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On the structure and chiroptical properties of (*S*)-4-isopropyl-oxazolidin-2-one

David Benoit,[a] Elliot Coulbeck,[b] Jason Eames[b,*] and Majid Motevalli[c]

[a]*Nachwuchsgruppe Theorie im SFB 569, Albert-Einstein-Allee 11, University of Ulm, D-89081 ULM, Germany*
[b]*Department of Chemistry, University of Hull, Cottingham Road, Kingston Upon Hull HU6 7RX, UK*
[c]*School of Biological and Chemical Sciences, Queen Mary, University of London, Mile End Road, London E1 4NS, UK*

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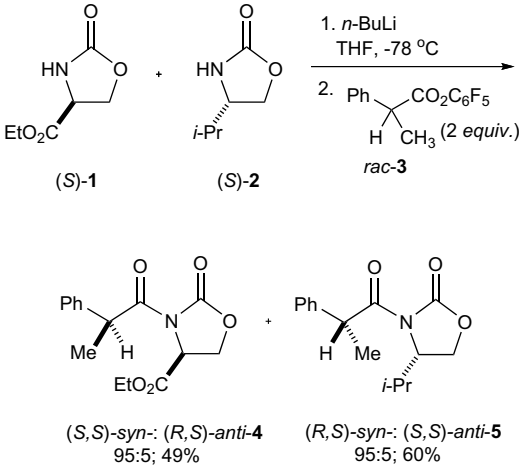
Abstract—The specific rotation of (*S*)-4-isopropyl-oxazolidin-2-one is extremely solvent dependent. In chloroform it is dextrorotatory $\{[\alpha]_D^{26} = +15.5$ (*c* 5.2, $CHCl_3)\}$, whereas in ethanol it is levorotatory $\{[\alpha]_D^{26} = -16.1$ (*c* 5.2, EtOH)$\}$.

1. Introduction

Over the last few years, we have been interested in the parallel kinetic resolution of profen-based active esters,[1] such as *rac*-**3**, using a combination of *quasi*-enantiomeric Evans' oxazolidin-2-ones (*S*)-**1** and (*S*)-**2**[2] to give oxazolidin-2-one adducts (*S*,*S*)-*syn*-**4** and (*R*,*S*)-*syn*-**5** in 49% and 60% yields, respectively, with excellent levels of diastereocontrol (Scheme 1).



Scheme 1. Parallel kinetic resolution of active ester *rac*-**3** using *quasi*-enantiomeric oxazolidin-2-ones (*S*)-**1** and (*S*)-**2**.

In recent years, we have extended this methodology towards the resolution of oxazolidin-2-ones, such as *rac*-**1**,[3] using a combination of complementary *quasi*-enantiomeric active esters, such as (*R*)-**3** and (*S*)-**6** to give the related oxazolidin-2-one adducts (*R*,*R*)-*syn*-**4** and (*S*,*S*)-*syn*-**7** in 55% and 59% yields, respectively, with excellent levels of diastereocontrol (Scheme 2).

2. Results and discussion

By using our standard protocol,[1–3] we were interested in the kinetic resolution of 4-isopropyl-oxazolidin-2-one *rac*-**2** using a novel active ester, pentafluorophenyl 2-(4-isobutylphenyl)propionate (*S*)-**9** [derived from the DCC coupling of 2-(4-isobutylphenyl)propionic acid (*S*)-**8** and pentafluorophenol in 92% yield—Scheme 3]. The treatment of an excess of oxazolidin-2-one *rac*-**2** (5 equiv) in THF at −78 °C with *n*-BuLi, followed by the addition of the active ester (*S*)-**9**, gave two separable diastereoisomeric adducts (*S*,*R*)-*syn*- and (*S*,*S*)-*anti*-**10** in a combined 79% yield with a high level of diastereoselectivity (ratio: *syn*-:*anti*- 88:12) as shown in Scheme 4.[4] The remaining 4-isopropyl-oxazolidin-2-one **2**, which was presumed to have an (*S*)-configuration $\{[\alpha]_D^{25} = +2.6$ (*c* 4.8, $CHCl_3)\}$ was re-isolated in 64% yield with ~16% ee.[5] The enantiomeric excess was determined by use of a chiral shift NMR

* Corresponding author. Tel.: +44 1482 466401; fax: +44 1482 466410; e-mail: j.eames@hull.ac.uk

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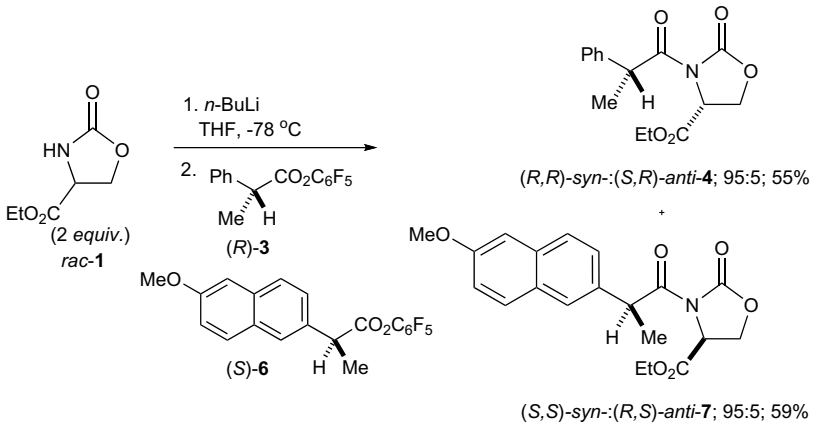
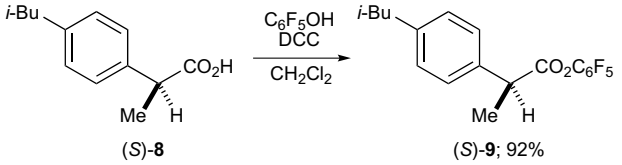


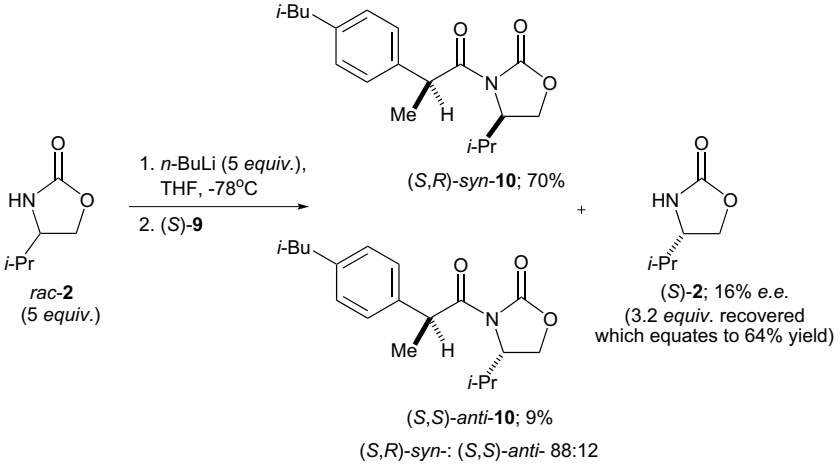
Scheme 2. Parallel kinetic resolution of oxazolidin-2-one (*rac*)-**1** using *quasi*-enantiomeric active esters (*R*)-**3** and (*S*)-**6**.



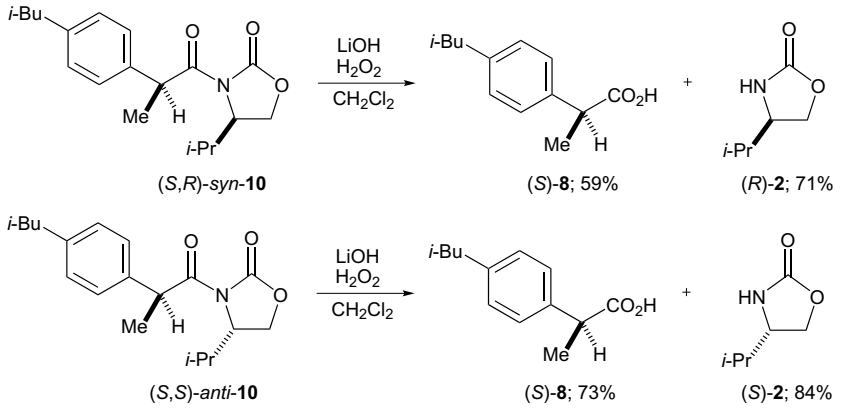
Scheme 3. Synthesis of pentafluorophenyl 2-(4-isobutylphenyl)propionate (*S*)-**9**.

reagent, tris[3-(trifluoromethylhydroxymethylene)-d-camphorato] europium(III). Simple hydrolysis of these separable oxazolidin-2-ones (*S*,*R*)-*syn*-and (*S*,*S*)-*anti*-**10** using LiOH/H_2O_2[6] in THF/H_2O (3:1) gave the corresponding enantiomerically pure 4-isopropyl-oxazolidin-2-ones (*R*)- and (*S*)-**2**,[1,2] and the recovered 2-(4-isobutylphenyl)propionic acid (*S*)-**8** in high yields (Scheme 5). In an attempt to confirm the configurations of these 4-isopropyl-oxazolidin-2-ones (*R*)- and (*S*)-**2** [and their parent adducts (*S*,*R*)-*syn*- and (*S*,*S*)-*anti*-**10**], we chose to simply compare their specific rotations with known literature values. However, closer examination of the literature revealed what appeared to be some ambiguity in their assignment of configuration and solvent dependence on the sign of (specific) rotation (Table 1).

In an attempt to solve this uncertainty, we chose to check the synthesis of both enantiomers of 4-isopropyl-oxazolidin-2-ones (*R*)- and (*S*)-**2** by treatment of the corresponding 2-amino-3-methyl-butanol (*R*)- and (*S*)-**11** with diethylcarbonate (Scheme 6). The addition of 2-amino-3-methyl-butanol (*R*)-**11** {$[\alpha]_D^{26} = -23.2$ (*c* 3.7, $CHCl_3$); $[\alpha]_D^{26} = -15.0$ (*c* 4.2, EtOH); lit.[14] $[\alpha]_D^{20} = -16.6$ (*c* 0.09, EtOH)} {formed by $LiAlH_4$ reduction of (−)-(*R*)-valine; $[\alpha]_D^{26} = -23.3$ (*c* 2.8, 2 M HCl); lit.[27] $[\alpha]_D^{26} = -27.5$ (*c* 5.0, 5 M HCl)} to diethylcarbonate, gave the levorotatory 4-isopropyl-oxazolidin-2-one (*R*)-**2** {$[\alpha]_D^{26} = -13.1$ (*c* 4.2, $CHCl_3$)} in 90% yield (Scheme 6). In comparison, the treatment of 2-amino 3-methyl-butanol (*S*)-**11** {$[\alpha]_D^{26} = +20.8$ (*c* 5.8, $CHCl_3$); $[\alpha]_D^{20} = +15.6$ (*c* 3.8, EtOH); lit.[28] $[\alpha]_D^{20} = +18.5$ (*c* 7.83, EtOH)} {formed by $LiAlH_4$ reduction of (+)-(*S*)-valine; $[\alpha]_D^{26} = +24.0$ (*c* 2.4, 2 M HCl); lit.[27] $[\alpha]_D^{20} = +28.0$ (*c* 8.0, 6 M HCl)} with diethylcarbonate, gave the dextrorotatory 4-isopropyl-oxazolidin-2-one (*S*)-**2** {$[\alpha]_D^{20} = +15.6$ (*c* 3.0, $CHCl_3$)} in 80% yield (Scheme 6). These oxazolidin-2-ones were determined to be enantiomerically pure (>96% ee) by using a chiral shift NMR



Scheme 4. Kinetic resolution of 4-isopropyl-oxazolidin-2-one (*rac*)-**2** using active ester (*S*)-**9**.



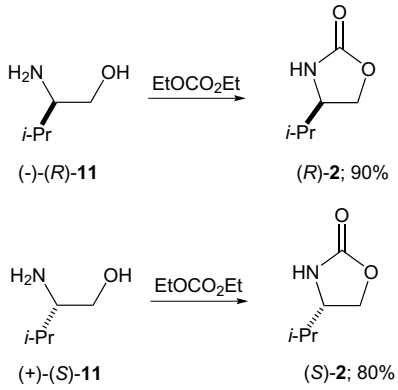
Scheme 5. Hydrolysis of adducts (*S*,*R*)-*syn*- and (*S*,*S*)-*anti*-**10**.

Table 1. Literature values for the specific rotation of 4-isopropyl-oxazolidin-2-one **2**[7]

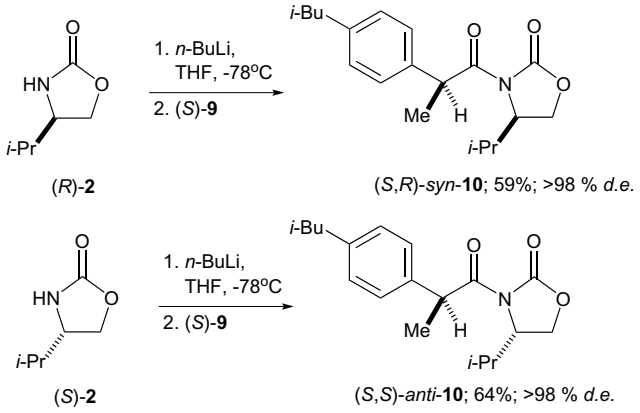
	Sign	Specific rotation	λ	c	T (°C)	Solvent
(*S*)-**2**	+	+13.3[8]	—	6.8	—	$CHCl_3$
(*S*)-**2**	+	+16.8[9]	D	0.17	25	$CHCl_3$
(*S*)-**2**	+	+14.8[10]	D	7.0	—	$CHCl_3$
(*S*)-**2**	+	+12.0[11]	D	15.0	25	$CHCl_3$
(*S*)-**2**	+	+5.3[12]	D	—	—	$CHCl_3$
(*S*)-**2**	+	+14.0[13]	D	7.0	20	$CHCl_3$
(*R*)-**2**	−	−5.1[12]	D	—	—	$CHCl_3$
(*R*)-**2**	−	−15.5[14]	D	0.07	25	$CHCl_3$
(*R*)-**2**	−	−14.0[13]	D	7.0	20	$CHCl_3$
(*R*)-**2**	+	+17.5[15]	D	—	—	EtOH
(*R*)-**2**	+	+19.3[16]	D	1.0	22	EtOH
(*R*)-**2**	+	+17.0[18]	D	6.0	20	EtOH
(*R*)-**2**	+	+17.5[17]	D	6.0	20	EtOH
(*S*)-**2**	−	−18.0[18]	D	6.0	20	EtOH
(*S*)-**2**	−	−17.0[19]	D	6.0	30	EtOH
(*S*)-**2**	−	−17.5[17]	D	6.0	20	EtOH
(*S*)-**2**	−	−16.6[20]	D	—	—	EtOH
(*S*)-**2**	−	−20.0[21]	D	1.0	20	EtOH
(*S*)-**2**	−	−16.5[22]	D	6.0	20	EtOH
(*S*)-**2**	−	−16.6[23]	D	1.02	25	EtOH
(*S*)-**2**	−	−18.5[24]	D	6.0	25	EtOH
(*S*)-**2**	−	−18.0[25]	D	1.0	20	EtOH
(*S*)-**2**	−	−18.0[26]	—	1.6	—	EtOH
(*S*)-**2**	−	−18.0[27]	D	1.0	20	EtOH
(*R*)-**2**	−	−18.0[27]	D	1.0	20	EtOH

reagent, tris[3-(trifluoromethylhydroxymethylene)-d-camphorato] europium(III).[5]

With this information in hand, we next determined the configurational assignment of their parent adducts (*S*,*R*)-*syn*- and (*S*,*S*)-*anti*-**10** by the addition of the corresponding lithiated oxazolidin-2-one to a stirred solution of pentafluorophenyl 2-(4-isobutylphenyl)propionate (*S*)-**9** in THF at −78 °C (Scheme 7). The deprotonation of the oxazolidin-2-ones (*R*)- and (*S*)-**2** in THF at −78 °C using *n*-BuLi, followed by the addition of active ester (*S*)-**9**, gave the corresponding diastereoisomerically pure oxazolidin-2-one adducts (*S*,*R*)-*syn*-and (*S*,*S*)-*anti*-**10** in 59% and 64% yields, respectively (Scheme 7). The levels of diastereocontrol were determined to be >98% de by ^{1}H NMR spectroscopy (at 400 MHz).



Scheme 6. Synthesis of 4-isopropyl-oxazolidin-2-ones (*R*)- and (*S*)-**2**.



Scheme 7. Stereospecific synthesis of oxazolidin-2-one adducts (*S*,*R*)-*syn*- and (*S*,*S*)-*anti*-**10**.

Slightly puzzled by the ambiguity within the literature, we next chose to investigate the role of the solvent (structural nature and polarity) on the magnitude and the sign of the specific rotation for 4-isopropyl-oxazolidin-2-one (*S*)-**2** (Table 2). From this particular study, it was evident that the specific rotation of this oxazolidin-2-one **2** was extremely solvent dependent. By using protic solvents, such as methanol, 4-isopropyloxazolidin-2-one (*S*)-**2** was found to

Table 2. The specific rotations of 4-isopropyl-oxazolidin-2-one **2** in different solvents at 26 °C

Entry		Sign	Specific rotation	λ	C	Solvent
1	(*S*)-**2**	−	−21.9	D	2.8	MeOH
2	(*S*)-**2**	−	−20.2	D	4.2	DMSO
3	(*S*)-**2**	−	−17.4	D	2.6	EtOH
4	(*S*)-**2**	−	−13.2	D	5.0	DMF
5	(*S*)-**2**	−	−11.7	D	4.6	MeCN
6	(*S*)-**2**	−	−9.2	D	2.8	*i*-PrOH
7	(*S*)-**2**	−	−4.6	D	6.2	Acetone
8	(*S*)-**2**	+	+0.25	D	3.2	1,4-Dioxane
9	(*S*)-**2**	+	+0.3	D	5.2	THF
10	(*S*)-**2**	+	+2.8	D	3.4	EtOAc
11	(*S*)-**2**	+	+5.1	D	2.8	CCl_4
12	(*S*)-**2**	+	+6.8	D	4.4	$EtOCO_2Et$
13	(*S*)-**2**	+	+9.7	D	2.6	CH_2Cl_2
14	(*S*)-**2**	+	+15.6	D	3.0	$CHCl_3$
15	(*S*)-**2**	+	+25.1	D	2.4	Et_2O
16	(*R*)-**2**	+	+15.0	D	2.8	EtOH
17	(*R*)-**2**	−	−13.1	D	4.2	$CHCl_3$

be levorotatory $\{[\alpha]_D^{26} = -21.9$ (*c* 2.8, MeOH)$\}$, whereas in aprotic solvents, such as diethyl ether, it was found to be dextrorotatory $\{[\alpha]_D^{26} = +25.1$ (*c* 2.4, Et_2O)$\}$ for a similarly concentrated sample (Table 2: entries 1 vs 15). Interestingly, changing the solvent from methanol, to ethanol and then isopropanol, the magnitude of the specific rotation $\{[\alpha]_D^{26}\}$ decreased from −21.9 (*c* 2.8, MeOH) to −9.2 (*c* 2.8, *i*-PrOH) presumably due to changes in polarity and intermolecular hydrogen bonding (Table 2: entries 1, 3 and 6). By comparison, changing the solvent from aprotic carbon tetrachloride to dichloromethane and then to chloroform increased the magnitude of the specific rotation $\{[\alpha]_D^{26}\}$ from +5.1 (*c* 2.8, CCl_4) to +15.6 (*c* 3.0, $CHCl_3$) (Table 2: entries 11, 13 and 14). Whereas, using a polar aprotic solvent, such as DMSO, DMF and acetonitrile, 4-isopropyl-oxazolidin-2-one (*S*)-**2** was levorotatory $\{[\alpha]_D^{26} = -20.2$ (*c* 4.2, DMSO); $[\alpha]_D^{26} = -13.2$ (*c* 5.0, DMF) and $[\alpha]_D^{26} = -11.7$ (*c* 4.6, MeCN)$\}$ (Table 2: entries 2, 4 and 5). Re-evaluation of the original literature in Table 1 is now clearer; 4-isopropyl-oxazolidin-2-one (*S*)-**2** is dextrorotatory $\{[\alpha]_D^{26} = +15.6$ (*c* 3.0, $CHCl_3$)$\}$ in chloroform, but levorotatory $\{[\alpha]_D^{26} = -17.4$ (*c* 2.4, EtOH)$\}$ in ethanol (Table 2: entries 3 and 14).[29] The reverse has also been shown to be true for its enantiomeric 4-isopropyl-oxazolidin-2-one (*R*)-**2** (Table 2: entries 16 and 17).[3] The magnitude of these specific rotations $\{[\alpha]_D^{26}\}$ were also shown to be concentration dependent; for higher concentrations of (*S*)-**2** in chloroform, the magnitude increased from +10.0 (for *c* 0.6, $CHCl_3$) to +16.5 (for *c* 10.4, $CHCl_3$) (Table 3: entries 1–3), whereas in ethanol, the magnitude decreased from −16.0 (for *c* 0.7, EtOH) to −14.6 (for *c* 11.0, $CHCl_3$) (Table 3: entries 4–6). Interestingly, the position of null rotation corresponded to a solution of chloroform and ethanol in a ratio of 85:15; $[\alpha]_D^{26} = 0.0$ (*c* 6.2, $CHCl_3$/EtOH 85:15) (Table 4: entry 4).

We next probed this solvent effect using scalemic mixtures of oxazolidin-2-one **2** - formed by pre-mixing its (*S*)- and (*R*)-enantiomers (Table 5). From this study, there appeared to be a near-linear relationship between the enantiomeric excess and its specific rotation. In an attempt to obtain a better understanding of these scalemic oxazolidin-2-ones **2**, we next chose to measure their melting points (Table 6). The scalemic oxazoldin-2-ones (*S*)-**2**; 50% ee and (*R*)-**2**; 50% ee have identical melting points (64–68 °C) which were lower than their corresponding enantiomerically pure 4-isopropyl-oxazolidin-2-ones (*S*)- and (*R*)-**2**; >98% ee (mp 67–70 °C) due to their colligative behaviour. However, the racemic oxazolidin-2-one (*rac*)-**2** had a higher melting (73–76 °C) than the enantiomerically pure oxazolidin-2-ones (*S*)- and (*R*)-**2**; >98% ee (mp 67–70 °C). This change is particularly interesting as the crystalline 4-isopropyl-oxazo-

Table 3. The specific rotations of 4-isopropyl-oxazolidin-2-one (*S*)-**2** at different concentrations at 26 °C

Entry		Sign	Specific rotation	λ	*c*	Solvent
1	(*S*)-**2**	+	+10.0	D	0.6	$CHCl_3$
2	(*S*)-**2**	+	+15.6	D	3.0	$CHCl_3$
3	(*S*)-**2**	+	+16.5	D	10.4	$CHCl_3$
4	(*S*)-**2**	−	−16.0	D	0.7	EtOH
5	(*S*)-**2**	−	−15.7	D	4.4	EtOH
6	(*S*)-**2**	−	−14.6	D	11.0	EtOH

Table 4. The specific rotations of 4-isopropyl-oxazolidin-2-one **2** in varying amounts of chloroform and ethanol at 26 °C

Entry	Oxazoldin-2-one	Sign	Specific rotation	λ	*c*	Solvent
1	(*S*)-**2**	+	+15.5	D	5.2	$CHCl_3$
2	(*S*)-**2**	+	+14.3	D	6.2	$CHCl_3$/EtOH (99:1)
3	(*S*)-**2**	+	+2.9	D	5.2	$CHCl_3$/EtOH (90:10)
4	(*S*)-**2**		0.0	D	6.2	$CHCl_3$/EtOH (85:15)
5	(*S*)-**2**	−	−1.8	D	6.4	$CHCl_3$/EtOH (80:20)
6	(*S*)-**2**	−	−5.1	D	6.2	$CHCl_3$/EtOH (70:30)
7	(*S*)-**2**	−	−7.2	D	7.0	$CHCl_3$/EtOH (60:40)
8	(*S*)-**2**	−	−9.8	D	6.8	$CHCl_3$/EtOH (50:50)
9	(*S*)-**2**	−	−12.7	D	5.8	$CHCl_3$/EtOH (40:60)
10	(*S*)-**2**	−	−13.9	D	6.0	$CHCl_3$/EtOH (25:75)
11	(*S*)-**2**	−	−13.6	D	7.0	$CHCl_3$/EtOH (30:70)
12	(*S*)-**2**	−	−14.3	D	6.0	$CHCl_3$/EtOH (20:80)
13	(*S*)-**2**	−	−14.4	D	6.0	$CHCl_3$/EtOH (15:85)
14	(*S*)-**2**	−	−16.1	D	5.8	$CHCl_3$/EtOH (10:90)
15	(*S*)-**2**	−	−16.1	D	6.2	$CHCl_3$/EtOH (1:99)
16	(*S*)-**2**	−	−16.1	D	5.2	EtOH

Table 5. The specific rotations of 4-isopropyl-oxazolidin-2-one **2** with varying enantiomeric excesses at 26 °C

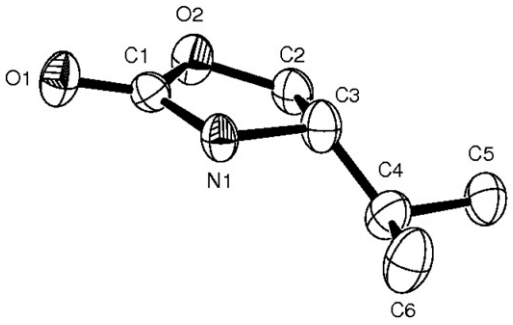
Entry	Oxazoldin-2-one	Sign	Specific rotation	λ	*c*	Solvent
1	(*S*)-**2**; >98% ee	+	+14.9	D	4.2	$CHCl_3$
2	(*S*)-**2**; >98% ee	−	−15.8	D	5.0	EtOH
3	(*S*)-**2**; 50% ee	+	+8.1	D	3.8	$CHCl_3$
4	(*S*)-**2**; 50% ee	−	−7.5	D	4.2	EtOH
5	*rac*-**2**; 0% ee		0.0	D	3.8	$CHCl_3$
6	*rac*-**2**; 0% ee		0.0	D	4.8	EtOH
7	(*R*)-**2**; 50% ee	+	+8.1	D	4.6	EtOH
8	(*R*)-**2**; 50% ee	−	−7.6	D	3.6	$CHCl_3$
9	(*R*)-**2**; >98% ee	+	+16.1	D	4.6	EtOH
10	(*R*)-**2**; >98% ee	−	−13.1	D	4.2	$CHCl_3$

Table 6. The melting points of 4-isopropyl-oxazolidin-2-one **2** with varying enantiomeric excesses

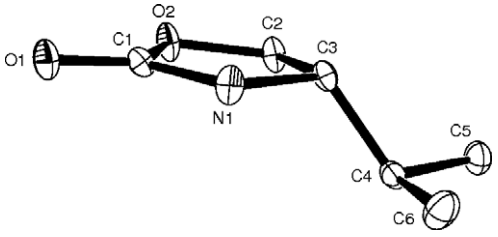
Entry	Oxazolidin-2-one	Mp (°C)
1	(*S*)-**2**; >98% ee	67–70
2	(*S*)-**2**; 50% ee	64–68
3	*rac*-**2**; 0% ee	73–76
4	(*R*)-**2**; 50% ee	64–68
5	(*R*)-**2**; >98% ee	67–70

lidin-2-one (*rac*)-**2** appeared to be more thermally stable than either the (*R*)- or (*S*)-oxazolidin-2-one **2**. Single crystal X-ray diffraction of oxazolidin-2-ones (*rac*)- and (*S*)-**2** gave two related oxazolidin-2-one structures (as shown in Schemes 8 and 9). However, closer inspection of their crystallographic packing arrangements revealed two fundamentally different packing arrangements (Schemes 10 and 11). The racemic oxazolidin-2-one **2** appeared as a hydrogen bonded *meso*-dimer (as shown in Schemes 10 and 12), whereby, the (*S*)-enantiomer (of **2**) recognised the (*R*)-enantiomer (of **2**), whereas, the related enantiomerically pure (*S*)-oxazolidin-2-one **2** prefers to form a hydrogen bonded 'head-to-tail' polymer as shown in Scheme 11.

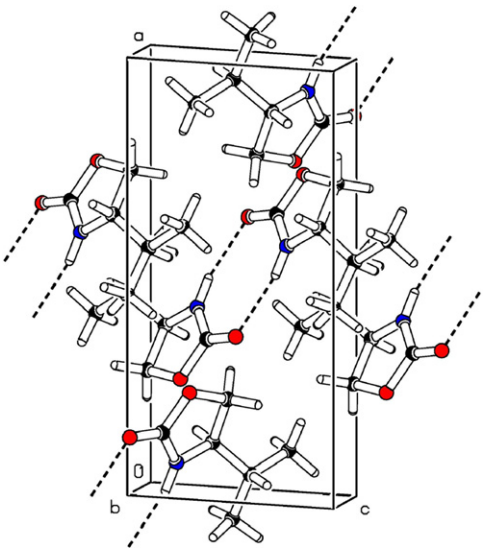
We performed the density functional perturbation theory (DFPT) calculations in order to investigate the possible origin of this difference in stability. This DFPT approach enables the change in electronic density generated in one molecule in response to the presence of another to be modelled. This particular methodology has also already been applied successfully to investigate the water dimer and crystalline silicon.[31] The computed total interaction energy



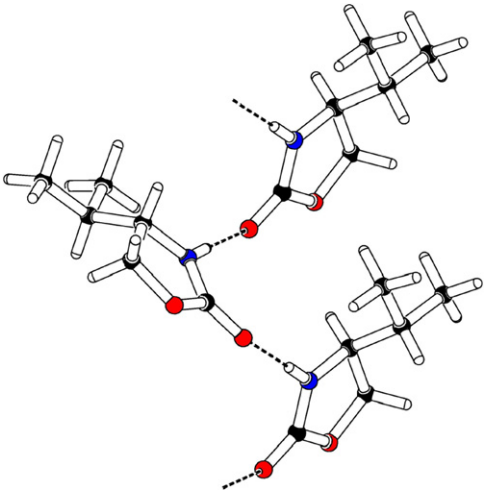
Scheme 8. Molecular structure of oxazolidin-2-one (*rac*)-**2**, showing the atom labelling scheme. Displacement ellipsoids are drawn at 25% probability level and the H atoms have been omitted.



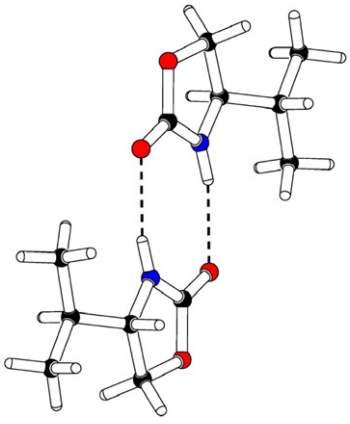
Scheme 9. Molecular structure of oxazolidin-2-one (*S*)-**2**, showing the atom labelling scheme. Displacement ellipsoids are drawn at 25% probability level and the H atoms have been omitted.



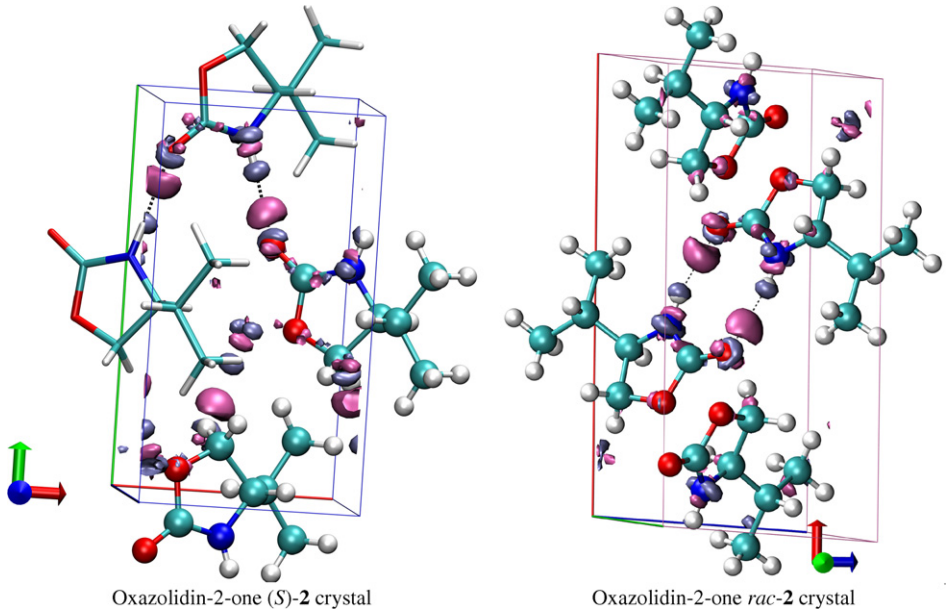
Scheme 10. A view along the *B*-axis of the unit cell of oxazolidin-2-one (*rac*)-**2**, showing the intermolecular C=O···H–N hydrogen bonding.



Scheme 11. Intermolecular C=O···H–N hydrogen bonding present in the unit cell of oxazolidin-2-one (*S*)-**2** [where (*S*)-**2** is hydrogen bonded to another molecule of (*S*)-**2** in a 'head-to-tail' arrangement].



Scheme 12. Intermolecular C=O···H–N hydrogen bonding present in the unit cell of oxazolidin-2-one (*rac*)-**2** [where (*S*)-**2** is hydrogen bonded to (*R*)-**2** and vice versa].



Scheme 13. Isosurface plots of the correction to the electronic density of the monomers upon formation of hydrogen bonds for the oxazolidin-2-one (*S*)-**2** crystal (left) and the racemic oxazolidin-2-one (*rac*)-**2** crystal (right). The blue zones correspond to regions where the electronic density is reduced and the purple zones to regions where the density in increased, compared to the non-interacting molecules. Note that the blue and purple zones enclose the same displaced charge in both cases.

per unit cell is −23.5 kcal/mol for oxazolidin-2-one (*S*)-**2** and −29.7 kcal/mol for the oxazolidin-2-one (*rac*)-**2**, or −5.88 kcal/mol and −7.43 kcal/mol per molecule, respectively, showing that the racemate crystal is energetically favoured. For both structures, we observed a significant displacement of the π electrons around to the amide bond (see correction-density plots in Scheme 13). This mechanism enables the molecules to shift their electronic density from the electron-rich nitrogen atom to the adjacent electron-deficient carbon, thus pushing the carbonyl oxygen to become more negative, whilst the amide proton becomes more positive. Interestingly, the cyclic arrangement observed for the racemate crystal seems to enhance the *co-operative* participation of the π electrons of the C═O bond, an effect that is barely seen in the *S*-only crystal. For the racemic crystal, this enables the carbonyl oxygen to accumulate more electron density, in response to the charge displacement created in the (H–)N–C(═O) bond, thus increasing the binding affinity with the amide proton of the neighbouring oxazolidin-2-one. This enhancement suggests that in the racemic case, there is a genuine communication between the hydrogen bond donating part of the oxazolidin-2-one and the hydrogen bond accepting part. In the case of the (*S*)-only crystal, the two parts of the molecule that participate in the hydrogen bonding are nearly independent and are much less reinforced by each others electronic re-arrangement.

3. Conclusion

In conclusion, we have reported the kinetic resolution of racemic 4-isopropyl-oxazolidin-2-one **2** using pentafluorophenyl 2-(4-isobutylphenyl)propionate (*S*)-**9** as the resolving component to give access to both enantiomers of the parent oxazolidin-2-ones (*R*)- and (*S*)-**2** in good yield. Assigning the enantiomeric purity and configuration of these oxazolidin-2-ones (*R*)- and (*S*)-**2** proved problematic as the specific rotation was found to be solvent and concentration dependent; in chloroform it was shown to be dextrorotatory $\{[\alpha]_D^{26} = +15.5$ (*c* 5.2, $CHCl_3)\}$, whereas in ethanol it was levorotatory $\{[\alpha]_D^{26} = -16.1$ (*c* 5.2, EtOH)}. Due to this unusual behaviour where, both specific rotations were of similar magnitude but opposite sign (for the rotation of the plane of plane polarised light), it is understandable that some literature assignments were incorrectly assigned,[27] and therefore stereochemically misleading when considering its nomenclature.[13] This type of solvent dependence on the sign of the specific rotation has been reported.[32–35] In certain cases, changes in the specific rotation occur through conformational effects due to H-bonding[36–38] and (de)-protonation processes have been reported.[39,40] The role of aggregates[41,42] and counter-ions[43] have also been shown to play a significant role. The nearest analogy to our study is that reported by Fueno[44] and Furstoss.[45] Fueno[44] has shown that the sign of the specific rotation for a conformationally rigid heterocycle, propylene oxide, can be changed from dextrorotatory (using hydrocarbon and organic solvents) to levorotatory when using water as the solvent. Whereas, Furstoss[45] has reported similar findings for α-methylstyrene when using either chloroform or acetone as the solvent.

4. Experimental

4.1. General

All solvents were distilled before use. All reactions were carried out under a nitrogen using oven-dried glassware. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography

(TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel 60F254 silica). Proton and carbon NMR spectra were recorded on a Bruker 400 MHz Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Infrared spectra were recorded on a Shimadzu 8300 FTIR spectrometer. Optical rotation was measured using an automatic AA-10 Optical Activity Ltd polarimeter with a cell of path length 2.5 cm. The samples (~20–30 mg) were prepared using 0.5 mL of the specified solvent.

4.2. Pentafluorophenyl 2-(4-isobutylphenyl)propionate (*S*)-9

2-(4-Isobutylphenyl)propionic acid (*S*)-**8** (2.03 g, 9.84 mmol) {$[\alpha]_D^{20} = +54.2$ (*c* 3.8, $CHCl_3$)} was added to a stirred solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (2.23 g, 10.82 mmol) in dichloromethane (10 mL). The resulting solution was stirred for 10 min. A solution of pentafluorophenol (1.81 g, 9.81 mmol) in dichloromethane (10 mL) was slowly added, and the resulting solution was stirred for 12 h. The resulting precipitate (*N*,*N*′-dicyclohexylurea) was filtered off (using suction filtration). Brine (10 mL) was added and the solution was extracted with dichloromethane (3 × 50 mL) and dried over $MgSO_4$. The combined organic layers were evaporated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)/diethyl ether (9:1) to give pentafluorophenyl 2-(4-isobutylphenyl)propionate (*S*)-**9** (3.55 g, 92%) as a colourless liquid; R_f [light petroleum (bp 40–60 °C)/diethyl ether (9:1)] 0.63; $[\alpha]_D^{26} = +91.7$ (*c* 29.6, $CHCl_3$) {for (*R*)-**9**; $[\alpha]_D^{26} = -91.4$ (*c* 5.0, $CHCl_3$)}; $\nu_{max}(CHCl_3)$ cm^{-1} 1782 (C=O); δ_H (400 MHz; $CDCl_3$) 7.26 (2H, dt, *J* 8.2 and 2.2, 2 × CH; Ar), 7.14 (2H, dt, *J* 8.2 and 2.2, 2 × CH; Ar), 4.04 (1H, q, *J* 7.2, ArC*H*CH_3), 2.46 (2H, d, *J* 7.2, CH_2Ar), 1.92–1.80 (1H, m, C*H*$(CH_3)_2$), 1.62 (3H, d, *J* 7.2, ArCH*C*H_3), 0.99 (3H, d, *J* 6.7, C*H*$_3^A$CHCH_3^B) and 0.88 (3H, d, *J* 6.7, CH_3^ACHC*H*$_3^B$); δ_C (100 MHz; $CDCl_3$) 170.3 (OC=O), 140.8 (*i*-C; Ar), 141.2 (142.92 and 139.42, 2C, ddt, $^1J_{C,F} = 251.3$ Hz, $^2J_{C,F} = 11.9$ Hz and $^3J_{C,F} = 4.2$ Hz, C(2)–F), 138.9 (140.18 and 137.66, 1C, dtt, $^1J_{C,F} = 253.2$ Hz, $^2J_{C,F} = 13.8$ Hz and $^3J_{C,F} = 3.8$ Hz, C(4)–F), 137.3 (138.61 and 136.08, 2C, dtdd, $^1J_{C,F} = 254.7$ Hz, $^2J_{C,F} = 14.5$ Hz, $^3J_{C,F} = 5.3$ and $^4J_{C,F} = 3.0$ Hz, C(3)–F), 135.5 (*i*-C; Ar), 129.1 and 126.7 (2 × CH; Ar), 124.7 (1C, tdt, $^2J_{C,F} = 14.2$ Hz, $^4J_{C,F} = 4.6$ Hz and $^3J_{C,F} = 2.3$ Hz, *i*-CO; OC_6F_5), 44.5 (*C*H_2Ar), 44.4 (ArCHCH_3), 29.7 (*C*H$(CH_3)_2$), 21.9 (CH$(CH_3)_2$) and 18.0 (ArCH*C*H_3); δ_F (378 MHz; $CDCl_3$) −152.6 (2 F, d, $^3J_{F,F}$ 18.5, F_{ortho}), −158.1 (1F, t, $^3J_{F,F}$ 20.8, F_{para}) and −162.4 (2 F, dd, $^3J_{F,F}$ 20.8 and 18.5, F_{meta}) (Found M^+, 372.1144; $C_{19}H_{17}F_5O_2$ requires M^+, 372.1143).

4.3. Kinetic resolution of racemic 4-isopropyl oxazolidin-2-one *rac*-2 using pentafluorophenyl 2-(4-isobutylphenyl) propionate (*S*)-9

n-BuLi (0.54 mL, 2.5 M in hexane, 1.34 mmol) was added to a stirred solution of 4-isopropyl oxazolidin-2-one (*rac*)-**2** (0.17 g, 1.34 mmol) in THF (10 mL) at −78 °C. After stirring for 1 h, a solution of (+)-pentafluorophenyl 2-(4-isobutylphenyl)propionate (*S*)-**9** (0.10 g, 0.27 mmol) in THF (1 mL) was added. The resulting mixture was stirred for 2 h at −78 °C. The reaction was quenched with water (10 mL). The organic layer was extracted with dichloromethane (3 × 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give two diastereoisomeric oxazolidin-2-one (*S*,*R*)-*syn*- and (*S*,*S*)-*anti*-**10** [*syn*-:*anti*-88:12—determined by 400 MHz ^{1}H NMR spectroscopy]. The crude mixture was purified by flash column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)/diethyl ether (7:3) to give 3-[2-(4-isobutylphenyl)propionyl]-4-isopropyl-oxazolidin-2-one (*S*,*S*)-*anti*-**10** (7 mg, 9%) as a colourless oil; R_f [light petroleum (bp 40–60 °C)/diethyl ether (1:1)] 0.77; $[\alpha]_D^{22} = +123.7$ (*c* 1.2, $CHCl_3$); $\nu_{max}(CHCl_3)$ cm^{-1} 1776 (C=O) and 1692 (C=O); δ_H (400 MHz; $CDCl_3$) 7.23 (2H, d, *J* 8.2, 2 × CH; Ar), 7.07 (2H, d, *J* 8.2, 2 × CH; Ar), 5.11 (1H, q, *J* 7.2, ArC*H*CH_3), 4.37–4.32 (1H, dt, *J* 7.2 and 3.8, *i*-PrC*H*N), 4.15–4.07 (2H, m, CH_2O), 2.46–2.39 (2H, m, CH_2Ar), 1.87–1.77 (1H, m, C*H*$(CH_3)_2$), 1.49 (3H, d, *J* 7.2, ArCHCH_3) and 0.92–8.86 (12H, m, 2 × CH$(CH_3)_2$); δ_C (100.6 MHz; $CDCl_3$) 174.9 (NC=O), 153.6 (OC=O), 140.6 (*i*-C; Ar), 137.5 (*i*-C; Ar), 129.3 and 127.8 (2 × CH; Ar), 63.1 (CH_2O), 59.0 (*i*-PrC*H*N), 45.1 (*C*H$(CH_3)_2$), 42.6 (Ar*C*HCH_3), 30.2 (CH_2), 28.6 (*C*H$(CH_3)_2$), 22.7 (*C*H$_3^A$CHCH_3^B; *i*-BuC_6H_4–), 22.4 (CH$_3^A$CH*C*H$_3^B$; *i*-BuC_6H_4–), 19.7 (*C*H$_3^A$CHCH_3^B; oxazolidin-2-one), 18.0 (CH$_3^A$CH*C*H$_3^B$; oxazolidin-2-one) and 14.7 (ArCH*C*H_3) (Found MH^+, 318.2062; $C_{19}H_{28}NO_3$ requires 318.2064); 3-[2′-(4-isobutylphenyl)propionyl]-4-isopropyl-oxazolidin-2-one (2*S*,4*R*)-*syn*-**10** (60 mg, 70%) as a colourless oil; R_f [light petroleum (bp 40–60 °C)/diethyl ether (1:1)] 0.55; $[\alpha]_D^{22} = +32.7$ (*c* 3.6, $CHCl_3$) {for (2*R*,4*S*)-*syn*-**10**; $[\alpha]_D^{22} = -33.0$ (*c* 1.2, $CHCl_3$)}; $\nu_{max}(CHCl_3)$ cm^{-1} 1778 (C=O) and 1699 (C=O); δ_H (400 MHz; $CDCl_3$) 7.23 (2H, d, *J* 8.2, 2 × CH; Ar), 7.03 (2H, d, *J* 8.2, 2 × CH; Ar), 5.11 (1H, q, *J* 6.9, ArC*H*CH_3), 4.50–4.44 (1H, dt, *J* 8.80 and 3.48, *i*-PrC*H*N), 4.21 (1H, t, *J* 8.6, C*H*$_A$H$_B$O), 4.07 (1H, dd, *J* 8.6 and 3.5, CH$_A$*H*$_B$O), 2.40 (2H, d, *J* 7.2, CH_2), 2.19–2.07 (1H, m, C*H*$(CH_3)_2$; oxazolidin-2-one), 1.87–1.75 (1H, m, C*H*$(CH_3)_2$; *i*-BuC_6H_4–), 1.44 (3H, d, *J* 6.9, ArCHCH_3), 0.85 (3H, d, *J* 6.7, CH_3; C*H*$_3^A$CHCH_3^B; *i*-BuC_6H_4–), 0.84 (3H, d, *J* 6.7, CH_3; CH$_3^A$CHC*H*$_3^B$; *i*-BuC_6H_4–), 0.76 (3H, d, *J* 6.9, C*H*$_3^A$CHCH_3^B; oxazolidin-2-one) and 0.38 (3H, d, *J* 6.9, CH$_3^A$CHC*H*$_3^B$; oxazolidin-2-one); δ_C (100.6 MHz; $CDCl_3$) 174.8 (NC=O), 153.5 (OC=O), 140.6 (*i*-C; Ar), 137.6 (*i*-C; Ar), 129.3 and 127.8 (2 × CH; Ar), 62.8 (CH_2O), 58.0 (*i*-PrC*H*N), 45.0 (*C*H$(CH_3)_2$), 42.9 (Ar*C*HCH_3), 30.2 (CH_2Ar), 27.8 (*C*H$(CH_3)_2$; oxazolidin-2-one), 22.7 (*C*H$_3^A$CHCH_3^B; *i*-BuC_6H_4–), 22.3 (CH$_3^A$CH*C*H$_3^B$; *i*-BuC_6H_4–), 18.5 (*C*H$_3^A$CHCH_3^B; oxazolidin-2-one), 17.7 (CH$_3^A$CH*C*H$_3^B$; oxazolidin-2-one) and 14.0 (ArCH*C*H_3) (Found M^+, 317.1979; $C_{19}H_{27}NO_3$ requires M^+, 317.1985); and 4-isopropyl-oxazolidin-2-one (*S*)-**2** (0.11 g, 64%) as a white solid; R_f [diethyl ether] 0.30; mp 64–66 °C (~16% ee); {$[\alpha]_D^{22} = +2.6$ (*c* 4.8, $CHCl_3$) (which equates to ~16% ee by specific rotation and ~16% ee using a chiral shift reagent)}.[5]

4.4. Synthesis of 4-isopropyl-oxazolidin-2-one (*S*)-2

Potassium carbonate (0.28 g, 2.02 mmol) was added to a stirred solution of L-valinol (2.0 g, 20.7 mmol) in diethylcarbonate (4.76 g, 4.88 mL, 40.33 mmol) in a 50 mL round bottom flask. A short-path distillation apparatus was connected to this flask and the resulting solution was heated to 130 °C for 3 h. The residue was purified by aqueous extraction into dichloromethane (3 × 50 mL) using brine (50 mL) to give the oxazolidin-2-one (*S*)-**2** (2.01 g, 80%) as a white crystalline solid; R_f [diethyl ether] 0.30; mp 67–70 °C; $[\alpha]_D^{22} = +15.6$ (*c* 3.0, $CHCl_3$)] and $[\alpha]_D^{22} = -17.4$ (*c* 2.4, EtOH)]; $\nu_{max}(CHCl_3)$ cm^{-1} 3263 (N–H) and 1751 (C=O); δ_H (400 MHz; $CDCl_3$) 6.78 (1H, br s, NH), 4.37 (1H, t, *J* 8.6, CH_AH_BO), 4.04 (1H, dd, *J* 8.6 and 6.4, CH_AH_BO), 3.55 (1H, br dt, *J* 8.6 and 6.4, CHN), 1.65 (1H, appears as an octet, *J* 6.8, $CH(CH_3)_2$), 0.90 (3H, d, *J* 6.6, $CH_3^ACHCH_3^B$) and 0.83 (3H, d, *J* 6.8, $CH_3^ACHCH_3^B$); δ_C (100 MHz; $CDCl_3$) 160.2 (C=O), 68.6 (CH_2O), 58.4 (*i*-PrCHN), 32.7 ($CH(CH_3)_2$), 18.0 and 17.7 ($2 \times CH_3$; $CH(CH_3)_2$) (Found MH^+, 130.0880; $C_6H_{12}NO_2$ requires MH^+, 130.0868).

4.5. Synthesis of 4-isopropyl-oxazolidin-2-one (*R*)-2

Under the same conditions as described above, D-valinol (2.0 g, 20.17 mmol) and potassium carbonate (0.28 g, 2.02 mmol) in diethylcarbonate (4.76 g, 4.88 mL, 40.33 mmol) gave the oxazolidin-2-one (*R*)-**2** (2.34 g, 90%) as a white crystalline solid; R_f [diethyl ether] 0.30; mp 67–70 °C; $[\alpha]_D^{22} = -13.1$ (*c* 4.2, $CHCl_3$)] and $[\alpha]_D^{22} = +15.0$ (*c* 2.8, EtOH)] (Found MH^+, 130.0880; $C_6H_{12}NO_2$ requires MH^+, 130.0868), which was spectroscopically identical to that obtained previously.

4.6. Stereospecific coupling of 4-isopropyloxazolidin-2-one (*S*)-2 with pentafluorophenyl 4-isobutylphenylpropionate (*S*)-9

n-BuLi (0.41 mL, 2.5 M in hexane, 1.02 mmol) was added to a stirred solution of 4-isopropyl-oxazolidin-2-one (*S*)-**2** (0.12 g, 0.93 mmol) in THF (10 mL) at −78 °C. After stirring for 1 h, a solution of pentafluorophenyl 2-(4-isobutylphenyl)propionate (+)-(*S*)-**9** (0.34 g, 0.93 mmol) in THF (1 mL) was added. The resulting mixture was stirred for 2 h at −78 °C. The reaction was quenched with water (10 mL). The organic layer was extracted with dichloromethane (3 × 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the diastereoisomerically pure oxazolidin-2-ones (*S*,*S*)-*anti*-**10** [*syn*-:*anti*- > 98:2—determined by 400 MHz ^1H NMR spectroscopy]. The crude mixture was purified by flash column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)/diethyl ether (7:3) to give 3-[2′-(4-isobutylphenyl)propionyl]-4-isopropyl-oxazolidin-2-one (2*S*,4*S*)-*anti*-**10** (0.19 mg, 64%) as a colourless oil; R_f [light petroleum (bp 40–60 °C)/diethyl ether (1:1)] 0.64; $[\alpha]_D^{22} = +108.9$ (*c* 9.7, $CHCl_3$) (Found MH^+, 318.2062; $C_{19}H_{28}NO_3$ requires 318.2064); which was spectroscopically identical to that obtained previously.

4.7. Stereospecific coupling of 4-isopropyloxazolidin-2-one (*R*)-2 with pentafluorophenyl 4-isobutylphenylpropionate (*S*)-9

Under the same conditions as described above, *n*-BuLi (0.40 mL, 2.5 M in hexane, 1.00 mmol), 4-isopropyl-oxazolidin-2-one (*R*)-**2** (0.117 g, 0.91 mmol) and pentafluorophenyl 2-(4-isobutylphenyl)propionate (+)-(*S*)-**9** (0.34 g, 0.91 mmol), gave after purification by column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)/diethyl ether (7:3) the oxazolidin-2-one (2*S*,4*R*)-*syn*-**10** (0.171 g, 59%) as a colourless oil; R_f [light petroleum (bp 40–60 °C)/diethyl ether (1:1)] 0.33; $[\alpha]_D^{22} = +31.5$ (*c* 8.4, $CHCl_3$) {for (2*R*,4*S*)-*syn*-**10**; $[\alpha]_D^{22} = -33.0$ (*c* 1.2, $CHCl_3$)} (Found M^+, 317.1979; $C_{19}H_{27}NO_3$ requires M^+, 317.1985); which was spectroscopically identical to that obtained previously.

4.8. X-ray crystallographic data and structure determination

For 4-isopropyl-oxazolidin-2-one *rac*-**2**: the intensity data were collected on an Enraf Nonius CAD-4 diffractometer using Mo Kα radiation (λ 0.71069 Å) with an ω-2θ scan at 160 K. The unit cell parameters were determined by least-squares refinement on diffractometer angles $9.277 \leqslant \theta \leqslant 13.361°$ for 25 automatically centred reflections.[46]

4.9. Crystallographic data for 4-isopropyl-oxazolidin-2-one *rac*-2

$C_6H_{11}NO_2$, M_r 129.16, monoclinic, space group $P21/n$, $a = 12.223(9)$ Å, $b = 10.177(9)$ Å, $c = 5.777(7)$ Å, $\alpha = 90°$, $\beta = 93.75(7)°$, $\gamma = 90°$, $V = 717.1(12)$ Å^3, $Z = 4$, D_{ca} 1.196 Mg m^{-3}, $\mu = 0.090$ mm^{-1}, $F(000) = 280$. Data were collected using a crystal of size $0.40 \times 0.20 \times 0.10$ mm^3. A total of 1429 reflections were collected for $2.61° < \theta < 24.99°$ and $-6 \leqslant h \leqslant 14$, $-4 \leqslant k \leqslant 12$, $0 \leqslant l \leqslant 6$. There were 1245 independent reflections [$R_{int} = 0.0120$] with full-matrix least squares on F^2 used in the refinement. The final *R* indices were [$I > 2\sigma(I)$] $R_1 = 0.0696$, $wR_2 = 0.1796$; (all data) $R_1 = 0.1320$, $wR_2 = 0.2138$. The largest difference peak and hole were 0.427 and −0.224 e Å^{-3}.

4.10. X-ray crystallographic data and structure determination

For 4-isopropyl-oxazolidin-2-one *rac*-**2**: the intensity data were collected on an Enraf Nonius CAD-4 diffractometer using Mo Kα radiation (λ 0.71073 Å) with an ω-2θ scan at 160 K. The unit cell parameters were determined by least-squares refinement on diffractometer angles $2.64 \leqslant \theta \leqslant 24.95°$ for 25 automatically centred reflections.[46]

4.11. Crystallographic data for 4-isopropyl-oxazolidin-2-one (*S*)-2

$C_6H_{11}NO_2$, M_r 129.16, orthorhombic, space group $P2_12_12_1$, $a = 5.607(3)$ Å, $b = 10.149(5)$ Å, $c = 11.907(8)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 677.6(7)$ Å^3, $Z = 4$, D_{ca}

1.266 Mg m^{-3}, $\mu = 0.095$ mm^{-1}, $F(000) = 280$. Data were collected using a crystal of size $1.13 \times 0.38 \times 0.30$ mm^3. A total of 1465 reflections were collected for $2.64° < \theta < 24.95°$ and $-6 \leqslant h \leqslant 6$, $-12 \leqslant k \leqslant 12$, $-14 \leqslant l \leqslant 14$. There were 1186 independent reflections [$R_{int} = 0.0127$] with full-matrix least squares on F^2 used in the refinement. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.0389$, $wR_2 = 0.1024$; (all data) $R_1 = 0.0401$, $wR_2 = 0.1034$. The largest difference peak and hole were 0.296 and -0.227 e Å^{-3}.

All data were corrected for absorption by semi-empirical methods (ψ scan)[47] and for Lorentz-polarisation effects by XCAD4.[48] The structure was solved by direct method using SHELXS-97,[49] and refined anisotropically (non-hydrogen atoms) by full-matrix least-squares on F^2 using the SHELXL-97 program.[49] The H atoms were calculated geometrically and refined with a riding model. The program ORTEP-35[50] was used for drawing the molecules. WINGX6[51] was used to prepare material for publication. The data relating to the single crystal X-ray structures of (*S*)- and (*rac*)-**2** have been deposited at the Cambridge Crystallographic Database {CCDC reference numbers 679810 [for (*S*)-**2**] and 679811 [for *rac*-**2**]}.

4.12. Computational method

The theoretical modelling was performed using density functional theory as implemented in the CPMD *ab initio* pseudopotential plane-wave package.[52] We used the gradient-corrected Perdew-Burke-Ernzerhof (PBE) exchange and correlation functional,[53] a plane-wave cut-off energy of 100Ry, and Goedecker norm-conserving pseudopotentials[54,55] for each atom in the system. The atomic coordinates and cell parameters for both racemic and *S*-only crystals were taken from the X-ray structure without further optimisation. The density functional perturbation theory calculations were performed using a parallel implementation of the method described in Ref. 30. All calculations were performed on a cluster of Apple X-Serve computers at Queen Mary, University of London.

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30. This solvent effect has also been shown to occur for 4-phenylmethyl oxazolidin-2-one (derived from phenylalanine): (*R*)-enantiomer $[\alpha]_D^{26} = +35.0$ (*c* 5.4, $CHCl_3$) and $[\alpha]_D^{26} = -3.9$ (*c* 4.4, EtOH), whereas, (*S*)-enantiomer $[\alpha]_D^{26} = -37.3$ (*c* 5.0, $CHCl_3$); $[\alpha]_D^{26} = +4.8$ (*c* 4.0, EtOH). The specific rotation appears to be concentration dependent (*R*)-enantiomer $[\alpha]_D^{26} = +68.7$ (*c* 1.2, $CHCl_3$) and (*S*)-enantiomer $[\alpha]_D^{26} = -57.3$ (*c* 1.2, $CHCl_3$). Whereas, for related oxazolidin-2-ones such as 4-phenyl-oxazolidin-2-one {(*R*)-enantiomer $[\alpha]_D^{26} = -40.9$ (*c* 3.0, $CHCl_3$) and $[\alpha]_D^{26} = -55.5$ (*c* 3.8, EtOH),} and 4-methyl-5-phenyl-oxazolidin-2-one {(4*R*,5*S*)-enantiomer $[\alpha]_D^{26} = +156.8$ (*c* 4.0, $CHCl_3$) and $[\alpha]_D^{26} = +107.3$ (*c* 3.4, EtOH)} no change of sign occurred.
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