Organic & Biomolecular Chemistry

RSC Publishing

PAPER

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Cite this: *Org. Biomol. Chem.*, 2013, **11**, 7877

The development of highly active acyclic chiral hydrazides for asymmetric iminium ion organocatalysis†

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Received 22nd August 2013,
Accepted 27th September 2013

DOI: 10.1039/c3ob41719k

www.rsc.org/obc

Double asymmetric induction has been employed as a tool to optimise pyrazolidinone-derived organocatalysts for the asymmetric iminium ion catalysed Diels–Alder reaction. Mechanistic studies revealed a superior hydrazide catalyst deriving from methanolysis of the chiral pyrazolidinone precursor. This catalyst displays unusually high *endo* diastereoselectivity and good enantioselectivity with a range of β-arylenals and cyclic dienes at catalyst loadings as low as 1 mol%.

Introduction

Iminium ion-mediated organocatalysis represents a rapidly maturing area of research, beginning with the seminal work of MacMillan in 2000.[1] Within the field, the recurring catalytic motif is that of a secondary amine constrained within a five-membered ring and,[2] although often displaying outstanding levels of enantioselectivity, most reactions require relatively high catalyst loadings (>10 mol%)[3] and extended reaction times (>24 h).[1,4,5] Acyclic iminium ion catalysts have the potential to overcome the limited reactivity of their cyclic counterparts by decreasing the steric hindrance around the reactive centre.[6] Tomkinson *et al.* first demonstrated this reactivity benefit when they showed that acyclic acyl hydrazides, such as **1**, acted as highly reactive iminium ion organocatalysts in Diels–Alder reactions.[7] Subsequently Ogilvie and co-workers introduced the first asymmetric (cyclic) hydrazide catalyst **2**, derived from camphor (Fig. 1).[5] The enantioselectivity was optimised by the addition of an additional exocyclic stereodirecting group that served to rigidify the catalyst and thus control the iminium ion geometry. Lee[8] and Langlois[9] later reported related sulfonyl hydrazides, with Lee further developing primary sulfonyl hydrazide catalyst **3** for the cycloaddition of ketones.[10] More recently Suzuki *et al.* reported the first acyclic chiral hydrazide organocatalyst **4** that displayed good reactivity and enantioselectivity (though typically modest diastereocontrol) in Diels–Alder reactions at 5 mol% catalyst loading (up to 96% ee, *endo* product).[11] Ishihara and co-workers have also reported primary amine acyclic catalysts specifically for the Diels–Alder reaction of demanding α-substituted acroleins.[12]

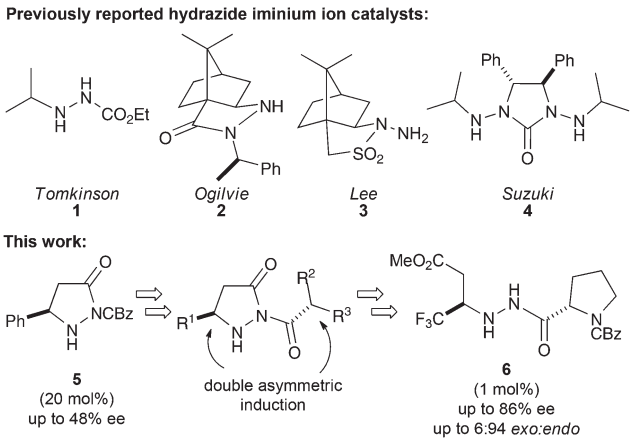

Fig. 1 New hydrazide iminium ion organocatalysts.

We have previously reported one example of pyrazolidinones acting as iminium ion organocatalysts in Diels–Alder cycloadditions with modest induced enantioselectivity.[13] Building upon these studies, we now report our efforts towards an improved asymmetric variant, employing the concept of double asymmetric induction as a tool in catalyst design (Fig. 1). These studies led from initial catalyst **5** to the discovery of catalytically efficient acyclic hydrazide organocatalyst **6** that displays an unusual *endo* diastereoselectivity preference as

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†Electronic supplementary information (ESI) available: Spectroscopic details for all novel compounds. Supplementary crystallographic data available for compounds **6**, **11**, **17**, **18**, **19**, **20**, **21**, and **29**. CCDC 915107, 956166, 956167, 956168, 956169, 956170, 956171, and 925705. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41719k

well as good enantioselectivity (up to 86% ee) in the Diels–Alder reaction of β-arylenals with dienes at catalyst loadings as low as 1 mol%.

Results and discussion

Catalyst synthesis and evaluation

Following our previously reported synthetic approach, a broad range of catalyst structures could be accessed *via* a single straightforward synthetic protocol (Fig. 2). The appropriate α,β-unsaturated ester can be condensed with hydrazine to generate the desired pyrazolidinone, followed by regioselective amide coupling with an enantiomerically pure acid to give diastereoisomeric products that are readily separated by either chromatography or recrystallisation.[13]

Initially, diastereoisomeric pyrazolidinone catalysts bearing a stereogenic C(5)-phenyl substituent were synthesised by this method and screened as potential catalysts for the Diels–Alder reaction of cinnamaldehyde and cyclopentadiene (Table 1). (*R*)-Mandelic acid derived catalyst **7** shows an improvement in ee over both **5** and its diastereoisomer **8**, the (5*S*,2′*R*) configuration leading to a synergistic enhancement of stereoselectivity (entries 1–3). *O*-Methyl protected analogues **9** and **10** displayed the same trends with marginally enhanced stereoselectivity (entries 4 and 5). More prominent structural changes to the acyl unit were also well tolerated, with (*S*)-naproxen derived catalyst **12** displaying moderate enantioselectivity when matched with the (5*S*)-pyrazolidinone configuration (entry 7 superior to entry 6). However, superior stereocontrol came from incorporation of a CBz-protected proline, yielding catalysts **13** and **14**, with (5*R*)-configured **14** giving the better enantioselectivity of the two (entries 8 and 9). Catalysts **13** and **14** were also significant in that they displayed little or no *exo* diastereoselectivity compared to the other catalysts tested.

The influence of the pyrazolidinone C(5)-stereodirecting group was next explored using a common (*S*)-naproxen-derived acyl unit (Table 2). Again, for each diastereoisomeric pair a superior ee was observed with the 'matched' combination of stereocentres. Nonetheless, the incorporation of a *tert*-butyl (entries 1 and 2) or benzyl stereodirecting group (in analogy to the imidazolidinone catalysts of the MacMillan group, entries 3 and 4),[1] gave no selectivity benefit compared to a phenyl substituent (see Table 1). The highest overall enantioselectivity came when a (5*S*)-trifluoromethyl group was present with (2*S*)-products produced in 61% (*exo*) and 71% (*endo*) ee (entry 6). Alternatively the *gem*-dimethyl catalyst **21** allowed us to examine the extent of enantioinduction in the absence of a C(5)-pyrazolidinone stereodirecting group, with the poor ee's observed (13% *exo* and 27% *endo*) illustrating the value of a second, suitably matched stereodirecting group (entry 7). Again, diastereoselectivity was generally similar across the series with a small *exo* preference for all but trifluoromethyl catalyst **20** which displayed modest *endo* preference (46 : 54 *exo* : *endo*, entry 6).

With these results in hand, the diastereoisomeric catalysts **22** and **23** that combined a C(5)-trifluoromethyl substituent with an *N*-carboxyproline unit were prepared and evaluated (Fig. 3). Unsurprisingly, "matched" catalyst **23** proved the more

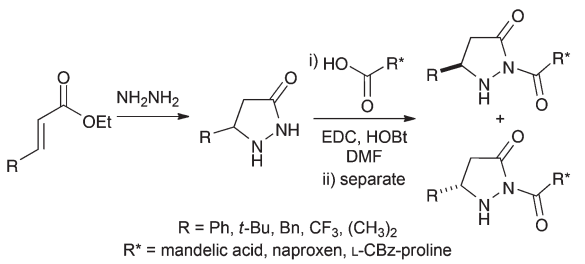
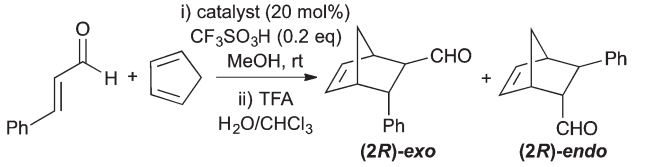
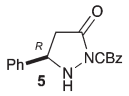
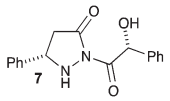
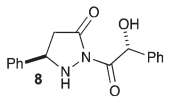
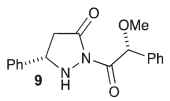
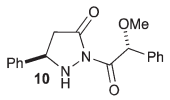
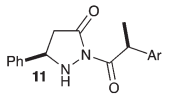
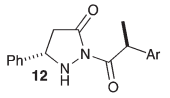
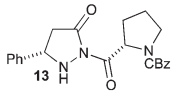
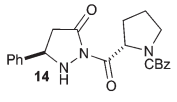


Fig. 2 Route to diastereoisomeric catalysts.

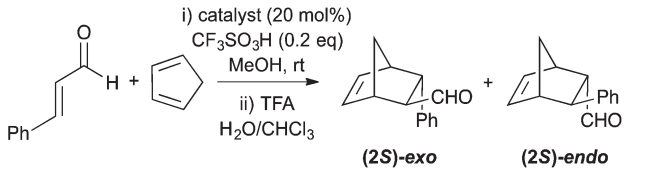
Table 1 Initial diastereoisomeric catalyst screen

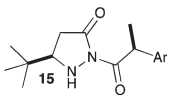
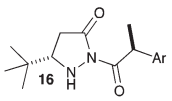
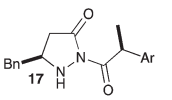
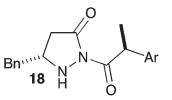
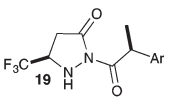
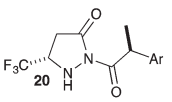
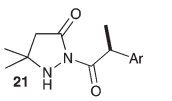


Entry	Catalyst	Yield (%)	*exo* : *endo*	*exo* % ee	*endo* % ee
1		89	66 : 34	48	28
2		82	62 : 38	54 (*ent*)	45 (*ent*)
3		86	62 : 38	28	22
4		77	67 : 33	63 (*ent*)	44 (*ent*)
5		81	65 : 35	33	31
6		69	66 : 34	26	<5
7		71	58 : 42	45 (*ent*)	52 (*ent*)
8		82	56 : 44	27 (*ent*)	18
9		80	50 : 50	57	67

Ar = 6-methoxynaphthalen-2-yl.

Table 2 Variation in enantioselectivity with change in stereodirecting group at C(5)[14]



Entry	Catalyst	Yield (%)	*exo* : *endo*	*exo* % ee	*endo* % ee
1		93	59 : 41	13	30
2		74	53 : 47	42	40
3		82	63 : 37	33	44
4		95	58 : 42	39	49
5		88	51 : 49	3	32
6		79	46 : 54	61	71
7		69	56 : 44	13	27

Ar = 6-methoxynaphthalen-2-yl.

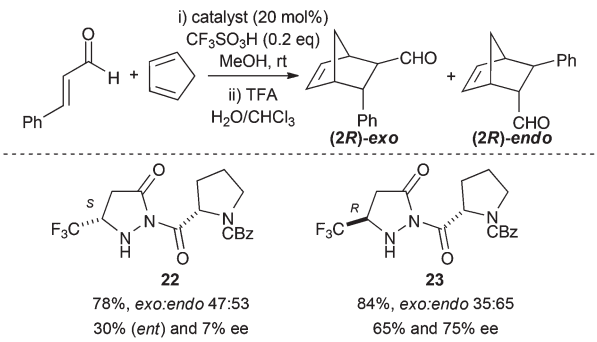


Fig. 3 Screening of optimised catalyst **20** and its diastereoisomer **19**.

enantioselective of the two compounds giving the (2*R*)-products in 65% (*exo*) and 75% (*endo*) ee. Interestingly, the catalyst proved to be significantly *endo* diastereoselective (35 : 65 *exo* : *endo*), an unusually high selectivity in comparison with the majority of other known iminium ion organocatalysts.[15] For this reason, combined with the high observed enantioselectivity, catalyst **23** was selected for further study.

Mechanistic insights

We next investigated the stability of catalyst **23** under the reaction conditions; **23** was treated with triflic acid (1 eq.) in CD_3OD and the reaction monitored by ^{19}F NMR spectroscopy (Fig. 4). Interestingly, **23** underwent rapid competitive methanolysis (orange line, $t^{1/2}$ 1.2 h) at both the C(3) and N(2) carbonyl groups, giving compounds **6** (red line) and **24** (blue line) respectively. Further breakdown of **6** to give **25** was not observed, but subsequent *in situ* methanolysis of **24** did lead to hydrazide **25** (green line).[16,17]

This complex product distribution led us to question the dominant catalytic species present in the iminium ion mediated process utilising catalyst **23** and other pyrazolidinone catalysts and so we attempted to isolate and evaluate these intermediates. Acyclic hydrazides **6**, **26** and **27** were prepared by acid-mediated methanolysis of their respective pyrazolidinones and tested in catalysis along with racemic pyrazolidinone **24** (Table 3). Isolated catalyst **6** gave superior enantioselectivity to **23** at standard 10 mol% catalyst loading but, more significantly, also at a low 1 mol% loading while maintaining good catalytic activity (Table 3, entries 1 and 2).[18] By contrast, another catalyst degradation product, racemic pyrazolidinone **24**, displayed very limited catalytic activity with only 82% conversion reached after an extended time (24 h) and giving products with no diastereoselectivity (entry 4). Alternative hydrazides **26** and **27** were both catalytically active at 1 mol% loading and gave modest improvements in enantioselectivity over their cyclic precursors (entries 5 and 6). Catalyst **27** in particular gave similar enantioselectivities to **6** though with markedly less diastereocontrol. In order to compare catalysts **23** and **6** in the absence of interconversion, the reaction solvent was changed to non-nucleophilic DMF. While both catalysts showed reduced reactivity compared with their respective reactions in

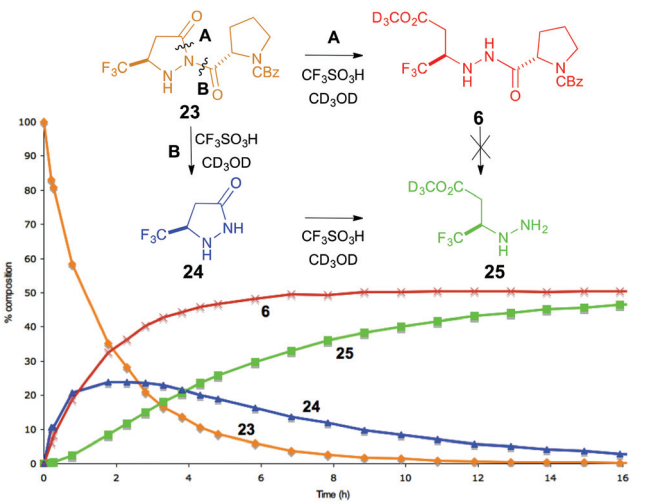
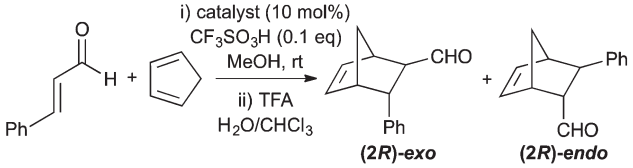
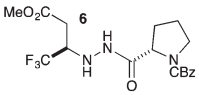
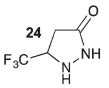
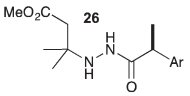
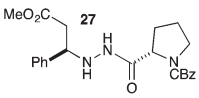
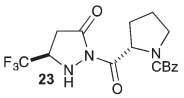


Fig. 4 Triflic acid-mediated methanolysis of **23** as monitored by ^{19}F NMR spectroscopy.[14,17]

Table 3 Testing of methanolysis products of **23** using both methanol and DMF as solvent



Entry	Catalyst	Solvent	Yield (%)	*exo* : *endo*	*exo* % ee	*endo* % ee
1	 **6**	MeOH	81	37 : 63	62	81
2[a]		MeOH	71	35 : 65	60	79
3[a]		DMF	40	41 : 59	57	69
4	 **24**	MeOH	82[b]	50 : 50	n/a	n/a
5[a]	 **26**	MeOH	41	61 : 39	27 (*ent*)	43 (*ent*)
6[a]	 **27**	MeOH	83	45 : 55	63	77
7	 **23**	DMF	25	45 : 55	21	38

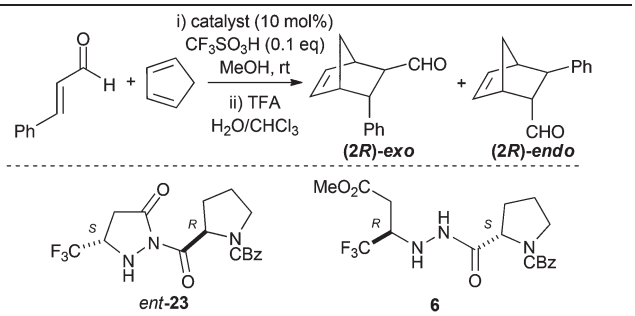
Ar = 6-methoxynaphthalen-2-yl. [a] 1 mol% catalyst loading (0.01 eq. triflic acid). [b] % conversion after 24 h.

methanol, catalysis by 10 mol% **23** was particularly sluggish, with only 25% yield and significantly lower enantioselectivities after extended reaction time (48 h, entry 7). By comparison, just 1 mol% of catalyst **6** gave superior yield after 24 h (40%), while maintaining reasonable enantioselectivity (entry 3).

To compare the catalytic activities of **6** and **23** under catalytically relevant conditions, competition experiments in methanol utilising varying mixtures of **6** and *ent*-**23** were undertaken (amounting to 10 mol% in total) to catalyse the model cycloaddition (Table 4). With each catalyst favouring the opposite product enantiomers, the observed ee of the products serves as a partial measure of the relative reaction rates of the two species (although *ent*-**23** inevitably undergoes *in situ* ring-opening during the experiments, leading to formation of *ent*-**6**). Notably at both 5 : 5 and 9 : 1 ratios of *ent*-**23** : **6**, the (2*R*)-enantiomer of the *endo* product is still favoured (68% and 50% ee respectively, entries 2 and 3) indicating the dominance of **6** as a catalyst, even at 9 times lower concentration than catalytic species arising from *ent*-**23**.

As a final comparison, the rate of *exo* and *endo* product formation (as the di-CD_3 acetals) in d_4-methanol under catalysis by **23** (4 mol%, orange line) and **6** (2 mol%, red line) was monitored by ^{1}H NMR spectroscopy (Fig. 5).[19] The rate of product formation with catalyst **6** was appreciably faster compared to **23** after 256 min (4.27 h), reaction with 4 mol% **23** having reached 76% conversion whereas 2 mol% **6** gave 75% conversion in just 98 min (1.63 h). These studies as a whole indicate that **23** itself is not an effective catalyst for this transformation and that the principle active species when **23** is employed is in fact acyclic **6**.

Table 4 Competition experiments between *ent*-**23** and **6**



Entry	*ent*-**23** : **6** (mol%)	Yield (%)	*exo* : *endo*	*endo* % ee
1	0 : 10	81	37 : 63	81
2	5 : 5	93	38 : 62	68
3	1 : 9	95	37 : 63	50

With regards to the origin of enantiocontrol, iminium ion salt **28**, derived from the combination of **6** and cinnamaldehyde, was successfully isolated and characterised (Fig. 6a). Although we have been unable to obtain an X-ray crystal structure of **28**, nOe spectroscopic analysis in d_3-acetonitrile indicated a *Z*-geometry in the key carbon–nitrogen double bond. A racemic iminium ion derived from ring-opened **5** (compound

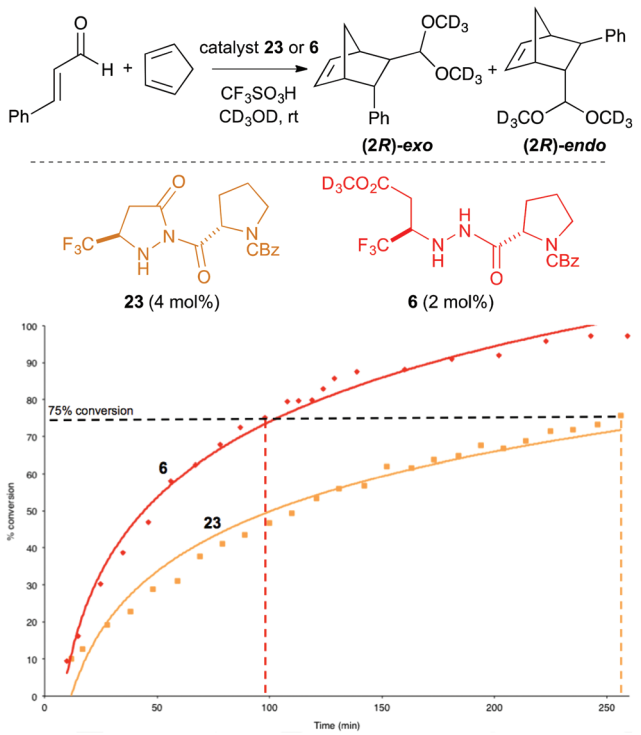


Fig. 5 Graph of % conversion (against standard) *vs.* time (min) for Diels–Alder reactions catalysed by **6** (red) and **23** (orange).

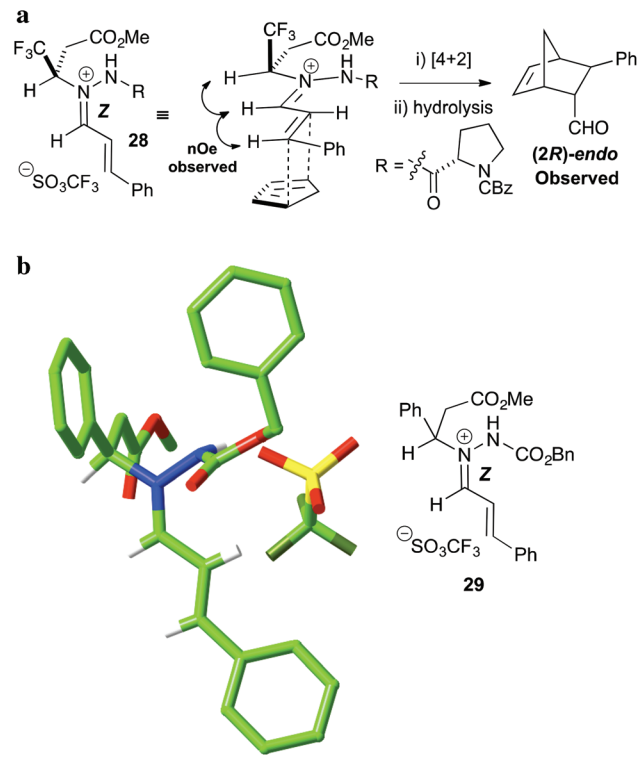


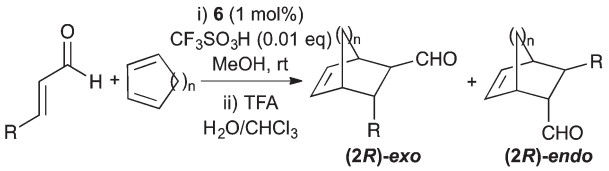
Fig. 6 (a) Key nOe correlations for iminium ion **28**.[14] (b) Crystal structure of compound **29**.

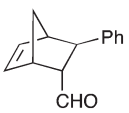
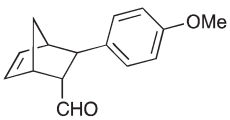
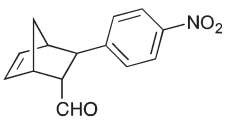
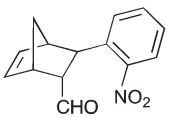
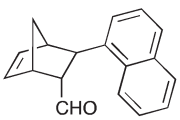
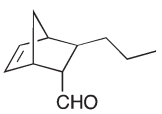
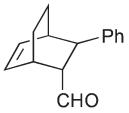
29) was successfully crystallised and this was also found to display a *Z*-configuration in the C=N bond in both the solution and solid phase (Fig. 6b). Such a geometry is consistent with reaction upon the *Re* face of the dienophile, *anti* to the trifluoromethyl stereodirecting group (as drawn) leading to the observed (2*R*)-enantioselectivity in the cycloaddition products.

Substrate scope

Finally, the substrate scope of catalyst **6** at low catalyst loadings (1–5 mol%) was explored, initially by changing the β-substituent of the enal (Table 5). Catalysis using **6** tolerated a range of β-aryl substituted enals, including electron-donating and withdrawing groups while maintaining good ee and *endo* diastereoselectivity (entries 1–3). *ortho*-Substitution on the aromatic ring was also tolerated with high *endo* selectivity (entries 4 and 5), however, more modest enantioselectivities were observed

Table 5 Diels–Alder reactions catalysed by **6**



	Product	Yield (%)	*exo* : *endo*	*exo* % ee	*endo* % ee
1		71	35 : 65	60	79
2[a]		86	36 : 64	71	86
3[b]		91	36 : 64	62	75
4[b]		78	15 : 85	67	83
5		83	21 : 79	62	81
6		90	31 : 69	38	54
7[c]		43	6 : 94	—	85

[a] Reaction run at 5 °C. [b] 5 mol% catalyst loading.[20] [c] 10 mol% catalyst (0.1 eq. triflic acid), yield is for *endo* product only.

with an aliphatic aldehyde (entry 6). Further studies allowed extension of this protocol to other dienes, with the reaction of cinnamaldehyde and cyclohexadiene giving the *endo* product in 85% ee (entry 7). Notably, the successful organocatalysed Diels–Alder reaction of these two components has not been reported previously and cannot be realised with MacMillan's first or second-generation imidazolidinone catalysts.[21,22]

Conclusions

In summary, double asymmetric induction was used to maximise the enantioselectivity of a series of chiral pyrazolidinones in the iminium ion catalysed Diels–Alder reaction. Subsequent investigations on optimised structure **23** led to the discovery that acyclic hydrazide **6** represented the active catalytic species, giving Diels–Alder products with preferential *endo* diastereoselectivity and good enantioselectivity (up to 86% ee). Current investigations are focused on other uses of pyrazolidinones and hydrazides in asymmetric catalysis.

The authors acknowledge the Royal Society for a URF (ADS), MSD (Case award to EG) and the EPSRC National Mass Spectrometry Service Centre (Swansea).

Experimental

General experimental

For general experimental details see ESI.† The ESI also contains spectroscopic data for compounds **6–8**, **11–23** and **25–29**.

General procedure A: amide coupling of pyrazolidin-3-one to a chiral acid. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1 eq.), 1-hydroxybenzotriazole (1 eq.) and the appropriate chiral acid (1 eq.) were combined in DMF (0.1 M) and stirred at room temperature for 15 minutes. The appropriate pyrazolidin-3-one (1 eq.) was then added and the resultant solution stirred at rt overnight. The reaction mixture was then concentrated *in vacuo* and the resultant residue taken up in dichloromethane, washed twice with 0.1 M hydrochloric acid solution followed by single washes with saturated sodium bicarbonate solution and brine before being dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure B: screening of aldehyde substrates with catalyst 6. Catalyst **6** (X mol%) was suspended in a solution of triflic acid (X mol%) in methanol. After 2 min of stirring, the appropriate aldehyde (1 eq.) was added, followed by a further 15 min of stirring. Cyclopentadiene (3 eq.) was then added and the resulting mixture left to stir at the appropriate temperature overnight. The reaction mixture was concentrated *in vacuo* then hydrolysed in a chloroform (2 mL), water (1 mL), trifluoroacetic acid (1 mL) mixture for 2 h. Saturated sodium hydrogen carbonate solution (20 mL) was then added and the resulting biphasic mixture extracted with chloroform (2 × 20 mL). The combined organic layer were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure C: acetalisation of products with (+)-(*R*,*R*)-hydrobenzoin. Following the method of Fujioka *et al.*,[23] to a suspension of aldehyde (1 eq.) in toluene (0.1 M) was added (+)-(*R*,*R*)-hydrobenzoin (1.1 eq.) and tosic acid (20 mol%) and the resulting mixture stirred at room temperature until reaction was complete by TLC analysis. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (×3). The combined organic layer were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Screening of catalysts in Diels–Alder reaction of (*E*)-cinnamaldehyde and cyclopentadiene. To a suspension of catalyst (20 mol%, 0.378 mmol) in methanol (2 mL) was added triflic acid (35.0 μl, 0.378 mmol). After 2 min of stirring, (*E*)-cinnamaldehyde (0.240 mL, 1.89 mmol) was added, followed by a further 5 min of stirring. Cyclopentadiene (370 mg, 5.60 mmol) was then added and the resulting mixture left to stir at rt. Reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated *in vacuo* then worked-up as in general procedure B. The crude material was purified by column chromatography, eluting with 5% diethyl ether in petrol to yield the cycloaddition products as an inseparable mixture of *exo* and *endo* diastereoisomers, with spectroscopic data in accordance with the literature.[7] Enantiomeric excesses were determined by acetalisation with (+)-(*R*,*R*)-hydrobenzoin following general procedure C and ^{1}H NMR analysis: (500 MHz, C_6D_6) *exo* isomers δ 5.74 (d, *J* 4.8, C*H*O_2, 2*R*) and 5.72 (d, *J* 5.8, C*H*O_2, 2*S*), *endo* isomers δ 5.37 (d, *J* 8.1, C*H*O_2, 2*R*) and 5.33 (d, *J* 8.2, C*H*O_2, 2*S*).

Experimental procedures

The synthesis of compounds **5**, **9**, **10** and **24** have been reported previously.[13]

(*R*)-Methyl 3-(2-((*S*)-1′-((benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)hydrazinyl)-4,4,4-trifluorobutanoate 6. To a solution of (*R*)-2-((*S*)-1′-((benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)-5-(trifluoromethyl)-pyrazolidin-3-one (300 mg, 0.779 mmol) in methanol (5 mL) was added triflic acid (0.140 mL, 1.56 mmol) and the resulting mixture stirred at rt overnight. The excess acid was then quenched with saturated sodium hydrogen carbonate solution (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with 60% ethyl acetate in petrol to give the title compound as a colourless solid (120 mg, 39%).

$[\alpha]_D^{20}$ −33.2 (*c* 0.5, methanol); mp 90–91 °C; ν_{max} (KBr disc)/cm^{-1} 3299 (N–H), 3271 (N–H), 3125 (Ar–H), 3033 (Ar–H), 2986 (C–H), 2953 (C–H), 1737 (C═O), 1709 (C═O), 1646 (N–H bend) and 1578 (Ar C═C); δ_N ($(CD_3)_2S(O)$) 138 (*N*HC(O)), 96.5 (N_{Pro}C-(O)O), 65.9 (*N*HCHCF_3); δ_F (376 MHz, CD_3OD, rotamers A : B 1.1 : 1) −76.86 (B, 3F, d, *J* 7.7, CF_3) and −76.89 (A, 3F, d, *J* 7.7, CF_3); δ_H (300 MHz, CD_3OD, rotamers A : B 1.1 : 1) 7.37–7.28 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 5.11 (B, 2H, br s, PhCH_2), 5.09 (A, 2H, br s, PhCH_2), 4.25–4.21 (A, 1H, m, N_{Pro}C*H* & B, 1H, m, N_{Pro}C*H*), 3.93 (B, 1H, app sext, *J* 7.0, C*H*CF_3), 3.80–3.68 (A, 1H,

m, C*H*CF_3), 3.72 (A, 3H, s, OCH_3 & B, 3H, s, OCH_3), 3.62–3.45 (A, 2H, m, $N_{Pro}CH_2$ & B, 2H, m, $N_{Pro}CH_2$), 2.69 (B, 2H, d, *J* 6.2, C(O)CH_2), 2.61 (A, 2H, d, *J* 6.5, C(O)CH_2), 2.31–2.13 (A, 1H, m, $N_{Pro}CHCH_AH_B$ & B, 1H, m, $N_{Pro}CHCH_AH_B$) and 2.04–1.86 (A, 3H, m, $N_{Pro}CHCH_AH_BCH_2$ & B, 3H, m, $N_{Pro}CHCH_AH_BCH_2$); δ_C (75 MHz, CD_3OD) 174.8 (*C*(O)NH), 174.7 (*C*(O)NH), 171.8 (*C*(O)OCH_3), 171.6 (*C*(O)OCH_3), 156.3 ($N_{Pro}C$(O)O), 138.0 (*C*Ar*ipso*), 137.9 (*C*Ar*ipso*), 129.5 (*C*Ar), 129.1 (*C*Ar), 128.9 (*C*Ar), 128.8 (*C*Ar), 123.6 (q, *J* 218, *C*F_3), 68.3 (*C*H_2Ph), 60.5 ($N_{Pro}CH$), 60.0 ($N_{Pro}CH$), 59.6 (q, *J* 28.1, *C*HCF_3), 59.4 (q, *J* 28.3, *C*HCF_3), 52.7 (OCH_3), 48.0 ($N_{Pro}CH_2$), 32.9 (C(O)*C*H_2), 32.5 ($N_{Pro}CHCH_2$), 31.4 ($N_{Pro}CHCH_2$) 25.4 ($N_{Pro}CHCH_2CH_2$) and 24.6 ($N_{Pro}CHCH_2CH_2$); *m*/*z* HRMS (ESI$^+$) $C_{18}H_{23}N_3O_5F_3$ ([M + H]$^+$) requires 418.1584, found 418.1586 (+0.4 ppm).

(*S*)-2-((*R*)-2′-Hydroxy-2′-phenylacetyl)-5-phenylpyrazolidin-3-one 7 and (*R*)-2-((*R*)-2′-hydroxy-2′-phenylacetyl)-5-phenylpyrazolidin-3-one 8. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (250 mg, 1.54 mmol), 1-hydroxybenzotriazole (208 mg, 1.54 mmol), (*R*)-mandelic acid (234 mg, 154 mmol) and (*RS*)-5-phenylpyrazolidin-3-one[13] (250 mg, 1.54 mmol) were combined in THF according to general procedure A. The crude material was purified by column chromatography, eluting with 25% ethyl acetate in petrol then 50% ethyl acetate in petrol to give title compound **7** as a white solid (59 mg, 13%) and title compound **8** as a clear yellow oil (67 mg, 15%). 24 mg of mixed fractions were also collected (150 mg of compounds **7** and **8** over all fractions, 33% combined yield).

Compound **7** (upper spot): $[\alpha]_D^{20}$ −77.0 (*c* 0.2, chloroform); ν_{max} (KBr disc)/cm^{-1} 3422 (O–H), 3228 (N–H), 3038 (Ar–H), 3025 (Ar–H), 2947 (C–H), 1751 (C=O) and 1686 (C=O); mp 143–145 °C; δ_N ($CDCl_3$) 189 (*N*(2)C(O)), 105 (*N*(1)H); δ_H (300 MHz, $CDCl_3$) 7.47–7.32 (10H, m, Ar*H*), 6.00 (1H, s, C*H*(OH)), 5.17 (1H, bs, O*H*), 4.68 (1H, app dt, *J* 10.1, 7.7, C(5)-*H*), 4.06 (1H, d, *J* 7.4, N(2)*H*), 3.01 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 10.1, C(4)H_AH_B) and 2.90 (1H, dd, ABX system, J_{BA} 17.2, J_{BX} 7.7, C(4)H_AH_B); δ_C (100 MHz, $CDCl_3$) 170.8 (*C*(O)), 170.3 (*C*(O)), 138.3 (*C*Ar*ipso*), 137.0 (*C*Ar*ipso*), 129.2 (*C*Ar), 129.0 (*C*Ar), 128.9 (*C*Ar), 128.8 (*C*Ar), 127.8 (*C*Ar), 126.6 (*C*Ar), 73.4 (*C*H(OH)), 58.0 (*C*(5)H) and 41.0 (*C*(4)H_2); *m*/*z* HRMS (ESI$^+$) $C_{17}H_{17}N_2O_3$ ([M + H]$^+$) requires 297.1234, found 297.1237 (+1.1 ppm).

Compound **8** (lower spot): $[\alpha]_D^{20}$ −47.3 (*c* 0.1, chloroform); ν_{max} (KBr disc)/cm^{-1} 3424 (O–H), 3226 (N–H), 3058 (Ar–H), 3025 (Ar–H), 1752 (C=O) and 1700 (C=O); mp 125–126 °C; δ_H (300 MHz, $CDCl_3$) 7.39–7.24 (8H, m, Ar*H*), 7.22–7.16 (2H, m, Ar*H*), 5.96 (1H, s, C*H*(OH)), 5.41 (1H, bs, O*H*), 4.62 (1H, app t, *J* 8.0, C(5)*H*), 3.92 (1H, bs, N(2)*H*), 2.99 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 7.4, C(4)H_AH_B) and 2.77 (1H, dd, ABX system, J_{BA} 17.2, J_{BX} 8.9, C(4)H_AH_B); δ_C (75 MHz, $CDCl_3$) 170.6 (*C*(O)), 170.0 (*C*(O)), 138.1 (*C*Ar*ipso*), 137.7 (*C*Ar*ipso*), 129.1 (*C*Ar), 128.9 (*C*Ar), 128.84 (*C*Ar), 128.82 (*C*Ar), 127.8 (*C*Ar), 126.5 (*C*Ar), 73.4 (*C*H(OH)), 58.2 (*C*(5)H) and. 41.2 (*C*(4)H_2); *m*/*z* HRMS (ESI$^+$) $C_{17}H_{17}N_2O_3$ ([M + H]$^+$) requires 297.1234, found 297.1237 (+1.1 ppm).

(*R*)-2-((*S*)-2′-(6-Methoxynaphthalen-2-yl)propanoyl)-5-phenylpyrazolidin-3-one 11 and (*S*)-2-((*S*)-2′-(6-methoxynaphthalen-2-yl)propanoyl)-5-phenylpyrazolidin-3-one 12. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (26.5 g. 138 mmol), 1-hydroxybenzotriazole (18.7 g, 138 mmol), (*S*)-naproxen (31.9 g, 138 mmol) and (*RS*)-5-phenylpyrazolidin-3-one[13] (22.5 g, 138 mmol) were combined according to general procedure A. The crude material was purified by Biotage Isolera on silica gel, eluting with a gradient of 10–90% ethyl acetate in heptane to give title compound **11** as a colourless solid (7.20 g, 14%) and 20.9 g of mixed fractions (28.1 g of compounds **11** and **12** over all fractions, 54% combined yield). In order to access pure compound **12**, 2.02 g of mixed fractions were further purified by column chromatography on silica gel, eluting with 1–2% ethyl acetate in dichloromethane to give 480 mg of fractions enriched in **12** and 1.50 g mixed fractions. These enriched fractions were further purified by column chromatography on silica gel, eluting with 1–2% ethyl acetate in dichloromethane to give pure compound **12** as a colourless oil (60.0 mg, 0.1%).

Compound **11** (upper spot): $[\alpha]_D^{20}$ +64.8 (*c* 1.0, dichloromethane); ν_{max} (KBr disc)/cm^{-1} 3255 (N–H) 3050 (Ar–H), 2966 (C–H), 2956 (C–H), 1744 (C=O), 1686 (C=O), 1630 (N–H bend) and 1603 (Ar C=C); mp 157–160 °C; δ_N ($CDCl_3$) 193 (*N*(2)C(O)), 104 (*N*(1)H); δ_H (300 MHz, $CDCl_3$) 7.74–7.68 (3H, m, Ar*H*), 7.48 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.38–7.32 (5H, m, Ar*H*), 7.10–7.05 (2H, m, Ar*H*), 5.04 (1H, q, *J* 6.9, C*H*(CH_3)), 4.58 (1H, dd, *J* 10.0, 8.2, C(5)*H*), 3.91 (3H, s, OCH_3), 2.95 (1H, d, *J* 8.2, C(4)H_AH_B), 2.93 (1H, d, *J* 10.0, C(4)H_AH_B) and 1.56 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 171.0 (N(2)*C*(O)), 169.7 (*C*(3)O), 157.8 (O*C*Ar*ipso*), 137.8 (*C*Ar*ipso*), 135.8 (*C*Ar*ipso*), 133.8 (*C*Ar*ipso*), 129.5 (*C*Ar), 129.0 (*C*Ar), 128.7 (*C*Ar), 127.2 (*C*Ar), 127.0 (*C*Ar), 126.7 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 57.2 (*C*(5)H), 55.0 (OCH_3), 44.2 (*C*H(CH_3)), 42.0 (*C*(4)H_2) and 19.4 (CH(*C*H_3)); *m*/*z* HRMS (ESI$^+$) $C_{23}H_{23}N_2O_3$ ([M + H]$^+$) requires 375.1703, found 375.1702 (−0.3 ppm).

Compound **12** (lower spot): $[\alpha]_D^{20}$ +20.8 (*c* 0.25, chloroform); ν_{max} (KBr disc)/cm^{-1} 3266 (N–H) 3059 (Ar–H), 2916 (C–H), 2842 (C–H), 1744 (C=O), 1692 (C=O), 1631 (N–H bend) and 1604 (Ar C=C); mp 47–51 °C; δ_H (300 MHz, $CDCl_3$) 7.72–7.68 (3H, m, Ar*H*), 7.47 (1H, dd, *J* 8.5, 1.7, Ar*H*), 7.28–7.21 (5H, m, Ar*H*), 7.15–7.11 (2H, m, Ar*H*), 5.60 (1H, d, *J* 6.8, N(1)*H*), 5.07 (1H, q, *J* 7.0, C*H*(CH_3)), 4.66 (1H, app dt, *J* 9.3, 7.1, C(5)*H*), 3.92 (3H, s, OCH_3), 3.05 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.3, C(4)-H_AH_B), 2.80 (1H, dd, J_{BA} 17.0, J_{BX} 9.3, C(4)H_AH_B) and 1.58 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 170.8 (N(2)*C*(O)), 169.6 (*C*(3)O), 157.8 (O*C*Ar*ipso*), 138.3 (*C*Ar*ipso*), 135.6 (*C*Ar*ipso*), 133.9 (*C*Ar*ipso*), 129.5 (*C*Ar), 129.1 (*C*Ar*ipso*), 129.0 (*C*Ar), 128.6 (*C*Ar), 127.3 (*C*Ar), 127.1 (*C*Ar), 126.6 (*C*Ar), 126.5 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 57.6 (*C*(5)H), 55.5 (OCH_3), 44.2 (*C*H(CH_3)), 42.1 (*C*(4)H_2) and 19.4 (CH(*C*H_3)); *m*/*z* HRMS (ESI$^+$) $C_{23}H_{22}N_2O_3Na$ ([M + Na]$^+$) requires 397.1528, found 375.1529 (+0.2 ppm).

(*S*)-2-((*S*)-1′-((Benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)-5-phenylpyrazolidin-3-one 13 and (*R*)-2-((*S*)-1′-((benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)-5-phenylpyrazolidin-3-one 14. Benzyl chloroformate (9.5 mL, 65 mmol) and 4 M sodium hydroxide solution (18.0 mL, 70 mmol) were added dropwise simultaneously (using addition funnels) over 30 min with

vigorous stirring to an ice-cooled solution of (*S*)-proline (5.80 g, 50 mmol) in 2 M sodium hydroxide solution (30.0 mL, 60 mmol). The reaction was then left to stir at room temperature for 1 h. The solution was then extracted with diethyl ether (2 × 50 mL) and the aqueous layer retained and acidified to approximately pH 4 with 2 M HCl. The resulting solution was extracted with ethyl acetate (3 × 50 mL), the organic layers dried ($MgSO_4$) and concentrated *in vacuo* to give crude (*S*)-*N*-(benzyloxycarbonyl)-proline (10.1 g) as a colourless oil with spectroscopic data in accordance with the literature.[24] Product was used without further purification.

δ_H (300 MHz, $CDCl_3$, rotamers A : B 1.4 : 1) 7.39–7.27 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 5.18 (A, 1H, d, AB system, J_{AB} 12.4, PhCH_AH$_B$), 5.15 (A, 1H, d, AB system, J_{AB} 12.4, PhCH$_A$$H_B$), 5.13 (B, 2H, s, PhC$H_2$), 4.42 (A, 1H, dd, *J* 8.2, 3.4, N_{Pro}C*H*), 4.38 (B, 1H, dd, *J* 8.7, 3.5, N_{Pro}C*H*), 3.67–3.42 (A, 2H, m, N_{Pro}CH_2 & B, 2H, m, N_{Pro}CH_2) and 2.35–1.86 (A, 4H, m, CH_2CH_2 & B, 4H, m, CH_2CH_2).

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.09 g, 5.67 mmol), 1-hydroxybenzotriazole (766 mg, 5.67 mmol), (*S*)-*N*-(benzyloxycarbonyl)-proline (1.55 g, 6.24 mmol, added as solution in 5 mL DMF) and (*RS*)-5-phenylpyrazolidin-3-one[13] (1.00 g, 5.67 mmol) were combined according to general procedure A. The crude material was purified by column chromatography, eluting with 40% ethyl acetate in petrol to give title compound **13** as a clear yellow oil (382 mg, 17%) and fractions containing title compound **14** and a minor impurity (176 mg). 392 mg of mixed fractions were also collected. The fractions containing impure **14** were purified by further column chromatography, eluting with diethyl ether to give title compound **14** as a colourless oil (100 mg, 4%) (668 mg of compounds **13** and **14** over all fractions, 30% combined yield).

Compound **13** (upper spot): $[\alpha]_D^{20}$ −82.2 (*c* 0.6, chloroform); ν_{max} (KBr disc)/cm^{-1} 3248 (N–H), 3063 (Ar–H), 3033 (Ar–H), 2978 (C–H), 2955 (C–H), 2883 (C–H), 1771 (C═O), 1746 (C═O), 1695 (C═O), 1605 (N–H bend) and 1586 (Ar C═C); δ_N ($CDCl_3$) 192 (*N*(2)C(O)), 103 (*N*(1)H), 97.8 (N_{Pro}C(O)O); δ_H (500 MHz, $(CD_3)_2S(O)$, rotamers A : B 1.1 : 1) 7.46 (A, 2H, d, *J* 7.3, Ar*H*), 7.39–7.36 (A, 4H, m, Ar*H* & B, 4H, m, Ar*H*), 7.33–7.27 (A, 4H, m, Ar*H* & B, 4H, m, Ar*H*), 7.24 (B, 2H, d, *J* 6.8, Ar*H*), 6.54 (B, 1H, d, *J* 9.0, N(1)*H*), 6.53 (A, 1H, d, *J* 8.9, N(1)*H*), 5.22–5.14 (A, 1H, m, N_{Pro}C*H* & B, 1H, m, N_{Pro}C*H*), 5.08 (A, 2H, s, PhCH_2), 5.03 (B, 1H, d, AB system, J_{AB} 13.1, PhCH_AH$_B$), 4.97 (B, 1H, d, AB system, J_{BA} 13.1, PhCH$_A$$H_B$), 4.67 (A, 1H, app q, *J* 8.3, C(5)-*H*), 4.58 (B, 1H, br s, C(5)*H*), 3.53–3.38 (A, 2H, m, N_{Pro}CH_2 & B, 2H, m, N_{Pro}CH_2), 3.10 (B, 1H, dd, ABX system, J_{AB} 16.9, J_{AX} 9.0, C(4)H_AH$_B$), 3.08 (A, 1H, dd, ABX system, J_{AB} 16.7, J_{AX} 7.1, C(4)H_AH$_B$), 2.92 (A, 1H, dd, ABX system, J_{BA} 16.7, J_{BX} 9.6, C(4)H$_A$$H_B$), 2.81 (B, 1H, dd, ABX system, J_{BA} 16.7, J_{BX} 8.7, C(4)H$_A$$H_B$), 2.31–2.19 (A, 1H, m, N_{Pro}CHCH_AH$_B$ & B, 1H, m, N_{Pro}CHCH_AH$_B$) and 1.95–1.84 (A, 3H, m, N_{Pro}CHCH$_A$$H_BCH_2$ & B, 3H, m, N_{Pro}CHCH$_A$$H_BCH_2$); δ_C (100 MHz, $CDCl_3$) 169.8 (*C*(3)-O), 169.7 (*C*(3)O), 169.1 (N(2)*C*(O)), 168.5 (N(2)*C*(O)), 155.0 (*C*(O)O), 154.1 (*C*(O)O), 137.9 (*C*Ar$_{ipso}$), 137.7 (*C*Ar$_{ipso}$), 136.9 (*C*Ar$_{ipso}$), 136.8 (*C*Ar$_{ipso}$), 129.1 (*C*Ar), 128.79 (*C*Ar), 128.77 (*C*Ar), 128.6 (*C*Ar), 128.5 (*C*Ar), 128.3 (*C*Ar), 128.2 (*C*Ar), 128.1 (*C*Ar), 127.9 (*C*Ar), 126.9 (*C*Ar), 126.7 (*C*Ar), 67.2 (*C*H$_2$Ph), 67.1 (*C*H$_2$Ph), 59.8 (N_{Pro}*C*H), 58.7 (N_{Pro}*C*H), 58.2 (*C*(5)H), 58.0 (*C*(5)H), 47.4 (N_{Pro}*C*H$_2$), 47.0 (N_{Pro}*C*H$_2$), 42.0 (*C*(4)H$_2$), 41.9 (*C*(4)H$_2$), 30.7 (N_{Pro}CH*C*H$_2$CH$_2$), 29.8 (N_{Pro}CH*C*H$_2$CH$_2$), 24.1 (N_{Pro}CHCH$_2$*C*H$_2$) and 23.6 (N_{Pro}CHCH$_2$*C*H$_2$); *m*/*z* HRMS (ESI$^+$) $C_{22}H_{24}N_3O_4$ ([M + H]$^+$) requires 394.1761, found 394.1765 (+0.9 ppm).

Compound **14** (lower spot): $[\alpha]_D^{20}$ −40.3 (*c* 0.9, chloroform); ν_{max} (KBr disc)/cm^{-1} 3226 (N–H), 3059 (Ar–H), 3029 (Ar–H), 2956 (C–H), 2926 (C–H), 1744 (C═O), 1708 (C═O), 1695 (C═O) and 1605 (N–H bend); δ_H (300 MHz, $CDCl_3$, rotamers A : B 1 : 1) 7.56–7.19 (A, 10H, m, Ar*H* & B, 10H, m, Ar*H*), 5.40 (A, 1H, d, *J* 8.7, N_{Pro}C*H*), 5.39 (B, 1H, d, *J* 8.5, N_{Pro}C*H*), 5.17 (A, 1H, d, AB system, J_{AB} 12.5, PhCH_AH$_B$), 5.10 (A, 1H, d, AB system, J_{BA} 12.5, PhCH$_A$$H_B$), 5.09 (B, 1H, d, AB system, J_{AB} 12.3, PhCH_AH$_B$), 5.03 (B, 1H, d, AB system, J_{BA} 12.3, PhCH$_A$$H_B$), 4.75 (A, 1H, app t, *J* 8.8, C(5)*H*), 4.64 (B, 1H, app t, *J* 8.6, C(5)*H*), 3.74–3.49 (A, 2H, m, N_{Pro}CH_2 & B, 2H, m, N_{Pro}CH_2), 3.039 (A, 1H, d, *J* 8.6, C(4)H_AH$_B$), 3.038 (A, 1H, d, *J* 9.4, C(4)H$_A$$H_B$), 2.97 (B, 1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.3, C(4)H_AH$_B$), 2.74 (B, 1H, dd, ABX system, J_{BA} 17.0, J_{BX} 10.5, C(4)H$_A$$H_B$), 2.44–2.30 (A, 1H, m, N_{Pro}CHCH_AH$_B$ & B, 1H, m, N_{Pro}CHCH_AH$_B$) and 2.08–1.89 (A, 3H, m, N_{Pro}CHCH$_A$$H_BCH_2$ & B, 3H, m, N_{Pro}CHCH$_A$$H_BCH_2$); δ_C (100 MHz, $CDCl_3$) 170.9 (*C*(3)O), 170.7 (*C*(3)O), 169.6 (N(2)*C*(O)), 169.1 (N(2)*C*(O)), 155.0 (*C*(O)O), 154.2 (*C*(O)O), 137.6 (*C*Ar$_{ipso}$), 137.5 (*C*Ar$_{ipso}$), 136.9 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 129.1 (*C*Ar), 129.0 (*C*Ar), 128.9 (*C*Ar), 128.6 (2 × *C*Ar), 128.05 (*C*Ar), 128.03 (*C*Ar), 128.0 (*C*Ar), 127.9 (*C*Ar), 126.8 (*C*Ar), 126.6 (*C*Ar), 67.2 (2 × *C*H$_2$Ph), 60.1 (N_{Pro}*C*H), 59.2 (N_{Pro}*C*H), 57.8 (*C*(5)H), 57.4 (*C*(5)H), 47.4 (N_{Pro}*C*H$_2$), 46.9 (N_{Pro}*C*H$_2$), 41.5 (*C*(4)H$_2$), 41.3 (*C*(4)H$_2$), 31.0 (N_{Pro}CH*C*H$_2$CH$_2$), 30.1 (N_{Pro}CH*C*H$_2$CH$_2$), 24.1 (N_{Pro}CHCH$_2$*C*H$_2$) and 23.5 (N_{Pro}CHCH$_2$*C*H$_2$); *m*/*z* HRMS (ESI$^+$) $C_{22}H_{24}N_3O_4$ ([M + H]$^+$) requires 394.1761, found 394.1755 (−1.6 ppm).

(*R*)-2-((*S*)-2′-(6-Methoxynaphthalen-2-yl)propanoyl)-5-(*tert*-butyl)-pyrazolidin-3-one 15 and (*S*)-2-((*S*)-2′-(6-methoxynaphthalen-2-yl)propanoyl)-5-(*tert*-butyl)-pyrazolidin-3-one 16. To a solution of hydrazine hydrate (5.00 mL, 101 mmol) in absolute ethanol (140 mL) was added crude (*E*)-ethyl 4,4-dimethylpent-2-enoate (13.3 g, 85.1 mmol) and the resulting solution stirred at reflux overnight before concentration *in vacuo*. The crude oil was then purified by trituration in diethyl ether followed by filtration to give 3.68 g of (*RS*)-5-(*tert*-butyl)pyrazolidin-3-one as a colourless solid. The filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel, eluting with 8% methanol in dichloromethane to give a further 3.20 g of the product (6.68 g in total, 53% combined yield).

ν_{max} (KBr disc)/cm^{-1} 3270 (N–H), 3219 (N–H), 2958 (C–H), 2870 (C–H) and 1667 (C═O); mp 85–89 °C; δ_H (300 MHz, $CDCl_3$) 4.95 (2H, bs, N(1)*H* and N(2)*H*), 3.47 (1H, app t, *J* 8.6, C(5)*H*), 2.45 (1H, dd, ABX system, J_{AB} 16.7, J_{AX} 8.2, C(4)H_AH$_B$), 2.38 (1H, dd, ABX system, J_{BA} 16.7, J_{BX} 8.9, C(4)-H$_A$$H_B$) and 0.95 (9H, s, C(C$H_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 176.8 (*C*(3)O), 67.5 (*C*(5)H), 33.1 (*C*(4)H$_2$), 33.0 (*C*(CH$_3$)$_3$) and 37.3 (C(CH_3)$_3$); *m*/*z* HRMS (ESI$^+$) $C_7H_{14}N_2ONa$ ([M + Na]$^+$) requires 165.1004, found 165.1001 (−1.7 ppm).

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (5.03 g, 25.9 mmol), 1-hydroxybenzotriazole (3.56 g, 25.9 mmol), (*S*)-naproxen (6.00 g, 25.9 mmol) and (*RS*)-5-(*tert*-butyl)pyrazolidin-3-one (3.68 g, 25.9 mmol) were combined according to general procedure A. The crude material was partially purified by column chromatography on silica gel, eluting with 60% diethyl ether in petrol to give first 700 mg of fractions enriched in title compound **15** (**15 : 16** 85 : 15) then 710 mg of fractions enriched in title compound **16** (**15 : 16** 9 : 91). 2.24 g of mixed fractions were also collected (**15 : 16** 42 : 58) (3.65 g of compounds **15** and **16** over all fractions, 40% combined yield). The fractions enriched in title compound **15** were further purified by column chromatography on silica gel, eluting with 40% diethyl ether in petrol to give title compound **15** as an amorphous white solid (360 mg, 4%) and 300 mg of mixed fractions. The fractions enriched in title compound **16** were further purified by dissolution in diethyl ether followed by cooling to 0 °C. Collection by filtration then gave title compound **16** as a colourless solid (264 mg, 3%).

Compound **15** (upper spot): $[\alpha]_D^{20}$ −1.0 (*c* 0.5, chloroform); ν_{max} (KBr disc)/cm^{-1} 3281 (N–H), 2960 (C–H), 2931 (C–H), 1744 (C=O), 1678 (C=O), 1631 (N–H bend) and 1607 (Ar C=C); mp 45–46 °C; δ_H (300 MHz, $CDCl_3$) 7.73–7.67 (3H, m, Ar*H*), 7.47 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.14–7.09 (2H, m, Ar*H*), 5.27 (1H, br s, N(1)*H*), 5.04 (1H, q, *J* 7.0, C*H*(CH_3)), 3.91 (3H, s, OCH_3), 3.21 (1H, dd, *J* 11.3, 7.6, C(5)*H*), 2.63 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 11.3, C(4)H_AH$_B$), 2.50 (1H, dd, J_{BA} 17.2, J_{BX} 7.6, C(4)H$_A$$H_B$), 1.56 (3H, d, *J* 7.0, CH(CH_3)) and 0.92 (9H, s, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 170.8 (N(2)*C*(O)), 170.2 (*C*(3)O), 157.7 (O*C*Ar$_{ipso}$), 135.9 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.4 (*C*Ar), 129.0 (*C*Ar$_{ipso}$), 127.1 (*C*Ar), 127.0 (*C*Ar), 126.6 (*C*Ar), 119.0 (*C*Ar), 105.6 (*C*Ar), 62.3 (*C*(5)H), 55.4 (O*C*H$_3$), 43.9 (*C*H(CH$_3$)), 35.9 (*C*(4)H$_2$), 32.4 (*C*(CH$_3$)$_3$), 25.7 (C(*C*H$_3$)$_3$) and 19.4 (CH(*C*H$_3$)); *m*/*z* HRMS (ESI$^+$) $C_{21}H_{27}N_2O_3$ ([M + H]$^+$) requires 355.2016, found 355.2015 (−0.3 ppm).

Compound **16** (lower spot): $[\alpha]_D^{20}$ +28.2 (*c* 0.5, chloroform); ν_{max} (KBr disc)/cm^{-1} 3290 (N–H), 2869 (C–H), 1741 (C=O), 1679 (C=O), 1634 (N–H bend) and 1606 (Ar C=C); mp 86–87 °C; δ_H (300 MHz, $CDCl_3$) 7.71–7.66 (3H, m, Ar*H*), 7.46 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.14–7.08 (2H, m, Ar*H*), 5.35 (1H, br s, N(1)*H*), 5.03 (1H, q, *J* 6.9, C*H*(CH_3)), 3.90 (3H, s, OCH_3), 3.26 (1H, dd, *J* 10.1, 8.0, C(5)*H*), 2.58 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 8.0, C(4)H_AH$_B$), 2.51 (1H, dd, J_{BA} 17.2, J_{BX} 10.1, C(4)H$_A$$H_B$), 1.56 (3H, d, *J* 6.9, CH(CH_3)) and 0.85 (9H, s, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 170.6 (N(2)*C*(O)), 170.4 (*C*(3)O), 157.7 (O*C*Ar$_{ipso}$), 135.5 (*C*Ar$_{ipso}$), 133.7 (*C*Ar$_{ipso}$), 129.4 (*C*Ar), 129.0 (*C*Ar$_{ipso}$), 127.1 (*C*Ar), 127.0 (*C*Ar), 126.6 (*C*Ar), 118.9 (*C*Ar), 105.6 (*C*Ar), 62.7 (*C*(5)H), 55.4 (O*C*H$_3$), 43.9 (*C*H(CH$_3$)), 35.9 (*C*(4)H$_2$), 32.7 (*C*(CH$_3$)$_3$), 25.7 (C(*C*H$_3$)$_3$) and 19.4 (CH(*C*H$_3$)); *m*/*z* HRMS (ESI$^+$) $C_{21}H_{26}N_2O_3Na$ ([M + Na]$^+$) requires 377.1841, found 377.1826 (−4.0 ppm).

(*S*)-2-((*S*)-2′-(6-Methoxynaphthalen-2-yl)propanoyl)-5-benzylpyrazolidin-3-one 17 and (*R*)-2-((*S*)-2′-(6-methoxynaphthalen-2-yl)propanoyl)-5-benzylpyrazolidin-3-one 18. To a solution of hydrazine hydrate (9.20 mL, 189 mmol) in absolute ethanol (120 mL) was added (*E*)-ethyl 4-phenylbut-2-enoate (12.0 g, 63.1 mmol) and the resulting solution stirred at reflux for 90 min. The suspension was then concentrated *in vacuo* and redissolved in toluene (120 mL) and stirred at reflux for a further 90 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography on silica gel, eluting with a gradient of 1–10% methanol in dichloromethane to give (*RS*)-5-benzylpyrazolidin-3-one as an off-white solid (6.96 g, 63%).

ν_{max} (KBr disc)/cm^{-1} 3234 (N–H), 3165 (N–H), 3054 (Ar–H), 1698 (C=O) and 1655 (N–H bend); mp 81–83 °C; δ_H (300 MHz, $CDCl_3$) 7.37–7.17 (5H, m, Ar*H*), 5.12 (1H, br s, N*H*), 3.95 (1H, app quin, *J* 7.2, C(5)*H*), 2.98 (1H, dd, ABX system, J_{AB} 13.8, J_{AX} 6.9, CH_AH$_B$Ph), 2.84 (1H, dd, ABX system, J_{BA} 13.8, J_{BX} 7.0, CH$_A$$H_B$Ph), 2.55 (1H, dd, ABX system, J_{AB} 16.4, J_{AX} 7.2, C(4)H_AH$_B$) and 2.32 (1H, dd, ABX system, J_{BA} 16.4, J_{BX} 7.5, C(4)H$_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 177.0 (*C*(3)O), 137.3 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 128.8 (*C*Ar), 127.0 (*C*Ar), 61.0 (*C*(5)H), 39.6 (*C*(4)H$_2$) and 37.3 (*C*H$_2$Ph); *m*/*z* HRMS (ESI$^+$) $C_{10}H_{13}N_2O$ ([M + H]$^+$) requires 177.1022, found 177.1019 (−1.9 ppm).

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (3.27 g, 17.0 mmol), 1-hydroxybenzotriazole (2.30 g, 17.0 mmol), (*S*)-naproxen (3.93 g, 17.0 mmol) and (*RS*)-5-benzylpyrazolidin-3-one (3.00 g, 17.0 mmol) were combined according to general procedure A. The crude material was dissolved in diethyl ether and a minimum of dichloromethane, cooled to 0 °C overnight and the resulting mixture filtered to give title compound **17** as a colourless solid (1.20 g, 18%). The filtrate was concentrated *in vacuo* and taken up in diethyl ether and a minimum of methanol. 560 mg of colourless solid composed of a 14 : 86 mixture of title compounds **17** and **18** respectively, was collected (1.76 g of compounds **17** and **18** over all fractions, 27% combined yield). In order to access pure compound **18**, this mixture was subjected to recrystallisation from methanol and the minimum quantity of dichloromethane to give title compound **18** as a colourless solid (342 mg, 5%).

Compound **17** (upper spot): $[\alpha]_D^{20}$ +31.2 (*c* 0.3, chloroform); ν_{max} (KBr disc)/cm^{-1} 3265 (N–H), 3060 (Ar–H), 2976 (C–H), 2935 (C–H), 1723 (C=O), 1687 (C=O), 1630 (N–H bend) and 1605 (Ar C=C); mp 147–148 °C; δ_N ($CDCl_3$) 193 (*N*(2)C(O)), 103 (*N*(1)H); δ_H (500 MHz, $CDCl_3$) 7.70–7.68 (3H, m, Ar*H*), 7.45 (1H, dd, *J* 8.5, 1.3, Ar*H*), 7.33–7.25 (3H, m, Ar*H*), 7.16–7.10 (4H, m, Ar*H*), 5.19 (1H, br s, N(1)*H*), 4.98 (1H, q, *J* 6.9, C*H*(CH_3)), 3.91 (3H, s, OCH_3), 3.69 (1H, app dq, *J* 9.4, 6.7, C(5)*H*), 2.89 (1H, dd, ABX system, J_{AB} 13.7, J_{AX} 6.8, CH_AH$_B$Ph), 2.83 (1H, dd, J_{BA} 13.7, J_{BX} 6.3, CH$_A$$H_B$Ph), 2.64 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 6.9, C(4)H_AH$_B$), 2.55 (1H, dd, J_{BA} 17.0, J_{BX} 9.4, C(4)H$_A$$H_B$) and 1.56 (3H, d, *J* 6.8, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 170.9 (N(2)*C*(O)), 170.1 (*C*(3)O), 157.8 (O*C*Ar$_{ipso}$), 136.4 (*C*Ar$_{ipso}$), 135.8 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.2 (*C*Ar), 129.1 (*C*Ar$_{ipso}$), 129.0 (*C*Ar), 127.3 (*C*Ar), 127.2 (*C*Ar), 126.9 (*C*Ar), 126.6 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 55.4 (O*C*H$_3$), 55.0 (*C*(5)H), 44.1 (*C*H(CH$_3$)), 40.1 (*C*H$_2$Ph), 39.6 (*C*(4)H$_2$) and 19.4 (CH(*C*H$_3$)); *m*/*z* HRMS (ESI$^+$) $C_{24}H_{24}N_2O_3Na$ ([M + Na]$^+$) requires 411.1685, found 411.1675 (−2.4 ppm).

Compound **18** (lower spot): $[\alpha]_D^{20}$ +68.0 (*c* 0.5, chloroform); ν_{max} (KBr disc)/cm^{-1} 3241 (N–H), 2970 (C–H), 2946 (C–H),

1769 (C=O), 1682 (C=O), 1629 (N–H bend) and 1604 (Ar C=C); mp 133–134 °C; δ_H (300 MHz, $CDCl_3$) 7.71–7.68 (3H, m, Ar*H*), 7.44 (1H, dd, *J* 8.4, 1.9, Ar*H*), 7.30–7.21 (3H, m, Ar*H*), 7.15–7.06 (4H, m, Ar*H*), 4.99 (1H, q, *J* 7.0, C*H*(CH_3)), 3.91 (3H, s, OCH_3), 3.79 (1H, app quin, *J* 7.3, C(5)*H*), 2.79 (1H, dd, ABX system, J_{AB} 13.8, J_{AX} 7.4, CH_AH$_B$Ph), 2.75 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.0, C(4)H_AH$_B$), 2.70 (1H, dd, J_{BA} 13.8, J_{BX} 6.7, CH$_A$$H_B$Ph), 2.48 (1H, dd, J_{BA} 17.0, J_{BX} 8.4, C(4)H$_A$$H_B$) and 1.54 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 170.9 (N(2)*C*(O)), 170.1 (*C*(3)O), 157.8 (O*C*Ar$_{ipso}$), 136.6 (*C*Ar$_{ipso}$), 135.6 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.1 (*C*Ar), 129.0 (*C*Ar$_{ipso}$), 128.9 (*C*Ar), 127.24 (*C*Ar), 127.21 (*C*Ar), 127.0 (*C*Ar), 126.7 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 55.5 (O*C*H$_3$ & *C*(5)H), 44.1 (*C*H(CH$_3$)), 40.1 (*C*(4)H$_2$), 39.7 (*C*H$_2$Ph) and 19.4 (CH(*C*H$_3$)); *m*/*z* HRMS (ESI^+) $C_{24}H_{25}N_2O_3$ ([M + H]$^+$) requires 389.1860, found 389.1858 (−0.4 ppm).

(*S*)-2-((*S*)-2′-(6-Methoxynaphthalen-2-yl)propanoyl)-5-(trifluoromethyl)pyrazolidin-3-one 19 and (*R*)-2-((*S*)-2′-(6-methoxynaphthalen-2-yl)propanoyl)-5-(trifluoromethyl)-pyrazolidin-3-one 20. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.55 g, 8.11 mmol), 1-hydroxybenzotriazole (1.10 g, 8.11 mmol), (*S*)-naproxen (1.87 g, 8.11 mmol) and (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **24**[13] (1.25 g, 8.11 mmol) were combined according to general procedure A. The crude material was purified by column chromatography, eluting with 25% ethyl acetate in petrol then pure ethyl acetate to give impure fractions of title compound **19** (766 mg) and fractions of title compound **20** contaminated with residual (*S*)-naproxen (474 mg). The fractions of **19** were purified by recrystallisation in methanol and the minimum of ethyl acetate to give title compound **19** as a colourless solid (229 mg, 8%). The fractions of **20** were taken up in dichloromethane (100 mL) and washed with saturated sodium bicarbonate solution (2 × 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give title compound **20** as a colourless solid (219 mg, 7%) (448 mg of compounds **19** and **20** over all fractions, 15% combined yield).

Compound **19** (upper spot): $[\alpha]_D^{20}$ +3.3 (*c* 0.6, chloroform); ν_{max} (KBr disc)/cm^{-1} 3259 (N–H), 2938 (C–H), 1760 (C=O), 1672 (C=O), 1635 (N–H bend) and 1610 (Ar C=C); mp 162–165 °C; δ_F (282 MHz, $CDCl_3$) −78.2 (3F, d, *J* 6.8, CF_3); δ_H (300 MHz, $CDCl_3$) 7.70–7.67 (3H, m, Ar*H*), 7.44 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.15–7.09 (2H, m, Ar*H*), 5.66 (1H, d, *J* 6.3, N(1)*H*), 4.99 (1H, q, *J* 7.0, C*H*(CH_3)), 4.00 (1H, app dsext, *J* 8.8, 6.6, C(5)*H*), 3.90 (3H, s, OCH_3), 3.00 (1H, dd, ABX system, J_{AB} 17.9, J_{AX} 8.8, C(4)H_AH$_B$), 2.91 (1H, dd, J_{BA} 17.9, J_{BX} 6.3, C(4)H$_A$$H_B$) and 1.57 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 170.8 (N(2)-*C*(O)), 167.0 (*C*(3)O), 157.8 (O*C*Ar$_{ipso}$), 135.1 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.4 (*C*Ar), 128.9 (*C*Ar$_{ipso}$), 127.2 (*C*Ar), 126.9 (*C*Ar), 126.8 (*C*Ar), 124.3 (q, *J* 280, *C*F$_3$), 119.1 (*C*Ar), 105.6 (*C*Ar), 55.4 (O*C*H$_3$), 52.8 (q, *J* 32.5, *C*(5)H), 43.9 (*C*H(CH$_3$)), 33.8 (*C*(4)H$_2$) and 19.3 (CH(*C*H$_3$)); *m*/*z* HRMS (ESI^+) $C_{18}H_{17}N_2O_3F_3Na$ ([M + Na]$^+$) requires 389.1089, found 389.1094 (+1.2 ppm).

Compound **20** (lower spot): $[\alpha]_D^{20}$ +18.5 (*c* 0.5, acetonitrile); ν_{max} (KBr disc)/cm^{-1} 3292 (N–H), 2988 (C–H), 2944 (C–H), 1757 (C=O), 1677 (C=O), 1631 (N–H bend) and 1605 (Ar C=C); mp 161–162 °C; δ_F (282 MHz, $(CD_3)_2S(O)$) −77.5 (3F, d, *J* 8.2, CF_3); δ_H (300 MHz, $(CD_3)_2S(O)$) 7.78 (1H, d, *J* 9.0, CAr(8)*H*), 7.76 (1H, d, *J* 8.6, CAr(4)*H*), 7.60 (1H, d, *J* 1.6, CAr(1)*H*), 7.33 (1H, dd, *J* 8.6, 1.6, CAr(3)*H*), 7.27 (1H, d, *J* 2.4, CAr(5)*H*), 7.14 (1H, dd, *J* 9.0, 2.4, CAr(7)*H*), 6.87 (1H, d, *J* 7.2, N(1)*H*), 4.88 (1H, q, *J* 6.8, C*H*(CH_3)), 4.35–4.22 (1H, m, C(5)*H*), 3.86 (3H, s, OCH_3), 3.25 (1H, dd, ABX system, J_{AB} 18.3, J_{AX} 10.1, C(4)H_AH$_B$), 2.67 (1H, dd, J_{BA} 18.3, J_{BX} 2.7, C(4)H$_A$$H_B$) and 1.42 (3H, d, *J* 6.8, CH(CH_3)); δ_C (75 MHz, $(CD_3)_2S(O)$) 170.7 (N(2)*C*(O)), 170.5 (*C*(3)O), 157.6 (O*C*Ar$_{ipso}$), 136.0 (*C*Ar$_{ipso}$), 133.6 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 128.7 (*C*Ar$_{ipso}$), 127.3 (*C*Ar), 126.9 (*C*Ar), 126.0 (*C*Ar), 125.6 (q, *J* 280, *C*F$_3$), 119.1 (*C*Ar), 106.0 (*C*Ar), 55.5 (O*C*H$_3$), 51.9 (q, *J* 30.7, *C*(5)H), 43.8 (*C*H(CH$_3$)), 33.6 (*C*(4)H$_2$) and 19.2 (CH(*C*H$_3$)); *m*/*z* HRMS (ESI^+) $C_{18}H_{17}N_2O_3F_3Na$ ([M + Na]$^+$) requires 389.1089, found 389.1094 (+1.2 ppm).

(*S*)-2-(2′-(6-Methoxynaphthalen-2-yl)propanoyl)-5,5-dimethylpyrazolidin-3-one 21. To a solution of hydrazine hydrate (2.35 mL, 48.2 mmol) in absolute ethanol (50 mL) was added methyl 3-methyl-2-butenoate (5.30 mL, 43.8 mmol) by dropwise addition. The resulting solution was stirred for 1 h at rt and then at reflux for 4 h before concentration *in vacuo* to give 5,5-dimethylpyrazolidin-3-one as a colourless oil with spectroscopic data in accordance with the literature (4.95 g, 99%).[25]

δ_H (400 MHz, $CDCl_3$) 7.28 (1H, br s, N(2)*H*), 4.08 (1H, br s, N(1)*H*), 2.31 (2H, s, C(4)H_2) and 1.29 (6H, s, C(CH_3)$_2$).

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.11 g, 5.80 mmol), 1-hydroxybenzotriazole (784 mg, 5.80 mmol), (*S*)-naproxen (1.34 g, 5.80 mmol) and 5,5-dimethylpyrazolidin-3-one (662 mg, 5.80 mmol) were combined according to general procedure A. The crude material was purified by column chromatography on silica gel, eluting with 75% diethyl ether in petrol to give the title compound as a colourless solid (1.15 g, 61%).

$[\alpha]_D^{20}$ +20.8 (*c* 0.25, chloroform); ν_{max} (KBr disc)/cm^{-1} 3226 (N–H) 2967 (C–H), 2927 (C–H), 1764 (C=O), 1747 (C=O), 1673 (N–H bend), 1633 (Ar C=C) and 1609 (Ar C=C); mp 109–111 °C; δ_N ($CDCl_3$) 190 (*N*(2)C(O)), 117 (*N*(1)H); δ_H (400 MHz, $CDCl_3$) 7.71–7.66 (3H, m, Ar*H*), 7.44 (1H, dd, *J* 8.6, 1.7, Ar*H*), 7.14–7.08 (2H, m, Ar*H*), 4.99 (1H, q, *J* 6.9, C*H*(CH_3)), 3.90 (3H, s, OCH_3), 2.53 (1H, d, AB system, J_{AB} 16.8, C(4)H_AH$_B$), 2.45 (1H, d, AB system, J_{BA} 16.8, C(4)H$_A$$H_B$), 1.55 (3H, d, *J* 7.0, ArCH(CH_3)), 1.28 (3H, s, (C((CH_3)$_A$(CH$_3$)$_B$)) and 1.14 (3H, s, (C((CH$_3$)$_A$(CH_3)$_B$)); δ_C (100 MHz, $CDCl_3$) 171.8 (*C*(O)), 171.7 (*C*(O)), 157.7 (O*C*Ar$_{ipso}$), 135.9 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.1 (*C*Ar$_{ipso}$), 127.2 (*C*Ar), 127.0 (*C*Ar), 126.5 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 55.5 (*C*(CH$_3$)$_2$), 55.4 (O*C*H$_3$), 47.9 (*C*(4)H$_2$), 44.5 (*C*H(CH$_3$)), 26.2 (C((*C*H$_3$)$_A$(CH$_3$)$_B$)), 26.1 (C((CH$_3$)$_A$(*C*H$_3$)$_B$)) and 19.4 (CH(*C*H$_3$)); *m*/*z* HRMS (ESI^+) $C_{19}H_{22}N_2O_3Na$ ([M + Na]$^+$) requires 349.1528, found 349.1534 (+0.6 ppm).

(*S*)-2-((*S*)-1′-((Benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)-5-(trifluoromethyl) pyrazolidin-3-one 22 and (*R*)-2-((*S*)-1′-((benzyloxy)-carbonyl)pyrrolidine-2′-carbonyl)-5-(trifluoromethyl)-pyrazolidin-3-one 23. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.57 g, 8.21 mmol), 1-hydroxybenzotriazole (1.10 g, 8.21 mmol), crude (*S*)-*N*-(benzyloxycarbonyl)-proline (1.87 g, 9.03 mmol, added as solution in 5 mL DMF) and (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **24**[13] (1.26 g, 8.21 mmol)

were combined according to general procedure A. The crude material was purified by column chromatography, eluting with 85% diethyl ether in petrol to give title compound **22** as a colourless oil (305 mg, 10%) and fractions containing title compound **23** and a minor impurity (286 mg). 135 mg of mixed fractions were also collected. The fractions containing title compound **23** were purified by further column chromatography, eluting with 60% ethyl acetate in petrol to give title compound **23** as a colourless foam (190 mg, 6%) (630 mg of compounds **22** and **23** over all fractions, 20% combined yield).

Compound **22** (upper spot): $[\alpha]_D^{20}$ −46.1 (*c* 0.6, chloroform); ν_{max} (KBr disc)/cm^{-1} 3256 (N–H), 3064 (Ar–H), 3034 (Ar–H), 2980 (C–H), 2957 (C–H), 1786 (C=O), 1757 (C=O), 1707 (C=O) and 1587 (N–H bend); δ_F (376 MHz, $CDCl_3$, rotamers A : B 1.5 : 1) −78.2 (B, 3F, d, *J* 6.5, CF_3), −78.3 (A, 3F, d, *J* 6.6, CF_3); δ_H (300 MHz, $CDCl_3$, rotamers A : B 1.5 : 1) 7.42–7.27 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 5.85 (A, 1H, d, *J* 7.2, N(1)*H*), 5.34–5.28 (A, 1H, m, $N_{Pro}CH$ & B, 2H, m, $N_{Pro}CH$ & N(1)*H*), 5.14 (A, 1H, d, AB system, J_{AB} 12.6, PhCH_AH_B), 5.13 (B, 1H, d, AB system, J_{AB} 12.1, PhCH_AH_B), 5.11 (A, 1H, d, AB system, J_{BA} 12.6, PhCH_AH_B), 4.94 (B, 1H, d, AB system, J_{BA} 12.1, PhCH_AH_B), 4.21–4.07 (A, 1H, m, C(5)*H*), 3.74–3.47 (A, 2H, m, $N_{Pro}CH_2$ & B, 3H, m, $N_{Pro}CH_2$ & C(5)*H*), 3.19 (A, 1H, dd, ABX system, J_{AB} 18.0, J_{AX} 9.6, C(4)H_AH_B), 2.88 (A, 1H, dd, ABX system, J_{BA} 18.0, J_{BX} 5.2, C(4)H_AH_B), 2.75 (B, 1H, d, *J* 7.4, C(4)H_2), 2.37–2.27 (A, 1H, m, $N_{Pro}CHCH_AH_B$ & B, 1H, m, $N_{Pro}CHCH_AH_B$) and 2.03–1.86 (A, 3H, m, $N_{Pro}CHCH_AH_BCH_2$ & B, 3H, m, $N_{Pro}CHCH_AH_BCH_2$); δ_C (100 MHz, $CDCl_3$) 169.6 (N(2)*C*(O)), 168.3 (N(2)*C*(O)), 168.9 (*C*(3)O), 168.5 (*C*(3)O), 155.1 (*C*(O)O), 154.1 (*C*(O)O), 136.9 (*C*Ar$_{ipso}$), 136.7 (*C*Ar$_{ipso}$), 128.7 (2 × *C*Ar), 128.6 (*C*Ar), 128.3 (*C*Ar), 128.1 (*C*Ar), 127.4 (*C*Ar), 124.5 (q, *J* 279, *C*F$_3$), 124.2 (q, *J* 279, *C*F$_3$), 67.2 (*C*H$_2$Ph), 67.1 (*C*H$_2$Ph), 59.9 ($N_{Pro}CH$), 58.8 ($N_{Pro}CH$), 53.3 (q, *J* 32.6, *C*(5)H), 53.2 (q, *J* 33.0, *C*(5)H), 47.3 ($N_{Pro}CH_2$), 47.0 ($N_{Pro}CH_2$), 33.5 (*C*(4)H$_2$), 33.4 (*C*(4)H$_2$), 30.5 ($N_{Pro}CHCH_2CH_2$), 29.7 ($N_{Pro}CHCH_2CH_2$), 24.0 ($N_{Pro}CHCH_2CH_2$) and 23.4 ($N_{Pro}CHCH_2CH_2$); *m*/*z* HRMS (ESI$^+$) $C_{17}H_{19}N_3O_4F_3$ ([M + H]$^+$) requires 386.1323, found 386.1322 (+0.9 ppm).

Compound **23** (lower spot): $[\alpha]_D^{20}$ −34.1 (*c* 0.5, chloroform); mp 50 °C; ν_{max} (KBr disc)/cm^{-1} 3240 (N–H), 3036 (Ar–H), 2985 (C–H), 2957 (C–H), 2886 (C–H), 1786 (C=O), 1761 (C=O) and 1701 (C=O); δ_N (CD_3OD) 184 (*N*(2)C(O)), 97.6 (*N*$_{Pro}$C(O)O), 86.4 (*N*(1)H); δ_F (282 MHz, $(CD_3)_2S(O)$), ^{1}H decoupled, rotamers A : B 1.1 : 1) −77.3 (A, 3F, s, CF_3), −77.5 (B, 3F, s, CF_3); δ_H (300 MHz, $(CD_3)_2S(O)$, rotamers A : B 1.1 : 1) 7.38–7.19 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 6.92 (B, 1H, d, *J* 8.6, N(1)*H*), 6.89 (A, 1H, d, *J* 7.8, N(1)*H*), 5.14 (B, 1H, dd, *J* 8.7, 2.5, $N_{Pro}CH$), 5.07 (A, 2H, s, PhCH_2), 5.03 (A, 1H, dd, *J* 8.9, 1.9, $N_{Pro}CH$), 4.98 (B, 2H, s, PhCH_2), 4.45–4.31 (A, 1H, m, C(5)*H* & B, 1H, m, C(5)*H*), 3.49–3.27 (A, 3H, m, $N_{Pro}CH_2$ & C(4)H_AH_B & B, 3H, m, $N_{Pro}CH_2$ & C(4)H_AH_B), 2.81 (B, 1H, dd, ABX system, J_{BA} 18.3, J_{BX} 3.1, C(4)H_AH_B), 2.78 (A, 1H, dd, ABX system, J_{BA} 18.4, J_{BX} 3.0, C(4)H_AH_B), 2.35–2.16 (A, 1H, m, $N_{Pro}CHCH_AH_B$ & B, 1H, m, $N_{Pro}CHCH_AH_B$) and 1.93–1.69 (A, 3H, m, $N_{Pro}CHCH_AH_BCH_2$ & B, 3H, m, $N_{Pro}CHCH_AH_BCH_2$); δ_C (75 MHz, $CDCl_3$) 169.7 (N(2)*C*(O)), 169.6 (N(2)*C*(O)), 169.4 (*C*(3)O), 169.0 (*C*(3)O), 154.9 (*C*(O)O), 154.1 (*C*(O)O), 136.6 (*C*Ar$_{ipso}$), 136.5 (*C*Ar$_{ipso}$), 128.6 (*C*Ar), 128.5 (*C*Ar), 128.0 (*C*Ar), 127.9 (*C*Ar), 127.6 (*C*Ar), 124.6 (q, *J* 279, *C*F$_3$), 124.5 (q, *J* 279, *C*F$_3$), 67.2 (*C*H$_2$Ph), 67.1 (*C*H$_2$Ph), 59.7 ($N_{Pro}CH$), 59.2 ($N_{Pro}CH$), 53.3 (q, *J* 32.3, *C*(5)H), 53.2 (q, *J* 32.6, *C*(5)H), 47.3 ($N_{Pro}CH_2$), 47.0 ($N_{Pro}CH_2$), 33.3 (*C*(4)H$_2$), 33.1 (*C*(4)H$_2$), 30.6 ($N_{Pro}CHCH_2CH_2$), 29.5 ($N_{Pro}CHCH_2CH_2$), 24.0 ($N_{Pro}CHCH_2CH_2$) and 23.0 ($N_{Pro}CHCH_2CH_2$); *m*/*z* HRMS (ESI$^+$) $C_{17}H_{22}N_4O_4F_3$ ([M + NH$_4$]$^+$) requires 403.1599, found 403.1589 (−2.4 ppm).

Upon heating to 100 °C, the observed rotamers coalesced:

δ_F (282 MHz, $(CD_3)_2S(O)$, ^{1}H decoupled) −77.1 (3F, s, CF_3); δ_H (300 MHz, $(CD_3)_2S(O)$) 7.36–7.26 (5H, m, Ar*H*), 6.74 (1H, d, *J* 7.4, N(1)*H*), 5.13 (1H, d, *J* 9.5, $N_{Pro}CH$), 5.05 (1H, s, PhCH_2), 4.41–4.26 (1H, m, C(5)*H*), 3.49 (2H, app t, *J* 6.8, $N_{Pro}CH_2$), 3.30 (1H, dd, ABX system, J_{AB} 18.1, J_{AX} 9.9, C(4)H_AH_B), 2.75 (1H, dd, ABX system, J_{BA} 18.1, J_{BX} 3.6, C(4)H_AH_B), 2.36–2.21 (1H, m, $N_{Pro}CHCH_AH_B$) and 1.94–1.78 (3H, m, $N_{Pro}CHCH_AH_BCH_2$).

2-(1,1,1-Trifluoro-4-methoxy-4-oxobutan-2-yl)hydrazin-1-ium trifluoromethanesulfonate 25. To a solution of crude (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **24**[13] (90.0 mg, 0.570 mmol) in methanol (1 mL) was added triflic acid (101 μL, 1.14 mmol) and the mixture stirred at rt overnight. The resulting solution was then concentrated *in vacuo* for 4 h to remove excess triflic acid to give the title compound as a colourless solid (175 mg, 91%).

ν_{max} (ATR)/cm^{-1} 3300 (N–H), 3144 (N–H), 2990 (C–H), 2968 (C–H) and 1717 (C=O); mp 73–77 °C; δ_F (375 MHz, CD_3OD) −77.3 (3F, d, *J* 6.9, CHCF_3) and −80.7 (3F, s, SO_3CF_3); δ_H (400 MHz, CD_3OD) 4.06 (1H, dqd, *J* 10.1, 6.9, 3.5, C*H*CF$_3$), 3.77 (3H, s, OCH_3), 2.91 (1H, dd, ABX system, J_{AB} 17.5, J_{AX} 3.5, C(O)H_AH_B) and 2.69 (1H, dd, ABX system, J_{BA} 17.5, J_{BX} 10.1, C(O)H_AH_B); δ_C (75 MHz, CD_3OD) 172.0 (*C*(O)OCH$_3$), 126.4 (q, *J* 281, *C*F$_3$), 121.8 (q, *J* 320, SO_3CF_3), 58.2 (q, *J* 30.1, *C*HCF$_3$), 53.0 (OCH_3) and 33.2 (C(O)CH_2); *m*/*z* HRMS (ESI$^+$) $C_5H_{10}F_3N_2O_2$ ([M − OTf]$^+$) requires 187.0689, found 187.0686 (−1.5 ppm).

(*S*)-Methyl 3-(2-(2-(6-methoxynaphthalen-2-yl)propanoyl)-hydrazinyl)-3-methylbutanoate 26. To a solution of (*S*)-2-(2′-(6-methoxynaphthalen-2-yl)propanoyl)-5,5-dimethylpyrazolidin-3-one **21** (300 mg, 0.920 mmol) in methanol (5 mL) was added triflic acid (0.160 mL, 1.85 mmol) and the resulting mixture stirred at rt for 3 days. The resulting heterogeneous mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis indicated incomplete reaction so the material was re-dissolved in dichloromethane (5 mL), more triflic acid (0.400 mL, 4.60 mmol) added and the mixture stirred for a further 3 days while being monitored by TLC. The resulting mixture was worked up as above. The crude material was purified by column chromatography on silica gel, eluting with 60% ethyl acetate in petrol to give the title compound as a colourless oil (48 mg, 15%).

$[\alpha]_D^{20}$ +18.1 (*c* 0.26, chloroform); ν_{max} (ATR)/cm^{-1} 3277 (N–H) 2971 (C–H), 2934 (C–H), 1732 (C=O), 1653 (N–H bend), 1635 (Ar C=C) and 1605 (Ar C=C); δ_N ($CDCl_3$) 190 (*N*(2)C(O)), 117

(*N*(1)H); δ_H (400 MHz, $CDCl_3$) 7.73–7.69 (3H, m, Ar*H*), 7.49 (1H, br s, N*H*), 7.41 (1H, dd, *J* 8.5, 1.9, Ar*H*), 7.17–7.09 (2H, m, Ar*H*), 3.92 (3H, s, OCH_3), 3.77 (1H, q, *J* 7.1, C*H*(CH_3)), 3.56 (3H, s, C(O)OCH_3), 2.31 (2H, s, CH_2), 1.62 (3H, d, *J* 7.1, CH(CH_3)), 1.09 (3H, s, (C((CH_3)$_A$(CH_3)$_B$)) and 1.08 (3H, s, (C((CH_3)$_A$(CH_3)$_B$)); δ_C (100 MHz, $CDCl_3$) 173.8 (*C*(O)NH), 172.1 (*C*(O)O), 157.9 (OCAr_{ipso}), 135.9 (CAr_{ipso}), 133.9 (CAr_{ipso}), 129.4 (*C*Ar), 129.1 (CAr_{ipso}), 127.6 (*C*Ar), 126.24 (*C*Ar), 126.20 (*C*Ar), 119.3 (*C*Ar), 105.8 (*C*Ar), 57.4 (*C*(CH_3)$_2$), 55.5 (O*C*H_3), 51.7 (C(O)O*C*H_3), 45.6 (*C*H(CH_3)), 44.4 (*C*H_2), 25.5 (C(*C*H_3)$_2$) and 18.5 (CH(*C*H_3)); *m*/*z* HRMS (ESI^+) $C_{20}H_{27}N_2O_4$ ($[M + H]^+$) requires 359.1965, found 359.1968 (+0.7 ppm).

(*R*)-Methyl 3-(2-((*S*)-1′-((benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)hydrazinyl)-3-phenylbutanoate 27. To a solution of (*R*)-2-((*S*)-1′-((benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)-5-phenylpyrazolidin-3-one **14** (500 mg, 1.60 mmol) in methanol (10 mL) was added triflic acid (0.300 mL, 3.20 mmol) and the resulting mixture stirred at rt overnight. The resulting solution was concentrated *in vacuo* then the excess acid was quenched with saturated sodium hydrogen carbonate solution (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with 60% ethyl acetate in petrol to give the title compound as a colourless oil (235 mg, 43%).

$[\alpha]_D^{20}$ −40.4 (*c* 0.5, chloroform); ν_{max} (ATR)/cm^{-1} 3279 (N–H), 3063 (Ar–H), 3032 (Ar–H), 2974 (C–H), 2953 (C–H), 2881 (C–H), 1734 (C═O), 1699 (C═O) and 1684 (C═O); δ_N ($(CD_3)_2S(O)$) 138 (*N*HC(O)), 96.5 (N_{Pro}C(O)O), 65.9 (*N*HCH); δ_H (300 MHz, $CDCl_3$, rotamers A : B 1.3 : 1) 7.40–7.28 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 5.09 (B, 2H, s, PhCH_2), 5.05 (A, 2H, s, PhCH_2), 4.41 (B, 1H, app t, *J* 7.1, C*H*Ph), 4.32 (A, 1H, app t, *J* 7.2, C*H*Ph), 4.13–4.09 (A, 1H, m, N_{Pro}C*H* & B, 1H, m, N_{Pro}C*H*), 3.59 (A, 3H, s, OCH_3 & B, 3H, s, OCH_3), 3.53–3.37 (A, 2H, m, N_{Pro}CH_2 & B, 2H, m, N_{Pro}CH_2), 2.89 (B, 1H, dd, ABX system, J_{AB} 15.7, J_{AX} 6.9, C(O)C$H_A$$H_B$), 2.80 (A, 1H, dd, ABX system, J_{AB} 15.5, J_{AX} 7.3, C(O)C$H_A$$H_B$), 2.65 (B, 1H, dd, ABX system, J_{BA} 15.7, J_{BX} 7.2, C(O)C$H_A$$H_B$), 2.60 (A, 1H, dd, ABX system, J_{BA} 15.5, J_{BX} 7.2, C(O)C$H_A$$H_B$), 2.13–1.96 (A, 1H, m, N_{Pro}CHC$H_A$$H_B$ & B, 1H, m, N_{Pro}CHC$H_A$$H_B$) and 1.81–1.64 (A, 3H, m, N_{Pro}CHC$H_A$$H_BCH_2$ & B, 3H, m, N_{Pro}CHC$H_A$$H_BCH_2$); δ_C (75 MHz, CD_3OD) 174.0 (*C*(O)NH), 173.9 (*C*(O)NH), 173.3 (*C*(O)OCH$_3$), 173.2 (*C*(O)OCH$_3$), 156.3 (N_{Pro}*C*(O)O), 141.5 (CH*C*Ar_{ipso}), 141.4 (CH*C*Ar_{ipso}), 138.0 (CH_2*C*Ar_{ipso}), 129.5 (*C*Ar), 129.4 (*C*Ar), 129.0 (*C*Ar), 128.9 (*C*Ar), 128.6 (*C*Ar), 68.2 (*C*H_2Ph), 68.1 (*C*H_2Ph), 62.3 (*C*HPh), 62.2 (*C*HPh), 60.5 (N_{Pro}*C*H), 60.1 (N_{Pro}*C*H), 52.2 (O*C*H_3), 48.0 (N_{Pro}*C*H_2), 40.8 (C(O)*C*H_2), 40.5 (C(O)*C*H_2), 32.5 (N_{Pro}CH*C*H_2), 31.3 (N_{Pro}CH*C*H_2) 25.2 (N_{Pro}CHCH$_2$*C*H_2) and 24.4 (N_{Pro}CHCH$_2$*C*H_2); *m*/*z* HRMS (ESI^+) $C_{23}H_{28}N_3O_5$ ($[M + H]^+$) requires 426.2023, found 426.2022 (−0.3 ppm).

Iminium ion of (*R*)-methyl 3-(2-((*S*)-1′-((benzyloxy)carbonyl)-pyrrolidine-2′-carbonyl)hydrazinyl)-4,4,4-trifluorobutanoate 28. (*R*)-Methyl 3-(2-((*S*)-1′-((benzyloxy)carbonyl)pyrrolidine-2′-carbonyl)hydrazinyl)-4,4,4-trifluorobutanoate **6** (52 mg, 0.124 mmol) was dissolved in a solution of (*E*)-cinnamaldehyde (62.0 mM) and triflic acid (68.0 mM) in deuterated acetonitrile (2 mL) and the mixture stirred at room temperature for 1 h. Analysis by ^{1}H NMR spectroscopy indicated full conversion to the iminium ion. The mixture was concentrated *in vacuo*, taken up in dichloromethane and filtered to remove insoluble impurities. Concentration *in vacuo* gave the product as a brown foam (73 mg, 89%).

$[\alpha]_D^{20}$ +129 (*c* 1.0, dichloromethane); mp 38–41 °C; ν_{max} (ATR)/cm^{-1} 3150 (N–H), 2972 (C–H), 2926 (C–H), 1732 (C═O), 1717 (C═O), 1694 (C═O), 1684 (C═N), 1599 (Ar C═C) and 1576 (N–H bend); δ_F (376 MHz, CD_3CN) −72.9 (3F, d, *J* 6.6, CHCF_3) and −79.9 (3F, s, SO_3CF_3); δ_H (500 MHz, CD_3CN) 10.4 (1H, br s, N*H*), 9.17 (1H, d, *J* 10.2, C(N)*H*)), 8.53 (1H, d, *J* 15.0, C(N)HCHC*H*), 8.13 (2H, d, *J* 14.9, Ar*H*), 7.75–7.68 (2H, m, C(N)HC*H* & Ar*H*), 7.60–7.57 (2H, m, Ar*H*), 7.34–7.29 (5H, m, Ar*H*), 5.50–5.43 (1H, m, C*H*CF_3), 5.26 (1H, d, AB system, J_{AB} 12.5, PhC$H_A$$H_B$), 5.11 (1H, d, AB system, J_{BA} 12.5, PhC$H_A$$H_B$), 4.40 (1H, dd, *J* 8.0, 4.4, N_{Pro}C*H*), 3.70 (3H, s, OCH_3), 3.60–3.52 (2H, m, N_{Pro}CH_2), 3.10 (1H, dd, ABX system, J_{AB} 18.2, J_{AX} 2.7, C(O)$H_A$$H_B$), 3.01 (1H, dd, ABX system, J_{BA} 18.2, J_{BX} 10.3, C(O)CH$_A$$H_B$), 2.42–2.33 (1H, m, N_{Pro}CHC$H_A$$H_B$) and 2.06–1.99 (3H, m, N_{Pro}CHCH$_A$$H_BCH_2$); δ_C (100 MHz, CD_3CN) 179.7 (*C*(N)), 173.5 (C(N)CH*C*H), 172.2 (*C*(O)NH), 169.3 (*C*(O)OCH$_3$), 156.6 (N_{Pro}*C*(O)O), 137.8 (*C*Ar), 137.6 (OCH$_2$*C*Ar_{ipso}), 134.6 (CHCH*C*Ar_{ipso}), 133.9 (*C*Ar), 130.8 (*C*Ar), 129.5 (*C*Ar), 129.1 (*C*Ar), 128.7 (*C*Ar), 123.5 (q, *J* 282, CH*C*F_3), 121.8 (q, *J* 320, SO_3CF_3), 118.1 (C(N)*C*H), 68.2 (*C*H_2Ph), 68.1 (q, *J* 33.2, *C*HCF$_3$), 60.7 (N_{Pro}*C*H), 53.4 (O*C*H_3), 47.8 (N_{Pro}*C*H_2), 31.0 (N_{Pro}CH*C*H_2), 30.3 (C(O)*C*H_2), and 25.6 (N_{Pro}CHCH$_2$*C*H_2); *m*/*z* HRMS (ESI^+) $C_{27}H_{29}N_3O_5F_3$ ($[M - OTf]^+$) requires 532.2054, found 532.2054 (+0.0 ppm).

(*Z*)-Iminium ion of (*RS*)-benzyl 2-(3-methoxy-3-oxo-1-phenylpropyl)hydrazinecarboxylate trifluoromethane- sulfonate 29. To a solution of (*RS*)-benzyl 5-oxo-3-phenylpyrazolidine-1-carboxylate **5** (100 mg, 0.337 mmol) in dichloromethane (1 mL) was added triflic acid (42.0 μL, 0.337 mmol) and the mixture stirred at room temperature for 2 h. Upon addition of petrol, 105 mg of the triflate salt precipitated as a colourless solid and was collected by filtration. This solid was taken up in dry methanol (2 mL) and (*E*)-cinnamaldehyde (35.0 μL, 0.260 mmol) added. The resulting mixture was left to stir at room temperature with occasional sampling and analysis by ^{1}H NMR spectroscopy to monitor reaction progress. After 3 weeks, the resultant dark red oil was triturated in diethyl ether and a minimum of dichloromethane to precipitate 10 mg of the title compound as a yellow solid. The filtrate was concentrated *in vacuo* and trituration repeated to yield a further 3 mg of title compound (13 mg in total, 9%).

ν_{max} (KBr disc)/cm^{-1} 3427 (N–H), 2925 (C–H), 2854 (C–H), 1751 (C═O), 1732 (C═O), 1613 (N–H bend) and 1588 (Ar C═C); mp 114–116 °C; δ_F (376 MHz, CD_3CN) −79.9 (3H, s, SO_3CF_3); δ_H (300 MHz, CD_3CN) 9.08 (1H, d, *J* 10.2, C(N)*H*)), 8.96 (1H, br s, N*H*), 8.29 (1H, d, *J* 15.4, C(N)HCHC*H*), 7.81 (2H, d, *J* 7.4, Ar*H*), 7.73–7.68 (1H, m, Ar*H*), 7.59–7.31 (12H, m, Ar*H*), 7.07 (1H, dd, *J* 15.4, 10.2, C(N)HC*H*), 5.81 (1H, dd, *J* 10.1, 4.4, C*H*CH$_2$), 5.07 (2H, bs, CH_2Ph), 3.67 (3H, s, OCH_3), 3.48 (1H,

dd, ABX system, J_{AB} 17.9, J_{AX} 10.1, C(O)H_AH_B) and 3.16 (1H, dd, ABX system, J_{BA} 17.9, J_{BX} 4.4, C(O)CH$_A$$H_B$); δ_C (125 MHz, CD_3CN) 174.1 (*C*(N)), 170.9 (*C*(O)CH_3), 167.8 (C(N)CH*C*H), 136.3 (*C*Ar), 134.3 (*C*Ar$_{ipso}$), 132.7 (*C*Ar$_{ipso}$), 132.4 (*C*Ar), 131.6 (*C*Ar), 130.3 (*C*Ar), 129.6 (2 × *C*Ar), 129.4 (*C*Ar), 129.1 (*C*Ar), 116.9 (C(N)*C*H), 72.5 (*C*HCH$_2$), 69.6 (*C*H$_2$Ph), 52.9 (O*C*H$_3$) and 34.8 (C(O)*C*H$_2$); *m*/*z* HRMS (ESI$^+$) $C_{27}H_{27}N_2O_4$ ([M − OTf]$^+$) requires 443.1965, found 443.1966 (+0.1 ppm).

***exo*-(1*R*,2*R*,3*R*,4*S*)-3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and *endo*-(1*S*,2*R*,3*R*,4*R*)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5, entry 1).** (*E*)-Cinnamaldehyde (0.120 mL, 0.950 mmol), triflic acid (19.0 mM solution in methanol, 0.5 mL, 9.50 μmol), catalyst **6** (1 mol%, 4.0 mg, 9.50 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure B. The crude material was then purified by column chromatography, eluting with 5% diethyl ether in petrol to yield the title compounds as a 35 : 65 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (133 mg, 71%).[7]

Compound (**2*R*)-*exo***: δ_H (300 MHz, $CDCl_3$) 9.93 (1H, d, *J* 2.1, C*H*O), 7.34–7.13 (5H, m, Ar*H*), 6.34 (1H, dd, *J* 5.8, 3.6, C*H*$_A$=CH$_B$), 6.08 (1H, dd, *J* 5.8, 3.3, CH$_A$=C*H*$_B$), 3.73 (1H, dd, *J* 5.2, 3.4, C*H*Ph), 3.24–3.21 (2H, m, C*H*CH$_2$), 2.60 (1H, app dt, *J* 5.2, 2.1, C*H*CHO) and 1.62–1.53 (2H, m, CH$_2$).

Compound (**2*R*)-*endo***: δ_H (300 MHz, $CDCl_3$) 9.60 (1H, d, *J* 2.2, C*H*O), 7.34–7.13 (5H, m, Ar*H*), 6.42 (1H, dd, *J* 5.7, 3.2, C*H*$_A$=CH$_B$), 6.18 (1H, dd, *J* 5.7, 2.8, CH$_A$=C*H*$_B$), 3.36–3.32 (1H, m, C*H*CH$_2$), 3.14–3.12 (1H, m, C*H*CH$_2$), 3.09 (1H, dd, *J* 4.8, 1.5, C*H*Ph), 2.98 (1H, ddd, *J* 4.8, 3.4, 2.2, C*H*CHO), 1.84–1.79 (1H, m, C*H*$_A$H$_B$) and 1.65–1.63 (1H, m, CH$_A$*H*$_B$).

Enantiomeric excess was determined by acetalisation with (+)-(*R*,*R*)-hydrobenzoin following general procedure C and ^{1}H NMR analysis:[5] (500 MHz, C_6D_6) *exo* isomers δ 5.74 (d, *J* 4.8, C*H*O$_2$, 2*R*) and 5.72 (d, *J* 5.8, C*H*O$_2$, 2*S*), *endo* isomers δ 5.37 (d, *J* 8.1, C*H*O$_2$, 2*R*) and 5.33 (d, *J* 8.2, C*H*O$_2$, 2*S*).

***exo*-(1*R*,2*R*,3*R*,4*S*)-3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and *endo*-(1*S*,2*R*,3*R*,4*R*)-3-(4-methoxyphenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5, entry 2).** (*E*)-4-Methoxycinnamaldehyde (77.0 mg, 0.480 mmol), triflic acid (0.0190 M solution in methanol, 0.25 mL, 4.80 μmol), catalyst **6** (1 mol%, 2.00 mg, 4.80 μmol) and cyclopentadiene (94 mg, 1.40 mmol) were combined at 5 °C according to general procedure B. The crude material was then purified by column chromatography, eluting with 10% diethyl ether in petrol to yield the title compounds as a 36 : 64 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (94 mg, 86%).[8]

(**2*R*)-*exo***: δ_H (400 MHz, $CDCl_3$) 9.91 (1H, d, *J* 2.0, C*H*O), 7.09–7.05 (2H, m, Ar*H*), 6.81–6.78 (2H, m, Ar*H*), 6.34 (1H, dd, *J* 5.6, 3.2, C*H*$_A$=CH$_B$), 6.07 (1H, dd, *J* 5.6, 2.9, CH$_A$=C*H*$_B$), 3.77 (3H, s, OC*H*$_3$), 3.66 (1H, dd, *J* 5.2, 3.5, C*H*Ar), 3.22–3.19 (1H, m, C*H*CH$_2$), 3.19–3.15 (1H, m, C*H*CH$_2$), 2.53 (1H, app dt, *J* 5.2, 2.0, C*H*CHO), 1.64–1.58 (1H, m, C*H*$_A$H$_B$) and 1.56–1.53 (1H, m, CH$_A$*H*$_B$).

(**2*R*)-*endo***: δ_H (400 MHz, $CDCl_3$) 958 (1H, d, *J* 2.3, C*H*O), 7.20–7.17 (2H, m, Ar*H*), 6.87–6.81 (2H, m, Ar*H*), 6.41 (1H, dd, *J* 5.6, 3.2, C*H*$_A$=CH$_B$), 6.16 (1H, dd, *J* 5.6, 2.8, CH$_A$=C*H*$_B$), 3.79 (3H, s, OC*H*$_3$), 3.33–3.29 (1H, m, C*H*Ar), 3.08–3.04 (1H, m, C*H*CH$_2$), 3.04–3.01 (1H, m, C*H*CH$_2$), 2.94 (1H, ddd, *J* 5.1, 3.2, 2.3, C*H*CHO), 1.79 (1H, app dt, *J* 8.7, 1.5, C*H*$_A$H$_B$) and 1.64–1.58 (1H, m, CH$_A$*H*$_B$).

Enantiomeric excess was determined by acetalisation with (+)-(*R*,*R*)-hydrobenzoin following general procedure C and ^{1}H NMR analysis:[8] (500 MHz, C_6D_6) *exo* isomers δ 5.76 (d, *J* 4.9, C*H*O$_2$, 2*R*) and 5.75 (d, *J* 7.0, C*H*O$_2$, 2*S*), *endo* isomers δ 5.39 (d, *J* 8.2, C*H*O$_2$, 2*R*) and 5.35 (d, *J* 8.2, C*H*O$_2$, 2*S*).

***exo*-(1*R*,2*R*,3*R*,4*S*)-3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and *endo*-(1*S*,2*R*,3*R*,4*R*)-3-(4-nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5, entry 3).** 4-Nitrocinnamaldehyde (84.0 mg, predominantly (*E*)-, 0.480 mmol), triflic acid (95.0 mM solution in methanol, 0.25 mL, 24.0 μmol), catalyst **6** (5 mol%, 10.0 mg, 24.0 μmol) and cyclopentadiene (94.0 mg, 1.40 mmol) were combined according to general procedure B. The crude material was then purified by column chromatography, eluting with 15% ethyl acetate in petrol to yield the title compounds as a 36 : 64 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (106 mg, 91%).[5]

(**2*R*)-*exo***: δ_H (300 MHz, $CDCl_3$) 9.92 (1H, d, *J* 1.7, C*H*O), 8.13–8.08 (2H, m, Ar*H*), 7.32–7.27 (2H, m, Ar*H*), 6.41 (1H, dd, *J* 5.7, 3.2, C*H*$_A$=CH$_B$), 6.05 (1H, dd, *J* 5.7, 2.8, CH$_A$=C*H*$_B$), 3.88 (1H, dd, *J* 5.0, 3.5, C*H*Ar), 3.36–3.32 (1H, m, C*H*CH$_2$), 3.27–3.33 (1H, m, C*H*CH$_2$), 2.62 (1H, br d, *J* 5.0, C*H*CHO) and 1.62–1.60 (2H, m, CH$_2$).

(**2*R*)-*endo***: δ_H (300 MHz, $CDCl_3$) 9.64 (1H, d, *J* 1.7, C*H*O), 8.19–8.14 (2H, m, Ar*H*), 7.45–7.40 (2H, m, Ar*H*), 6.44 (1H, dd, *J* 5.9, 3.6, C*H*$_A$=CH$_B$), 6.20 (1H, dd, *J* 5.7, 2.8, CH$_A$=C*H*$_B$), 3.45–3.41 (1H, m, C*H*CH$_2$), 3.22–3.18 (2H, m, C*H*Ar and C*H*CH$_2$), 2.95 (1H, ddd, *J* 5.0, 3.5, 1.7, C*H*CHO) and 1.78–1.68 (2H, m, CH$_2$).

Enantiomeric excess was determined by acetalisation with (+)-(*R*,*R*)-hydrobenzoin following general procedure C and ^{1}H NMR analysis:[5] (500 MHz, C_6D_6) *exo* isomers δ 5.60 (d, *J* 5.2, C*H*O$_2$, 2*R*) and 5.58 (d, *J* 5.9, C*H*O$_2$, 2*S*), *endo* isomers δ 5.26 (d, *J* 8.1, C*H*O$_2$, 2*R*) and 5.19 (d, *J* 8.2, C*H*O$_2$, 2*S*).

***exo*-(1*R*,2*R*,3*R*,4*S*)-3-(2-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and *endo*-(1*S*,2*R*,3*R*,4*R*)-3-(2-nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5, entry 4).** (*E*)-2-Nitrocinnamaldehyde (168 mg, 0.950 mmol), triflic acid (95.0 mM solution in methanol, 0.5 mL, 9.50 μmol), catalyst **6** (5 mol%, 20.0 mg, 47.5 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure B. The crude material was then purified by column chromatography, eluting with 15% ethyl acetate in petrol to yield the title compounds as a 15 : 85 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (180 mg, 78%).[5]

(**2*R*)-*exo***: δ_H (300 MHz, $CDCl_3$) 9.80 (1H, d, *J* 2.1, C*H*O), 7.72 (1H, dd, *J* 8.0, 1.4, Ar*H*), 7.46–7.30 (2H, m, Ar*H*), 7.17 (1H, dd, *J* 8.0, 1.0, Ar*H*), 6.46 (1H, dd, *J* 5.6, 3.0, C*H*$_A$=CH$_B$), 6.01 (1H, dd, *J* 5.6, 2.9, CH$_A$=C*H*$_B$), 4.09 (1H, dd, *J* 5.3, 3.1, C*H*Ar), 3.39–3.36 (1H, m, C*H*CH$_2$), 3.30–3.25 (1H, m, C*H*CH$_2$), 2.62–2.59 (1H, app dt, *J* 5.3, 2.1, C*H*CHO), 1.69–1.62 (1H, m, C*H*$_A$H$_B$) and 1.61–1.55 (1H, m, CH$_A$*H*$_B$).

(2*R*)-***endo***: δ_H (300 MHz, $CDCl_3$) 9.40 (1H, d, *J* 3.7, C*H*O), 7.82 (1H, dd, *J* 8.1, 1.2, Ar*H*), 7.61–7.51 (2H, m, Ar*H*), 7.46–7.30 (1H, m, Ar*H*), 6.50 (1H, dd, *J* 5.7, 3.3, CH_A=CH_B), 6.21 (1H, dd, *J* 5.7, 2.8, CH_A=CH_B), 3.43 (1H, dd, *J* 5.2, 1.2, C*H*Ar), 3.34–3.29 (1H, m, C*H*CH_2), 3.14–3.10 (1H, m, C*H*CH_2), 2.95 (1H, app dt, *J* 5.2, 3.7, C*H*CHO), 1.84 (1H, app dt, 9.0, 1.6, CH_AH_B) and 1.69–1.62 (1H, m, CH_AH_B).

Enantiomeric excess was determined by acetalisation with (+)-(*R*,*R*)-hydrobenzoin following general procedure C and ^{1}H NMR analysis:[5] (300 MHz, C_6D_6) *exo* isomers δ 5.59 (d, *J* 4.5, C*H*O_2, 2*R*) and 5.51 (d, *J* 5.1, C*H*O_2, 2*S*), *endo* isomers δ 5.21 (d, *J* 7.6, C*H*O_2, 2*R*) and 5.13 (d, *J* 7.6, C*H*O_2, 2*S*).

***exo*-(1*R*,2*R*,3*R*,4*S*)-3-(Naphthalen-1-yl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and *endo*-(1*S*,2*R*,3*R*,4*R*)-3-(naphthalen-1-yl)-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 5, entry 5).** Following the method of Moitessier *et al.*,[26] to a suspension of (*E*)-3-(naphthalen-1-yl)acrylic acid (990 mg, 5.00 mmol) and DMF (0.0400 mL, 0.500 mmol) in dichloromethane (30 mL) was added oxalyl chloride (0.65 mL, 7.500 mmol) dropwise, leading to significant gas evolution. The resulting mixture was stirred at room temperature for 1 h then concentrated *in vacuo* to a yellow solid which was subsequently dissolved in THF (30 mL) and cooled to −78 °C. Lithium tri-*tert*-butoxyaluminium hydride (1.33 g, 5.25 mmol) was then added portionwise and the resulting mixture left to stir for 1 h. The mixture was then allowed to warm to 0 °C and stirred for a further 2 h before being quenched by addition of water (30 mL). The resulting suspension was passed through a layer of Ceilte and the cake washed with dichloromethane (50 mL). The filtrate was diluted further with water (50 mL) and the resulting biphasic mixture extracted. The aqueous layer was washed with dichloromethane (50 mL) and the combined organic layers were washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with 60% dichloromethane in petrol to give (*E*)-3-(naphthalen-1-yl)acrylaldehyde as a yellow solid with spectroscopic data in accordance with the literature (463 mg, 51%).[27]

Mp 43–44 °C; δ_H (300 MHz, $CDCl_3$) 9.87 (1H, d, *J* 7.7, C*H*O), 8.35 (1H, d, *J* 15.7, C*H*CHCHO), 8.20 (1H, d, *J* 8.5, Ar*H*), 7.98–7.91 (2H, m, Ar*H*), 7.84 (1H, d, *J* 7.1, Ar*H*), 7.66–7.52 (3H, m, Ar*H*) and 6.86 (1H, dd, *J* 15.7, 7.7, C*H*CHO).

(*E*)-3-(Naphthalen-1-yl)acrylaldehyde (87.5 mg, 0.480 mmol), triflic acid (19.0 mM solution in methanol, 0.25 mL, 4.80 μmol), catalyst **6** (1 mol%, 2.00 mg, 4.80 μmol) and cyclopentadiene (94 mg, 1.40 mmol) were combined according to general procedure B. The crude material was then purified by column chromatography, eluting with 40% dichloromethane in petrol to yield the title compounds as a 21 : 79 mixture of diastereoisomers (99 mg, 83%).

$[\alpha]_D^{20}$ −47.3 (*c* 0.5, chloroform); ν_{max} (film)/cm^{-1} 3051 (Ar–H), 2975 (C–H), 2872 (C–H), 2815 (C–H), 2717 (C–H), 1716 (C=O), 1597 (C=C) and 1578 (Ar C=C)).

exo-(2*R*): δ_H (300 MHz, $CDCl_3$) 9.95 (1H, d, *J* 1.7, C*H*O), 8.32 (1H, d, *J* 8.4, Ar*H*), 7.89–7.84 (1H, m, Ar*H*), 7.76–7.70 (1H, m, Ar*H*), 7.61–7.42 (2H, m, Ar*H*), 7.35 (1H, t, *J* 7.7, Ar*H*), 7.09 (1H, d, *J* 8.4, Ar*H*), 6.45 (1H, dd, *J* 5.6, 3.2, CH_A=CH_B), 5.82 (1H, dd, *J* 5.6, 3.0, CH_A=CH_B), 4.58 (1H, dd, *J* 5.1, 3.5, C*H*Ar), 3.37–3.33 (1H, m, C*H*CH_2), 3.33–3.28 (1H, m, C*H*CH_2), 2.92 (1H, app dt, *J* 5.1, 1.7, C*H*CHO), 1.81 (1H, app dt, *J* 8.8, 1.5, CH_AH_B) and 1.62 (1H, ddd, *J* 8.8, 3.5, 1.8, CH_AH_B); δ_C (75 MHz, $CDCl_3$) 202.6 (*C*HO), 139.2 (CH_A=CH_B), 137.6 (*C*Ar$_{ipso}$), 136.2 (*C*Ar$_{ipso}$), 134.1 (CH_A=CH_B), 132.5 (*C*Ar$_{ipso}$), 129.1 (*C*Ar), 127.2 (*C*Ar), 126.2 (*C*Ar), 125.6 (*C*Ar), 125.1 (*C*Ar), 123.4 (*C*Ar), 58.4 (*C*HCHO), 48.6 (*C*HCH_2), 47.9 (*C*H_2), 46.0 (*C*HCH_2) and 40.4 (*C*HAr).

endo-(2*R*): δ_H (300 MHz, $CDCl_3$) 9.69 (1H, d, *J* 2.3, C*H*O), 8.05 (1H, dd, *J* 6.7, 2.5, Ar*H*), 7.89–7.84 (1H, m, Ar*H*), 7.76–7.70 (1H, m, Ar*H*), 7.61–7.42 (4H, m, Ar*H*), 6.58 (1H, dd, *J* 5.7, 3.2, CH_A=CH_B), 6.22 (1H, dd, *J* 5.7, 2.7, CH_A=CH_B), 3.82 (1H, dd, *J* 4.9, 1.1, C*H*Ar), 3.44–3.38 (1H, m, C*H*CH_2), 3.22 (1H, ddd, *J* 4.9, 3.5, 2.3, C*H*CHO), 3.20–3.17 (1H, m, C*H*CH_2), 1.92 (1H, app dt, *J* 8.7, 1.5, CH_AH_B) and 1.67 (1H, ddd, *J* 8.7, 3.2, 1.6, CH_AH_B); δ_C (75 MHz, $CDCl_3$) 203.5 (*C*HO), 139.1 (CH_A=CH_B), 136.9 (*C*Ar$_{ipso}$), 135.9 (*C*Ar$_{ipso}$), 134.2 (CH_A=CH_B), 132.5 (*C*Ar$_{ipso}$), 129.0 (*C*Ar), 127.3 (*C*Ar), 126.3 (*C*Ar), 125.8 (*C*Ar), 125.4 (*C*Ar), 123.8 (*C*Ar), 123.0 (*C*Ar), 59.1 (*C*HCHO), 49.7 (*C*HCH_2), 47.6 (*C*H_2), 45.7 (*C*HCH_2) and 41.4 (*C*HAr); *m*/*z* HRMS (ESI^+) $C_{18}H_{17}O$ ($[M + H]^+$) requires 249.1279, found 249.1287 (+3.0 ppm).

Enantiomeric excess was determined by acetalisation with (+)-(*R*,*R*)-hydrobenzoin following general procedure C and ^{1}H NMR analysis: (500 MHz, C_6D_6) *exo* isomers δ 5.79 (d, *J* 3.8, C*H*O_2, 2*R*) and 5.77 (d, *J* 5.1, C*H*O_2, 2*S*), *endo* isomers δ 5.51 (d, *J* 7.5, C*H*O_2, 2*R*) and 5.43 (d, *J* 7.7, C*H*O_2, 2*S*).

***exo*-(1*R*,2*R*,3*R*,4*S*)-3-Propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and *endo*-(1*S*,2*R*,3*R*,4*R*)-3-propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5, entry 6).** (*E*)-2-Hexen-1-al (0.110 mL, 0.950 mmol), triflic acid (19.0 mM solution in methanol, 0.5 mL, 9.50 μmol), catalyst **6** (1 mol%, 4.00 mg, 9.50 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure B. The crude material was then purified by column chromatography, eluting with 2.5% diethyl ether in petrol to yield the title compounds as a 31 : 69 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (140 mg, 90%).[1,28]

exo: δ_H (300 MHz, $CDCl_3$) 9.78 (1H, d, *J* 2.8, C*H*O), 6.21 (1H, dd, *J* 5.7, 3.1, CH_A=CH_B), 6.13 (1H, dd, *J* 5.7, 2.9, CH_A=CH_B), 3.03–2.98 (1H, m, C*H*CH2), 2.89–2.85 (1H, m, C*H*CH2), 2.28 (1H, tdd, *J* 7.6, 4.7, 3.1 C*H*CH_2CH_2), 1.76 (1H, ddd, *J* 4.7, 2.8, 1.7, C*H*CHO), 1.77–1.06 (6H, m, CHCH_2CH & CH_2CH_2) and 0.88 (3H, t, *J* 7.2, CH_3).

endo: δ_H 9.37 (1H, d, *J* 3.4, C*H*O), 6.27 (1H, dd, *J* 5.7, 3.2, CH_A=CH_B), 6.06 (1H, dd, *J* 5.7, 2.8, CH_A=CH_B), 3.14–3.10 (1H, m, C*H*CH2), 2.68–2.64 (1H, m, C*H*CH2), 2.38 (1H, dt, *J* 4.4, 3.4, C*H*CHO), 1.72 (1H, m, C*H*CH_2CH_2), 1.77–1.06 (6H, m, CHCH_2CH & CH_2CH_2) and 0.88 (3H, t, *J* 7.2, CH_3).

Enantiomeric excess was determined by acetalisation with (+)-(*R*,*R*)-hydrobenzoin following general procedure C and ^{1}H NMR analysis:[8] (300 MHz, C_6D_6) *exo* isomers δ 5.62 (d, *J* 6.1, C*H*O_2, 2*R*) and 5.60 (d, *J* 6.2, C*H*O_2, 2*S*), *endo* isomers δ 5.24 (d, *J* 8.3, C*H*O_2, 2*R*) and 5.18 (d, *J* 8.3, C*H*O_2, 2*S*).

***endo*-(1*S*,2*R*,3*R*,4*R*)-3-Phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde (Table 5, entry 7).** (*E*)-Cinnamaldehyde (60.0 μL, 0.480 mmol), triflic acid (0.190 M solution in methanol, 0.250 mL, 47.5 μmol), catalyst **6** (10 mol%, 20.0 mg, 47.5 μmol) and cyclohexadiene (140 μL, 1.40 mmol) were combined according to general procedure B. After 3 days, ^{1}H NMR spectroscopic analysis indicated reaction had achieved 51% conversion (*exo* : *endo* 6 : 94) and reaction was quenched as outlined in general procedure B. The crude material was then purified by column chromatography, eluting with 7.5% diethyl ether in petrol to yield the title compound as a colourless solid with spectroscopic data in accordance with the literature (43 mg, 43%).[21]

$[\alpha]_D^{20}$ −35.7 (*c* 0.3, chloroform) (lit. $[\alpha]_D^{20}$ +82 ((1*R*,2*S*,3*S*,4*S*) enantiomer, >95% ee, *c* 1.0, dichloromethane));[21] mp 54–55 °C; δ_H (300 MHz, $CDCl_3$) 9.42 (1H, d, *J* 1.3, C*H*O), 7.29–7.12 (5H, m, Ar*H*), 6.45 (1H, ddd, *J* 8.1, 6.8, 1.3, CH_A=CH$_B$), 6.12 (1H, ddd, *J* 8.1, 6.5, 1.2, CH$_A$=CH_B), 3.13 (1H, app dt, *J* 6.3, 2.2, C*H*Ph), 3.03–2.98 (1H, m, C*H*CHCHO), 2.76 (1H, app dt, *J* 6.3, 1.5, C*H*CHO), 2.58–2.54 (1H, m, C*H*CHPh), 1.72–1.58 (2H, m, CH_AH$_B$CHCHCHO and CH_AH$_B$CHCHPh), 1.44–1.32 (1H, m, CH$_A$$H_B$CHCHCHO) and 1.07–0.94 (1H, m, CH$_A$$H_B$CHCHPh).

For the purpose of HPLC analysis, the product was derivatised to the benzoyl ester according to the method of Maruoka *et al.*[15,29]

To a solution of *endo*-(1*S*,2*R*,3*R*,4*R*)-phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde (31.0 mg, 0.146 mmol) in methanol (1 mL) was added sodium borohydride (17.0 mg, 0.450 mmol) and the resulting suspension stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* before being suspended in a mixture of water and brine and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting material was dissolved in dichloromethane (1 mL) and treated with triethylamine (30.0 μL, 0.216 mmol), DMAP (18.0 mg, 0.150 mmol) and benzoyl chloride (20.0 μL, 0.175 mmol) then stirred at room temperature overnight. Reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with 5% diethyl ether in petrol to give the desired product as a colourless solid (22 mg, 47%).

$[\alpha]_D^{20}$ −10.6 (*c* 0.5, chloroform); ν_{max} (KBr disc)/cm^{-1} 2931 (C–H), 2867 (C–H), 1711 (C=O), 1658 (Ar C=C) and 1601 (Ar C=C); mp 82–84 °C; δ_H (300 MHz, $CDCl_3$) 7.81 (2H, dd, *J* 8.3, 1.4, Ar*H*), 7.50 (1H, tt, *J* 7.4, 1.4, Ar*H*), 7.37–7.32 (5H, m, Ar*H*), 7.27–7.19 (2H, m, Ar*H*), 6.53 (1H, app t, *J* 7.4, CH_A=CH$_B$), 6.25 (1H, app t, *J* 7.3, CH$_A$=CH_B), 4.08 (1H, dd, ABX system, J_{AB} 10.6, J_{AX} 8.2, CH_AH$_B$O), 3.96 (1H, dd, ABX system, J_{BA} 10.6, J_{BX} 6.6, CH$_A$$H_B$O), 2.80–2.75 (1H, m, C*H*Ph), 2.51–2.39 (3H, m, C*H*CH$_2$O & C*H*CHPh), 1.74–1.68 (2H, m, CH_AH$_B$CHCHCHO & CH_AH$_B$CHCHPh), 1.49–1.41 (1H, m, CH$_A$$H_B$CHCHCHO) and 1.12–1.00 (1H, m, CH$_A$$H_B$CHCHPh); δ_C (100 MHz, $CDCl_3$) 203.5 (*C*HO), 139.1 (*C*H$_A$=CH$_B$), 136.9 (*C*Ar$_{ipso}$), 135.9 (*C*Ar$_{ipso}$), 134.2 (CH$_A$=*C*H$_B$), 132.5 (*C*Ar$_{ipso}$), 129.0 (*C*Ar), 127.3 (*C*Ar), 126.3 (*C*Ar), 125.8 (*C*Ar), 125.4 (*C*Ar), 123.8 (*C*Ar), 123.0 (*C*Ar), 59.1 (*C*HCHO), 49.7 (*C*HCH$_2$), 47.6 (*C*H$_2$), 45.7 (*C*HCH$_2$) and 41.4 (*C*HAr); *m*/*z* HRMS (ESI$^+$) $C_{22}H_{26}NO_2$ ([M + NH$_4$]$^+$) requires 336.1958, found 336.1963 (+1.5 ppm).

Enantiomeric excess was determined by HPLC with ChiralCel OJ-H column (0.5% isopropanol : hexane, flow rate = 1.0 mL min^{-1}, 211 nm), t_R(2*S*) 15.3 min and t_R(2*R*) 24.7 min.

In order to carry out HPLC analysis, a racemic sample of *endo*-3-phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde was obtained following the method of Deutsch, *et al.*,[30] and derivatised to the benzoyl ester by the same method described above.

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