=O); *m/z* (CI)) 414 (100%, *M*+H$^+$), 226 (3.8%, *M*−C$_6$H$_{10}$N$_2$Ph); *m/z* (EI) 84 (100%, *M*+H$^+$−C$_6$H$_{10}$N$_2$Ph and C$_{10}$H$_6$). Found: *M* 413.2460. $C_{27}H_{31}N_3O$ requires *M*, 413.2467. Anal. Calcd for $C_{27}H_{31}N_3O$; C, 78.42, H, 7.56, N, 10.16: Found C, 78.64, H, 7.70, N, 9.90.

4.1.9. (*M*,2′*R*,4′*S*)-*N*,*N*-Diethyl-2-(2-phenylperhydropyrrolo-[1,2*c*]-imidazol-3-yl)benzamide 12b. In the same way, 2-formyl-*N*,*N*-diethyl-1-benzamide **2b** gave, after purification by flash chromatography on alumina eluting with petrol/EtOAc (8:1)+0.1% Et$_3$N, the imidazolidine **12b** (294.2 mg, 81%) as an oil; R_f=0.76 (petrol/EtOAc 8:1); $[\alpha]_D^{21}$=−0.11 (*c*=25., ethanol); δ_H (300 MHz, $CDCl_3$) 7.28–7.16 (6H, m, Ar*H*), 6.70 (1H, t, *J*=7 Hz, ArH), 6.60 (2H, d, *J*=8 Hz, ArH), 6.00 (1H, s, C*H*N), 3.90 (1H, quintet, *J*=7 Hz, PhNCH$_2$C*H*N), 3.70 (1H, q, *J*=8 Hz, PhNC*H*$_2$), 3.65 (1H, t, *J*=8 Hz, NC*H*), 3.6–3.49 (1H, quintet, *J*=7 Hz, NC*H*), 3.35–3.22 (2H, m, PhNC*H*$_2$ and NCH*H*CH$_2$), 2.75–2.63 (2H, m, NC*H*$_2$CH$_2$), 2.09–1.81 (4H, m, PhNCH$_2$ CHC*H*$_2$C*H*$_2$), 2.58 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 2.51 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 1.89–1.66 (4H, m, NCH$_2$C*H*$_2$C*H*$_2$CH), 1.24 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 1.09 (3H, t, *J*=8 Hz, CH$_2$C*H*$_3$), 1.02 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 171.2 (CO), 146.5, 139.0, 137.9, 129.1, 127.9, 126.7, 126.54, 125.55, 115.8, 111.9 (aromatics), 79.3 (*C*HN), 60.7 (PhNCH$_2$*C*H), 52.7 (PhN*C*H$_2$), 52.4 (N*C*H$_2$CH$_2$), 51.0 (N*C*H), 45.5 (N*C*HCH$_2$), 25.4 (*C*H$_2$CH$_3$), 23.9 (NCH$_2$CH$_2$*C*H$_2$), 14.7 (NCH$_2$*C*H$_3$), 13.1 (NCH$_2$*C*H$_3$), 13.0 (CH$_2$*C*H$_3$); ν_{max} (thin film)/cm^{-1} 1625 (C=O); *m/z* (CI)) 364 (100%, *M*+H$^+$), 363 (1.3%, *M*); *m/z* (EI) 363 (3.8%, *M*). Found: *M* 363.2620. $C_{23}H_{29}N_3O$ requires *M*, 363.2624.

4.1.10. (*M*,2′*R*,4′*S*)-*N*,*N*,2-Triethyl-6-(2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl)benzamide 12c. In the same way, *N*,*N*-2-triethyl-6-formylbenzamide **2c** (132.6 mg) gave, after purification by flash chromatography on alumina, eluting with petrol/EtOAc (11:1), the imidazolidine **12c** (130.9 mg, 59%) as an oil, $[\alpha]_D^{24}$=−11.7 (*c*=0.463, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.12–7.05 (.4H, m, Ar*H*), 6.91 (1H, t, *J*=5 Hz, Ar*H*), 6.56 (1H, t, *J*=7 Hz, ArH), 6.44 (2H, d, *J*=8 Hz, ArH), 5.55 (1H, s, C*H*NN), 3.81–3.69 (2H, m, NC*H*$_2$CH$_3$ and NC*H*CH$_2$CH$_2$), 3.59 (1H, t, *J*=8 Hz, PhNC*H*H), 3.39 (1H, dq, *J*=14, 7 Hz, NC*H*$_2$CH$_3$), 3.20 (1H, dq, *J*=14, 7 Hz, NC*H*$_2$CH$_3$), 3.11 (1H, dq, *J*=15, 7 Hz, NC*H*$_2$CH$_3$), 3.06–2.98 (2H, m, NC*H*$_2$CH$_2$ and PhNC*H*$_2$ CH$_2$), 2.58 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 2.51 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 1.89–1.66 (4H, m, NCH$_2$C*H*$_2$C*H*$_2$ CH), 1.24 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 1.09 (3H, t, *J*=8 Hz, CH$_2$C*H*$_3$), 1.02 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$); δ_C (75 MHz,

$CDCl_3$) 164.9 (C=O), 146.0 (NCC_5H_5), 104.0, 143.8, 136.0, 129.0, 128.0, 126.9, 123.4, 115.9, 112.1, 80.1 (*C*HNN), 60.6 (N*C*HCH$_2$), 53.2 (N*C*H$_2$CH$_2$), 52.5 (PhN*C*H$_2$), 43.2 (N*C*H$_2$CH$_3$), 38.4 (N*C*H$_2$CH$_3$), 28.0 (NCH$_2$*C*H$_2$), 25.4 (*C*H$_2$CH$_3$), 23.9 (NCH$_2$CH$_2$*C*H$_2$), 14.7 (NCH$_2$*C*H$_3$), 13.1 (NCH$_2$*C*H$_3$), 13.0 (CH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 2963–2931 (CH_3), 1627 (C=O); *m/z* (CI) 392 (100%, M+H$^+$); *m/z* (EI) 394 (8.9%, M+H$^+$). Found: M+H$^+$ 392.5641; $C_{25}H_{33}N_3O$ requires M+H$^+$ 392.5692.

4.1.11. (*P*,2′*R*,4′*S*)-*N*,*N*-Diisopropyl-2-(1-methoxy-1-methylethyl)-6-(2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl)benzamide 12d. In the same way, aldehyde **2d** gave the imidazolidine **12d** (96 mg, 85%) as an amorphous solid, $[\alpha]_D^{25}$=+34.8 (*c*=0.145, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.24–7.15 (3H, m, Ar*H*), 7.09 (2H, d, *J*=8 Hz, ArH), 6.74 (2H, d, *J*=8 Hz, ArH), 6.62 (1H, t, *J*=7 Hz, ArH), 5.68 (1H, s, C*H*N), 4.32–4.22 (1H, m, PhNCH$_2$ C*H*CH$_2$), 3.84–3.76 (1H, m, PhNC*H*$_2$), 3.74–3.69 (1H, m, PhNC*H*$_2$), 3.66–3.54 (2H, m, NCH), 3.37–3.26 (5H, m, NC*H*$_2$, NCH$_2$C*H*$_2$ and NCH$_2$CH$_2$C*H*$_2$), 2.74–2.62 (1H, m, NCH$_2$CH$_2$C*H*$_2$), 3.26 (3H, s, OCH_3), 1.70 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.66 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.64 (3H, s, CH_3), 1.55 (3H, s, CH_3), 0.99 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.95 (3H, d, *J*=7 Hz, NCHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.6 (C=O), 144.4 [N*C*(C_5H_5)], 142.8, 140.0, 135.6, 129.0, 127.7, 126.4, 125.4 (aromatics), 120.8, 115.6, 112.2 (aromatics), 79.4 (CHN), 60.4 (N*C*HCH$_2$), 53.7 (NCH), 52.6 (OCH_3), 50.8 (NCH), 49.2 (PhNCH$_2$), 45.9 (NCH$_2$), 29.0 (NCH$_2$CH$_2$), 27.9 (NCH$_2$CH$_2$*C*H$_2$), 25.7 (CCH_3), 23.3 (CH_3), 20.9, 20.6, 20.3, 19.6 (NCHC*H*$_3$); *m/z* (CI) 464 (100%, M+H$^+$), 388 (6.4%, M+H$^+$−C_4H_9O and CH_3); *m/z* (EI) 464 (23%, M+H$^+$), 463 (2%, *M*), 388 (100%, M+H$^+$−C_4H_9O and CH_3). Found: M+H$^+$ 464.3284; $C_{29}H_{41}N_3O_2$ requires M+H$^+$ 464.3278.

4.1.12. (*M*,2′*R*,4′*S*)-*N*,*N*-Dicylohexyl-2,4-dimethyl-6-(2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl)benzamide 12e. In the same way, benzamide **2e** (88 mg) gave, after flash chromatography eluting with petrol/EtOAc (8:1; R_f=0.42), the imidazolidine **12e** (80.1 mg, 62%) as a white solid, mp 154.5–157.2 °C; $[\alpha]_D^{21}$=+42.1 (*c*=0.28, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.06 (2H, t, *J*=8 Hz, ArH), 6.78 (1H, s, Ar*H*), 6.64 (1H, s, Ar*H*), 6.53 (1H, t, *J*=7 Hz, ArH), 6.40 (2H, d, *J*=9 Hz, ArH), 5.60 (1H, s, C*H*N), 3.82–3.73 (1H, m, PhNCH$_2$C*H*CH$_2$), 3.56 (1H, t, *J*=8 Hz, PhNC*H*$_2$), 3.17–2.84 (5H, m, NCH, NCH, PhNC*H*$_2$ and NC*H*$_2$CH$_2$), 2.78–2.62 (3H, m, NC*H*$_2$CH$_2$ and NCH$_2$C*H*$_2$), 2.52–2.43 (2H, m, NCH$_2$CH$_2$C*H*$_2$), 2.24 (3H, s, ArC*H*$_3$), 2.11 (3H, s, ArC*H*$_3$), 2.06–0.65 (20H, m, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 170.7 (C=O), 146.2, 136.7, 134.8, 133.2, 129.8, 129.0, 128.8, 124.3, 119.2, 115.6, 111.8 (aromatics), 79.6 (*C*HNN), 60.6 (N*C*HCH$_2$), 60.1 (N*C*H), 56.0 (N*C*H), 52.7 (PhN*C*H$_2$), 52.0 (N*C*H$_2$), 30.9 (NCH$_2$*C*H$_2$), 30.8 (NCH$_2$CH$_2$*C*H$_2$), 30.7, 29.3, 27.6, 26.7, 26.7, 25.8, 25.8, 25.4, 25.3, 23.4 (cyclohexyl), 21.4 (*C*H$_3$), 19.3 (*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3005 (Ar–CH), 1609 (CO); *m/z* (CI) 500 (100%, M+H$^+$); *m/z* (EI) 499 (100%, *M*), 456 (34.6%, M−CH_3), 319 (28.2%, M−$C_{12}H_{22}N$), 303 (9%, M−ON(C_6H_{11})$_2$, 289 (52.6%, M+H$^+$−ON(C_6H_{11})$_2$ and CH_3), 187 (47.4%, M−$C_6H_2ON(C_6H_{11})_2$ and [CH_3]$_2$). Found: *M* 499.3560; $C_{22}H_{31}NO_2$ requires *M* 499.3562.

4.1.13. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-1-naphthamide 16a. 2-Formyl-*N*,*N*-diisopropyl-1-naphthamide **1a** (251 mg, 0.89 mmol) and (1*R*,2*S*)-ephedrine **13** (165 mg, 1.0 mmol, 1.1 equiv.) were heated to reflux in toluene (25 mL) for 16 h. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica, eluting with petrol/EtOAc (11:1) to afford the oxazolidine **16a** (328.1 mg, 86%) as a white crystalline solid, mp 214.0–217.1 °C; $[\alpha]_D^{20}$=−157.1 (*c*=0.252, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 8.08 (1H, d, *J*=9 Hz, ArH), 7.95 (1H, d, *J*=9 Hz, ArH), 7.94–7.86 (2H, m, ArH), 7.57–7.52 (4H, m, ArH), 7.42 (2H, t, *J*=7 Hz, ArH), 7.35 (1H, d, *J*=7 Hz, ArH), 5.18 (1H, d, *J*=8 Hz, OC*H*Ph), 4.99 (1H, s, C*H*OCHPh), 3.68 (2H, septet, 2×NC*H*), 3.01 (1H, d quintet, *J*=2, 9 Hz, CHPhC*H*CH$_3$), 2.23 (3H, s, NCH_3), 1.82 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.75 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.15 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.99 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.86 (3H, d, *J*=7 Hz, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 168.4 (C=O), 139.6, 137.3, 133.9, 130.8, 129.2, 128.4, 128.1, 127.9, 127.9, 127.6, 126.6, 126.5, 125.3, 125.0 (aromatics), 94.8 (*C*HNCH$_3$), 82.4 (O*C*HPh), 64.1 (CHPh*C*HCH$_3$), 51.3 (N*C*H), 46.2 (N*C*H), 35.8 (NCH$_3$), 20.9, 20.5, 20.3, 20.3 (CNHC*H*$_3$C*H*$_3$), 15.3 (CH*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3062–2756 (CH_3), 1626 (C=O); *m/z* (CI) 431 (100%, M+H$^+$), 313 (7.7%, M+H$^+$−$C_6H_{14}ON$); *m/z* (EI) 431 (28%, M+H$^+$), 313 (7.7%, M+H$^+$−$C_6H_{14}ON$), 212 (100%, M+H$^+$−$C_{11}H_{14}NO$ and C_3H_7), 155 (9%, M+H$^+$−$C_{15}H_{14}NO$ and $C_6H_{14}N$), 127 (10.2%, $C_{15}H_{14}NO$ and $C_6H_{14}NOC$). Found: M+H$^+$ 431.2700; $C_{28}H_{34}N_2O_2$ requires M+H$^+$ 431.2699. Anal. Calcd for $C_{28}H_{34}N_2O_2$: C, 78.1; H, 7.96; N, 6.51. Found C, 77.73, H, 7.72, N, 6.31.

4.1.14. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diethyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-1-naphthamide 16b. In the same way, 2-formyl-*N*,*N*-diethyl-1-naphthamide **1b** gave the oxazolidine **16b** (196.2 mg, 87%) as white needles, mp 139.1–141.8 °C; $[\alpha]_D^{24}$=−93.6 (*c*=0.588, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 8.12 (1H, d, *J*=9 Hz, ArH), 7.95 (1H, d, *J*=9 Hz, ArH), 7.96–7.88 (1H, m, ArH), 7.86–7.79 (1H, m, ArH), 7.60–7.49 (5H, m, ArH), 7.41 (1H, dt, *J*=7, 1 Hz, ArH), 7.35 (1H, dd, *J*=7, 1 Hz, ArH), 5.2 (1H, d, *J*=9 Hz, OC*H*Ph), 4.98 (1H, s, C*H*OCHPh), 3.79 (2H, m, NC*H*$_2$), 3.16 (2H, m, NC*H*$_2$CH$_3$), 3.08 (1H, d quintet, *J*=2, 8 Hz, CHPhC*H*CH$_3$), 2.25 (3H, s, NC*H*$_3$), 1.46 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 0.97 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 0.86 (3H, d, *J*=7 Hz, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 168.7 (C=O), 139.7, 136.2, 133.8, 131.4, 129.2, 128.9, 128.1, 127.9, 127.9, 127.6, 126.7, 126.7, 125.1, 124.9 (aromatics), 94.9 (*C*HNCH$_3$), 82.5 (O*C*HPh), 63.8 (CHPh*C*HCH$_3$), 43.3 (N*C*H$_2$), 38.8 (N*C*H$_2$), 35.6 (NCH$_3$), 15.2, 13.8 (CNCH$_2$-*C*H$_3$), 12.8 (CH*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1629 (C=O); *m/z* (CI) 403 (100%, M+H$^+$), 212 (23%, M+H$^+$−$C_{11}H_{14}NO$ and CH_3); *m/z* (EI) 403 (19.2%, M+H$^+$), 254 (7.7%, M−$C_2H_{10}N$),212 (100%, M+H$^+$−$C_{11}H_{14}NO$ and CH_3), 127 (10.2%, M+H$^+$−$C_{11}H_{14}NO$ and $C_2H_{10}NO$). Found: M+H$^+$ 403.2388; $C_{26}H_{30}N_2O_2$ requires M+H$^+$ 403.2386.

4.1.15. (*M*,2′*S*,4′*S*,5′*S*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-1-naphthamide 17. Similarly, 2-formyl-*N*,*N*-diisopropyl-1-naphthamide **1a** (124 mg, 0.44 mmol) and (1*S*,2*S*)-(−)-pseudoephedrine **14** (80 mg,

0.48 mmol, 1.1 equiv.) gave, after purification by flash chromatography eluting with petrol/EtOAc (11:1), the oxazolidine **17** (165.9 mg, 88%) as a white crystalline solid, mp 114.8–116.4 °C; $[\alpha]_D^{19}=-135.2$ (c=0.5, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.92–7.85 (4H, m, ArH), 7.58–7.52 (2H, m, ArH), 7.46–7.34 (5H, m, ArH), 5.23 (1H, s, C*H*OCHPh), 4.87 (1H, d, J=9 Hz, OC*H*Ph), 3.65 (2H, septet, J=7 Hz, 2×NC*H*), 2.62–2.53 (1H, m, CHPhC*H*CH_3), 2.27 (3H, s, NCH_3), 1.84 (3H, d, J=7 Hz, NCHCH_3), 1.81 (3H, d, J=7 Hz, NCHCH_3), 1.28 (3H, d, J=7 Hz, NCHCH_3), 1.18 (3H, d, J=7 Hz, NCHCH_3), 0.99 (3H, d, J=7 Hz, CHCH_3); δ_C (75 MHz, $CDCl_3$) 168.5 (C=O), 140.3, 136.5, 133.7, 132.4, 128.4, 128.2, 128.1, 127.9, 126.7, 126.6, 126.5, 125.2 (aromatics), 85.7 (*C*HNCH_3), 87.4 (O*C*HPh), 68.9 (CHPh*C*HCH_3), 51.3 (N*C*H), 46.2 (N*C*H), 35.2 (NCH_3), 20.9, 20.5, 20.4, 20.2 (CNHCH_3*C*H_3), 14.2 (CH*C*H_3); ν_{max}(thin film)/cm^{-1} 1620 (C=O); m/z (CI) 431 (100%, M+H^+), 313 (7.7%, M+H^+–$C_6H_{14}ON$); m/z (EI) 431 (28%, M+H^+),313 (7.7%, M+H^+–$C_6H_{14}ON$), 212 (100%, M+H^+–$C_{11}H_{14}NO$ and C_3H_7). Found: M+H^+ 431.2700; $C_{28}H_{34}N_2O_2$ requires M+H^+ 431.2699.

4.1.16. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diisopropyl-2-(3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl)benzamide 18a. In a similar way, aldehyde **2a** (2.0 g) and (1*R*,2*S*)-ephedrine **13** (1.42 g) gave, after purification by flash chromatography on silica, eluting with 11:1 petrol/EtOAc, the oxazolidine **18b** (2.89 g, 89%) as an oil which crystallised to a yellow wax upon standing, $[\alpha]_D^{20}=-39.4$ (c=0.28, $CHCl_3$). δ_H (300 MHz; $CDCl_3$) 8.01 (1H, d, J=8 Hz, C*H*CCHNO), 7.54–7.28 (8H, m, ArH), 7.15 (1H, d, J=8 Hz, ArH), 5.13 (1H, d, J=8 Hz, COC*H*Ph), 4.89 (1H, s, C*H*OCHPh), 3.76 (1H, septet, J=6 Hz, NC*H*CH_3), 3.56 (1H, septet, J=6 Hz, NC*H*CH_3), 2.93 (1H, m, C*H*CH_3), 2.2 (3H, s, CHNCH_3), 1.58 (6H, d, J=6 Hz, NCHCH_3CH_3), 1.08 (3H, t, J=6 Hz, NCHCH_3), 1.01 (3H, t, J=6 Hz, NCHCH_3), 0.77 (3H, d, J=6 Hz, NCHCH_3); δ_C (400 MHz, $CDCl_3$) 169.5 (C=O), 140.1–124.5 (aromatics), 94.3 (*C*HNO), 82.3 (O*C*HPh), 63.9 (N*C*CH_3), 51 (N*C*H_3), 45.7 (NCH$_3$*C*HCH_3), 35.8 (CH*C*H_3), 20.5–15.1 (COCN*C*H$_3$CH_3); ν_{max}(thin film)/cm^{-1} 1621 (C=O); m/z (CI) 381 (100%, M+H^+), 162 (11.3%, M+H^+–$C_{11}H_{14}NO$ and C_3H_7); m/z (EI) 381 (10%, M+H^+), 162 (100%, M+H^+–$C_{11}H_{14}NO$ and C_3H_7). Found: M+H^+ 381.2549; $C_{24}H_{32}N_2O_2$ requires M+H^+ 381.2543.

4.1.17. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-2-Diethyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]benzamide 18b. In the same way, *N*,*N*-diethyl-2-formylbenzamide **2b** (125 mg) gave, after purification by flash chromatography eluting with petrol/EtOAc (11:1), the oxazolidine **18a** (80 mg, 34%) as an oil, $[\alpha]_D^{24}=-25.8$ (c=0.115, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.56 (1H, d, J=8 Hz, Ar*H*), 7.14 (2H, d, J=8 Hz, ArH), 7.1–6.98 (5H, m, Ar*H* and ArH), 4.79 (1H, d, J=8 Hz, OC*H*Ph), 4.23 (1H, s, C*H*OCHPh), 3.35 (1H, m, NCH_2CH$_3$), 2.63 (1H, d quintet, J=2, 7 Hz, CHPhC*H*CH_3), 2.43–2.23 (1H, m, NCH_2CH$_3$), 1.88 (3H, s, NCH_3), 0.99 (6H, d, J=7 Hz, NCH$_2$CH_3), 0.72 (3H, t, J=7 Hz, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$), 169.1 (C=O), 139.8, 139.0, 137.9, 133.9, 128.7–125.1 (aromatics), 94.8 (*C*HOCHPh), 82.3 (O*C*HPh), 63.7 (CHPHh*C*CH$_3$), 43.0 (N*C*H$_2$), 35.7 (N*C*H$_2$), 14.7, 13.4 (NCH$_2$*C*H$_3$×2), 12.6 (CH*C*H$_3$), 7.8 (CH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1627 (C=O); m/z (CI) 352 (100%, M+H^+), 175 (6.7%, M−$C_{11}H_{14}NO$); m/z (EI) 367 (100%, M+H^+), 175 (4.7%, M−$C_{11}H_{14}NO$). Found: M+H^+ 352.4817; $C_{23}H_{30}N_2O_2$ requires M+H^+ 352.4807.

4.1.18. (*P*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diisopropyl-2-(3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl)-6-ethylbenzamide 18c. In the same way aldehyde **2c** (100.1 mg) and (1*R*,2*S*)-ephedrine **13** gave, after flash chromatography on alumina, eluting with petrol/EtOAc (11:1), the oxazolidine **13c** (136.8 mg, 87%) as an oil which formed a yellow wax on standing, $[\alpha]_D^{24}=-11.7$ (c=0.463, $CHCl_3$). δ_H (300 MHz; $CDCl_3$) 7.56 (1H, d, J=8 Hz, Ar*H*), 7.14 (2H, d, J=8 Hz, Ar*H*), 7.1–6.98 (5H, m, Ar), 4.79 (1H, d, J=8 Hz, OC*H*Ph), 4.23 (1H, s, C*H*OCHPh), 3.35 (1H, m, NCH_2CH$_3$), 2.63 (1H, d quintet, J=2, 7 Hz, CHPhC*H*CH_3), 2.43–2.23 (1H, m, NCH_2CH$_3$), 1.88 (3H, s, NCH_3), 0.99 (6H, t, J=7 Hz, NCH$_2$CH_3 and CH$_2$CH_3), 0.72 (3H, t, J=7 Hz, NCH$_2$CH_3), 0.49 (3H, t, J=7 Hz, CHCH_3); δ_C (75 MHz, $CDCl_3$), 169.1 (C=O), 139.8, 139.0, 137.9, 133.9, 128.7–125.1 (aromatics), 94.8 (*C*HOCHPh), 82.3 (O*C*HPh), 63.7 (CHPHh*C*CH$_3$), 43.0 (N*C*H$_2$), 38.1 (*C*H$_2$), 35.7 (N*C*H$_3$), 25.6 (*C*H$_2$CH$_3$), 14.7, 13.4 (NCH$_2$*C*H$_3$×2), 12.6 (CH*C*H$_3$), 7.8 (CH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1627 (C=O); m/z (CI) 367 (100%, M+H^+), 190 (6.7%, M−$C_{11}H_{14}NO$); m/z (EI) 367 (100%, M+H^+), 190 (2.7%, M−$C_{11}H_{14}NO$). Found: M+H^+ 367.2380; $C_{23}H_{30}N_2O_2$ requires M+H^+ 367.2386.

4.1.19. (*M*)-(−)-2-Hydroxymethyl-*N*,*N*-diisopropyl-1-naphthamide 19a. (a) By hydrolysis-reduction of imidazolidine **10a**. A solution of 1 M HCl (2 mL, 2.5 equiv.) was added to a stirred solution of imidazolidine **10a** (331.6 mg, 0.79 mmol) in THF (20 mL) at 0 °C. After 35 min, a solution of sodium borohydride (2.7 equiv.) and sodium methoxide (1.0 equiv.) in methanol (20 mL) (a few droplets of ethanol was added to improved solubility) was added dropwise to the reaction mixture while keeping the temperature around 0 °C. The mixture was allowed to warm to room temperature over a period of 35 min. The mixture was concentrated under reduced pressure, without heating, to half of its original volume. It was extracted with diethyl ether (3×30 mL), and the combined extracts were washed with brine (2×30 mL), dried ($MgSO_4$) and evaporated under reduced pressure without heating. Purification by flash chromatography, eluting with petrol/EtOAc (5:1) gave enantiomerically enriched alcohol (−)-**19a** (202 mg, 94% yield) as a white solid, $[\alpha]_D^{20}=-105.7$ (c=0.5, $CHCl_3$); R_f=0.55 (petrol/EtOAc 7:1). Analytical HPLC on a chiral stationary phase (see below), eluting with 8% ethanol in hexane at 1 mL/min, indicated an ee of 89%.

(b) By hydrolysis-reduction of oxazolidine **16a**. A mixture of trifluroacetic acid (2.3 mL, 30 mmol, 20.0 equiv.) and water (0.5 mL, 3 mmol, 2.0 equiv.) was added dropwise to a solution of oxazolidine **16a** (346 mg, 1.51 mmol) in THF (30 mL) at 0 °C. After 60 min sodium methoxide (2.5 g, 33 equiv.) was added in small batches. The acidity of the solution reached pH 6. A slurry of sodium borohydride (10 equiv.) in ethanol (20 mL) was added at 0 °C. After 30 min, the mixture was allowed to warm to room temperature and evaporated under reduced pressure without applying heat until reduced to half its original volume. Cold water was added, and the mixture was extracted with diethyl

ether (3×30 mL). The combined organic extracts were washed with brine (2×30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure without applying any external heating. Purification by flash chromatography, as before, gave enantiomerically enriched alcohol (−)-**19a** (183 mg, 85%). HPLC on a chiral stationary phase (see below) indicated an enantiomeric excess of 74%.

4.1.20. (±)-2-Hydroxymethyl-*N*,*N*-diisopropyl-1-naphthamide (±)-19a. Sodium borohydride (80 mg, 2 equiv.) was added to a stirred solution of 2-formyl-*N*,*N*-diisopropyl-1-naphthamide **1a** (300 mg, 1.0 mmol) in ethanol (15 mL) at 0 °C. After 100 min, water (30 mL) was added. The mixture was extracted with ether (2×20 mL), and the combined extracts washed with brine (2×20 mL), dried ($MgSO_4$), evaporated under reduced pressure, and purified by flash column chromatography eluting with petrol/EtOAc (1:1) to afford alcohol (±)-**19a** (281.6 mg, 93%) as a white solid, mp 105–106.8 °C; R_f 0.25, petrol/EtOAc, 1:1); δ_H (300 MHz, $CDCl_3$) 7.80–7.70 (3H, m, ArH), 7.50–7.40 (3H, m, ArH), 4.77 (1H, dd, J=12, 3 Hz, CH_AH$_B$OH), 4.52 (1H, dd, J=12, 2 Hz, CH$_A$$H_B$OH), 3.56 (1H, septet, J=7 Hz, NCH), 3.51 (1H, septet, J=7 Hz, NCH), 3.10 (1H, br m, CH$_2$OH), 1.64 (3H, d, J=7 Hz, NCHCH_3), 1.62 (3H, d, J=7 Hz, NCHCH_3) 1.24 (3H, d, J=7 Hz, NCHCH_3) and 0.98 (3H, J=7 Hz, NCHCH_3); δ_C (75 MHz, $CDCl_3$) 170 (CHO), 134.3, 132.7, 129.2, 128.6, 128.2, 126.8, 126.3, 124.6 (aromatics), 63.4 (*C*H$_2$OH), 51.4 (N*C*H), 46.3 (N*C*H), 20.8 (*C*H$_3$), 20.5 (*C*H$_3$), 20.5 (*C*H$_3$); ν_{max}(thin film)/cm^{-1} 2941 (OH), 1610 (C=O); *m*/*z* CI 286 (100%, M+H$^+$), 254 (1.3%, M+H$^+$−CH$_2$OH); *m*/*z* (EI) 286 (100%, M+H$^+$), 285 (11.5% M), 254 (3.8%, M+H$^+$−CH$_2$OH), 168 (M+H$^+$−ONC$_6$H$_{14}$). Found: M+H$^+$ 286.1729; $C_{18}H_{23}NO_2$ requires M+H$^+$ 286.1708. Anal. Calcd for $C_{18}H_{23}NO_2$ C, 75.76; H, 8.12; N, 4.91%. Found C, 75.96; H, 8.05, N, 4.91%.

Analytical HPLC on a Chiralpak AD (250×4.6 mm) column, eluting with 10% EtOH in hexane at 1 mL/min, resolved two enantiomers at 6.49–6.59 min and 8.14–8.19 min.

4.1.21. (*M*)-(−)-2-Hydroxymethyl-*N*,*N*-diethyl-1-naphthamide (−)-19b. (a) By hydrolysis–reduction of imidazolidine **10b**. By the method used for hydrolysis-reduction of **10a**, imidazolidine **10b** (331.6 mg, 0.79 mmol) gave a product which was purified by flash column chromatography, eluting with petrol/EtOAc (3:1) to afford enantiomerically enriched alcohol (−)-**19b** (180.5 mg, 84%) as an oil, $[\alpha]_D^{18}$=−38.2 (c=0.5, $CHCl_3$). Analytical HPLC on a chiral stationary phase (see below), eluting with 16% ethanol in hexane at 1 mL/min, indicated an enantiomeric excess of 97%.

(b) By hydrolysis–reduction of oxazolidine **16b**. By the method used for oxazolidine **16a**, oxazolidine **16b** (331 mg) was reduced to give a crude alcohol which was purified by flash column chromatography, eluting with petrol/EtOAc (3:1), to afforded enantiomerically enriched alcohol (−)-**19b** (182.6 mg, 85%) as an oil. Analytical HPLC on a chiral stationary phase (see below) eluting with 6% ethanol in hexane at 1 mL/min indicated an enantiomeric excess of 74%.

4.1.22. (±)-2-Hydroxymethyl-*N*,*N*-diethyl-1-naphthamide 19b. By the method used for (±)-**19a**, 2-formyl-*N*,*N*-diethyl-1-naphthamide **1b** (250 mg) was reduced with sodium borohydride to give a crude product which was purified by flash chromatography, eluting with petrol/EtOAc (5:1), to give the corresponding alcohol (±)-**19b** as a oil (219.2 mg, 87% yield). δ_H (300 MHz; $CDCl_3$), 7.75 (1H, dd, J=2, 5 Hz, ArH), 7.72 (1H, d, J=8.9 Hz, ArH), 7.62 (1H, m, Ar*H*), 7.43 (3H, m, ArH), 4.65 (1H, d, J=13 Hz, CH$_A$$H_B$OH), 4.48 (1H, d, J=13 Hz, CH_AH$_B$OH), 3.74–3.52 (2H, m, NCH_2CH$_3$), 3.42 (1H, broad m, O*H*), 2.96 (2H, q, J=7 Hz, NCH_2CH$_3$), 1.30 (3H, t, J=7 Hz, NCH$_2$CH_3), 0.83 (3H, t, J=7 Hz, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 169.7 (C=O), 135.0, 132.7, 132.6, 129.2, 129.0, 128.2, 126.9, 126.4, 126.2, 124.5 (aromatics), 63.1 (*C*H$_2$OH), 43.2, 39.0 (N*C*H$_2$), 26.6, 13.8, 12.8 (NCH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3386 (broad s), 2974–2849, 1611 (C=O); *m*/*z* (CI) 258 (100%, M+H$^+$), 227 (1.7%, M+H$^+$−CH$_2$OH); *m*/*z* (EI) 258 (3.6%, M+H$^+$), 257 (100% M), 227 (3.8%, M+H$^+$−CH$_2$OH). Found: M+H$^+$ 258.3387; $C_{16}H_{19}NO_2$ requires M+H$^+$ 258.3432.

4.1.23. (*P*)-(−)-*N*,*N*-Diisopropyl-2-(hydroxymethyl)-6-(1-methoxy-1-methylethyl)benzamide (−)-20d. By the method used for the hydrolysis and reduction of imidazolidine **10a**, imidazolidine **12d** was reduced to give a crude residue which was purified by flash chromatography, eluting with petrol/EtOAc (11:1), to give the enantiomerically enriched alcohol (−)-**20d** (56 mg, 90%), $[\alpha]_D^{20}$=−14.1 (c=0.5, $CHCl_3$). Formation of the Mosher's ester[63] of this compound and integration of the resulting ^{1}H NMR spectrum (in comparison with the ester of racemic material) indicated an enantiomeric excess of 77%.

4.1.24. (±)-*N*,*N*-Diisopropyl-2-(hydroxymethyl)-6-(1-methoxy-1-methylethyl)benzamide (±)-20d. By the method used to make (±)-**19a**, aldehyde **2d** (250 mg) was reduced by sodium borohydride to yield a crude product which was purified by flash chromatography, eluting with petrol/EtOAc (5:1), to give the corresponding racemic alcohol (±)-**20d** (218.9 mg, 87%) as a white solid, mp 94.2–95.8 °C. δ_H (300 MHz; $CDCl_3$) 7.35–7.29 (3H, Benz-*H*), 4.79 (1H, d, J=13 Hz, CH_AH$_B$OH), 4.37 (1H, d, J=13 Hz, CH$_A$$H_B$OH), 3.53 (1H, septet, J=7 Hz, NC*H*), 3.41 (1H, septet, J=7 Hz, NC*H*), 3.25 (3H, s, OCH$_3$), 1.63 (3H, d, J=7 Hz, NCHCH_3), 1.59 (3H, d, J=7 Hz, NCHCH_3), 1.58 (3H, s, COHCH$_3$CH$_3$CH_3), 1.52 (3H, s, COHCH$_3$CH$_3$ CH_3), 1.16 (3H, d, J=7 Hz, NCHCH_3), 0.97 (3H, d, J=7 Hz, NCHCH_3); δ_C (75 MHz, $CDCl_3$) 171.6 (C=O), 143.8, 138.0, 134.4, 128.1, 128.0, 126.2 (aromatics), 77.9 (*C*OHCH$_3$), 63.4 (*C*H$_2$OH), 50.7 and 45.8 (NCH), 28.0 and 26.1 (C*C*H$_3$), 20.4, 20.2, 20.0, 19.6 (4×NCH*C*H$_3$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3367 (OH), 1607 (amide C=O); *m*/*z* (CI) 308 (20%, M+H$^+$), 276 (100%, M−OCH$_3$); *m*/*z* (EI) 308 (2%, M+H$^+$), 86 (100%, M−CH$_2$OH, C$_4$H$_9$O, C$_6$H$_3$, NO). Found: M+H$^+$ 308.2225; $C_{18}H_{29}NO_3$ requires M+H$^+$ 308.2226. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found C, 70.94, H, 9.60, N, 4.43.

4.1.25. (*M*)-(−)-*N*,*N*-Dicyclohexyl-2-hydroxymethyl-4,6-dimethylbenzamide (−)-8. By the method used for the hydrolysis–reduction of imidazolidine **10a**, but at a temperature of −15 °C, imidazolidine **12e** (250 mg) gave

a crude residue which was purified by flash chromatography eluting with petrol/EtOAc (5:1), to afford the enantiomerically enriched alcohol (−)-**8** (158 mg, 93%) as a white solid $[\alpha]_D^{18}=-72.1$ (c=0.5, $CHCl_3$); R_f 5:1 (petrol/EtOAc, 5:1). Integration of the ^1H NMR spectrum of this material in the presence of Pirkle's chiral shift reagent (*R*)-TFAE,[64] in comparison with the racemic alcohol **8**, indicated an enantiomeric excess of 53%.

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References and notes

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