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Structural effects in pyrazolidinone-mediated organocatalytic Diels–Alder reactions

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ABSTRACT

A range of pyrazolidin-3-ones have been prepared and their activity as catalysts for iminium-ion promoted Diels–Alder reactions evaluated. Systematic variation of the C(5)- and N(2)-substituents indicates that the incorporation of an electron withdrawing substitutent at N(2) and either a Ph or CF_3 substitution at C(5) results in optimal catalytic activity. The diastereoisomeric resolution of a model C(5)-Ph substituted pyrazolidinone and its ability to impart modest levels of asymmetric induction in the organocatalytic Diels–Alder reaction is also demonstrated.

1. Introduction

Within the last decade, the use of chiral secondary amines to act as catalysts for a plethora of iminium-ion catalysed transformations of α,β-unsaturated aldehydes has been developed,[1] inspired by the initial pioneering work of MacMillan and co-workers who used imidazolidinone **1** to promote the asymmetric Diels–Alder reaction of an enal and a diene (Fig. 1).[2] Since this landmark publication, a range of alternative catalyst architectures have been applied in iminium-ion promoted reactions, with other imidazolidinones, such as **2**[3] or diarylprolinols, such as **3**,[4] often used to perform a variety of asymmetric transformations with high enantioselectivity.[5] In the specific area of iminium-ion promoted Diels–Alder reactions, a number of catalysts with markedly different structures have been applied,[6] with pyrrolidines **4**[7] and **5**[8] representative. A five-membered ring is not a prerequisite for catalytic activity, however, as exemplified by aziridine **6**[9] and the acyclic catalysts **7**[10] and **8**.[11]

While extensive progress has been made in the development of highly stereoselective iminium-ion promoted reactions, relatively limited studies concerning a detailed mechanistic understanding of these processes, and the structural effects that lead to high catalytic efficiency, have been reported. Seminal work by Tomkinson and co-workers has investigated extensively the effect of structural changes to simple secondary hydrazides upon their catalytic activity in the iminium-ion promoted Diels–Alder reaction.[12] Notably, in a series of acyclic hydrazides, the introduction of an electron-withdrawing *N*-methyl carbamate adjacent to the reactive nitrogen centre (as in **9**) gave high catalytic activity, while in the cyclic series piperazines, such as **10**, showed better catalytic activity than their corresponding pyrazolidines **11** (Fig. 2).[13] In related studies, Ogilvie and co-workers have shown that camphor derived pyrazolidinones,

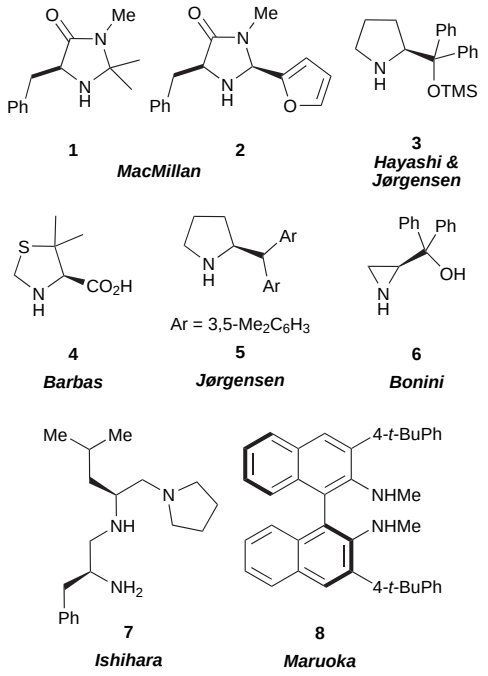

Fig. 1. Structural diversity in iminium-ion organocatalysts.

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such as **13** offer high levels of asymmetric induction in the Diels–Alder reaction (up to 94% ee),[14] while Lee and co-workers have introduced the related sulfonyl hydrazide **14** as asymmetric catalysts of this reaction.[15] Notably, recent kinetic studies by Tomkinson and co-workers have determined that the rate-determining step of the Diels–Alder reaction catalysed by pyrrolidine **12**, incorporating an electron withdrawing CF_3 group at C(2), was the C–C bond-forming step, rather than iminium-ion formation.[16]

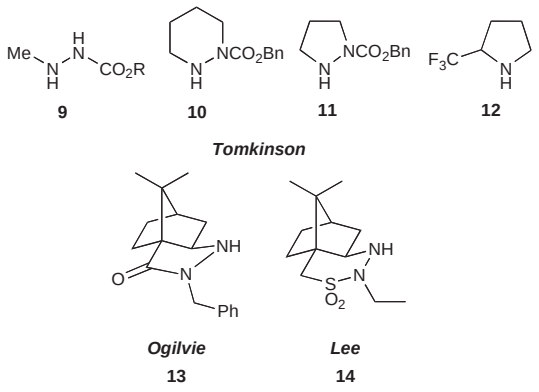


Fig. 2. Catalyst architectures explored by Tomkinson and related catalysts by Ogilvie and Lee.

Building upon these studies, and our interest in the development of catalytically efficient organocatalytic transformations,[17] we wished to prepare a series of structurally related pyrazolidin-3-ones and systematically evaluate substituent effects upon their catalytic efficiency in the iminium-ion catalysed Diels–Alder reaction.[18] In this manuscript we delineate a simple and flexible route to pyrazolidin-3-ones, that allows the incorporation of a range of C(5)-alkyl or aryl substituents, and N(2)-alkyl, N(2)-acyl or N(2)-carboxyl substituents. The effect of changing these substituents upon the catalytic efficiency of iminium-ion catalysed reactions is tested in the Diels–Alder reaction of cyclopentadiene with a range of enals, before a simple resolution protocol is used to prepare an enantiomerically pure pyrazolidinone for probing asymmetric induction in this reaction manifold (Fig. 3).

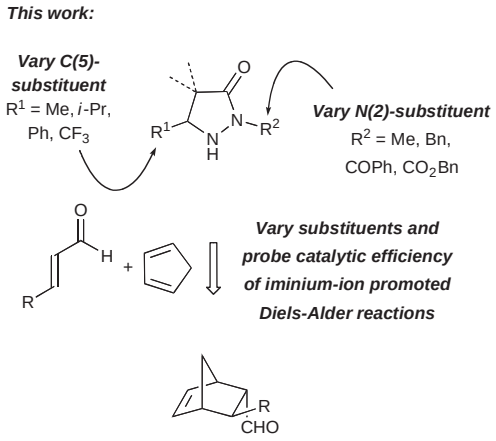
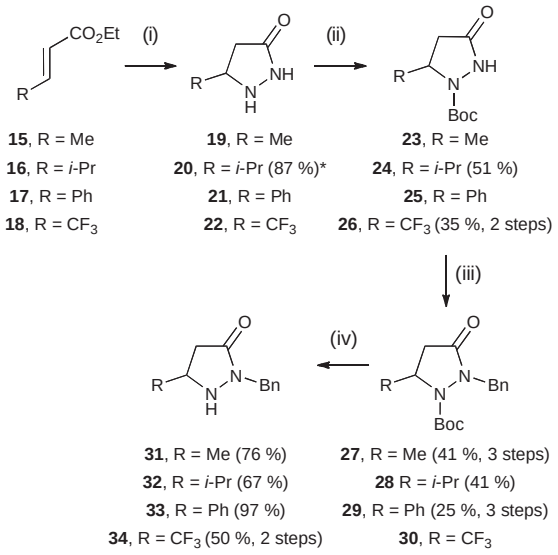


Fig. 3. Proposed pyrazolidin-3-one based iminium-ion catalysts.

2. Results and discussion

2.1. Pyrazolidin-3-one synthesis

Initial studies focused upon the preparation of a range of *N*-benzyl substituted pyrazolidin-3-ones bearing C(5)-methyl, *iso*-propyl, phenyl or trifluoromethyl substituents, respectively, in order to probe the effect of the C(5)-substituent upon catalytic efficiency and diastereoselectivity. The desired pyrazolidinones **31**–**34** were readily prepared by addition of hydrazine to the corresponding α,β-unsaturated ester,[19] regioselective *N*-Boc protection,[20] N-benzylation and *N*-Boc deprotection (Scheme 1). The structures of **21**, **27** and **34** were unambiguously confirmed by X-ray analysis, consistent with the expected regioselectivity of these transformations (Figs. 4–6).



Scheme 1. Reagents and conditions: (i) hydrazine hydrate, EtOH, reflux; (ii) di-*tert* butyl dicarbonate, Na_2CO_3, dioxane/H_2O, rt; (iii) benzyl bromide, DMF, K_2CO_3, rt; (iv) TFA, CH_2Cl_2, rt. *α,β-Unsaturated ester **16** was prepared directly from *iso*-butyraldehyde and ethyl (triphenylphosphoranylidene)acetate[21] and was not isolated due to its volatility. Yield refers to the two-step procedure.

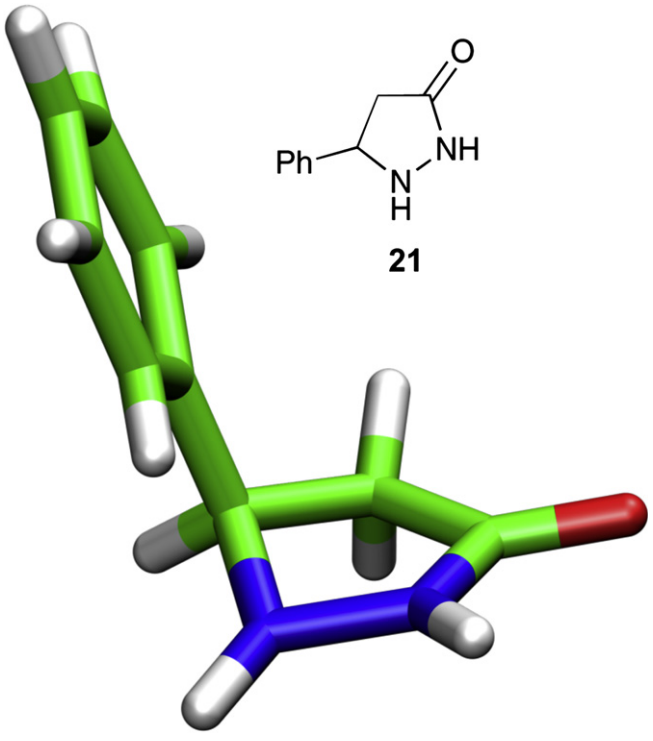


Fig. 4. Molecular representation of the X-ray crystal structure of **21**.

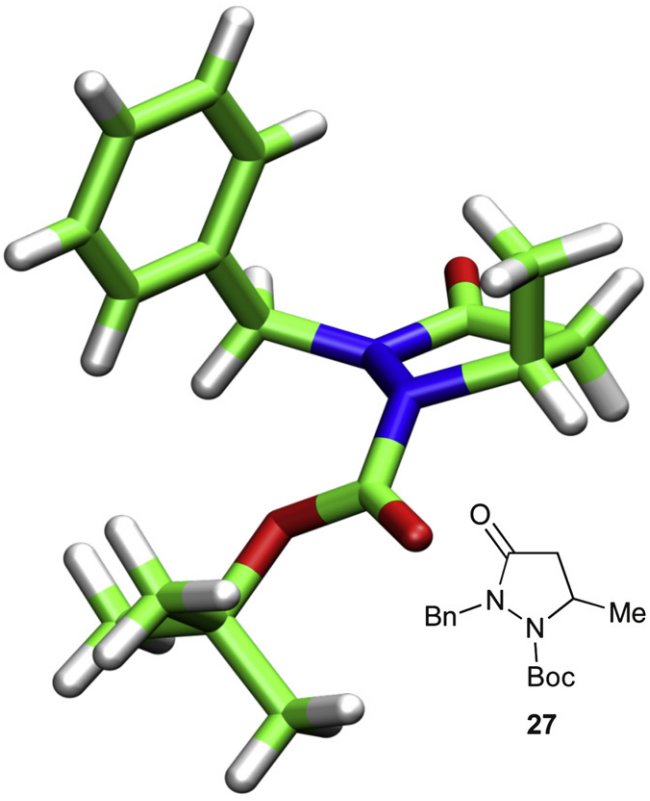


Fig. 5. Molecular representation of the X-ray crystal structure of **27**.

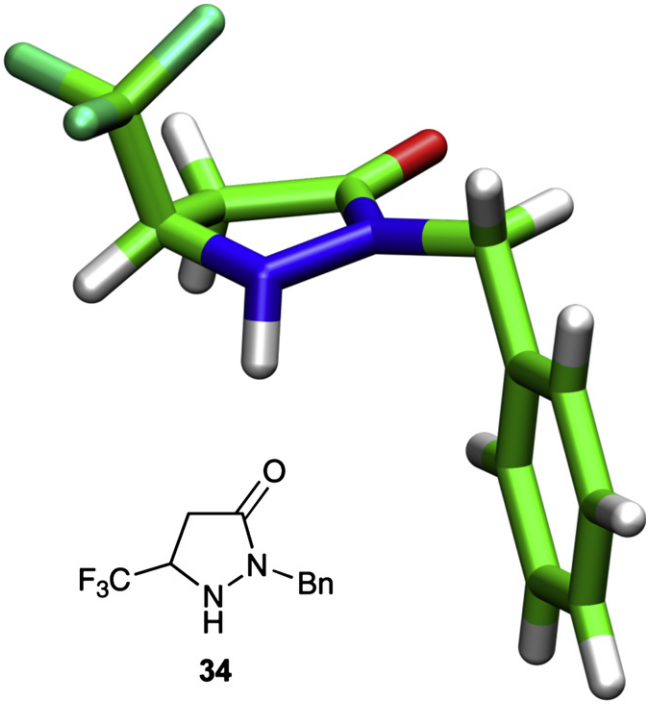
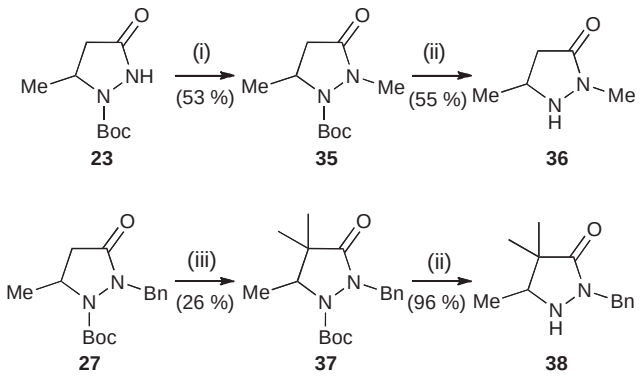


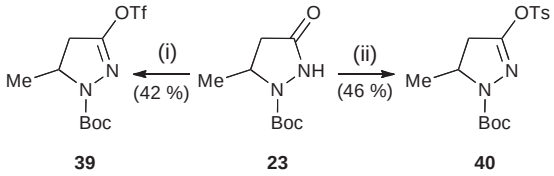
Fig. 6. Molecular representation of the X-ray crystal structure of **34**. The unit cell contains two molecules of **34** but for clarity only one is shown.

In order to probe structural effects upon the catalytic activity of pyrazolidin-3-ones, a series of C(5)methyl-substituted catalysts were prepared that differed in either skeletal complexity or N(2) substitution. *N*(2)-Methyl **36** was readily prepared by N-methylation and *N*-Boc deprotection from **23**, while *gem*-dimethyl substituted **38** was also prepared in an unoptimised procedure by bis-alkylation of **27** and *N*-Boc deprotection (Scheme 2).



Scheme 2. Reagents and conditions: (i) MeI, DMF, K_2CO_3, rt; (ii) TFA, CH_2Cl_2, rt; (iii) 5.0 equiv KHMDS, −78 °C, THF, then 10 equiv MeI, −78 °C to rt, then 5.0 equiv KHMDS, −78 °C, THF, then 10 equiv MeI, −78 °C to rt.

To further probe the effect of N(2)-substitution upon catalytic activity, the incorporation of electron withdrawing substituents, such as sulfonyl, acyl or carboxyl groups was desired. Following the method of Corey and co-workers,[22] N-triflation of **23** in the presence of triethylamine was attempted, but exclusive O-, rather than N-triflation to generate **39** was observed (Scheme 3). N-Tosylation of **23** was also attempted but only O-tosylation to give **40** was observed, irrespective of the choice of base (triethylamine, sodium hydride, *n*-butyllithium or potassium carbonate). The structure of *O*-tosyl **40** was unambiguously proven by X-ray crystallography (Fig. 7).



Scheme 3. Reagents and conditions: (i) NEt_3, CH_2Cl_2, then triflic anhydride, −78 °C to rt (52%), (ii) NEt_3, CH_2Cl_2, then tosyl chloride, −78 °C to rt (46%).

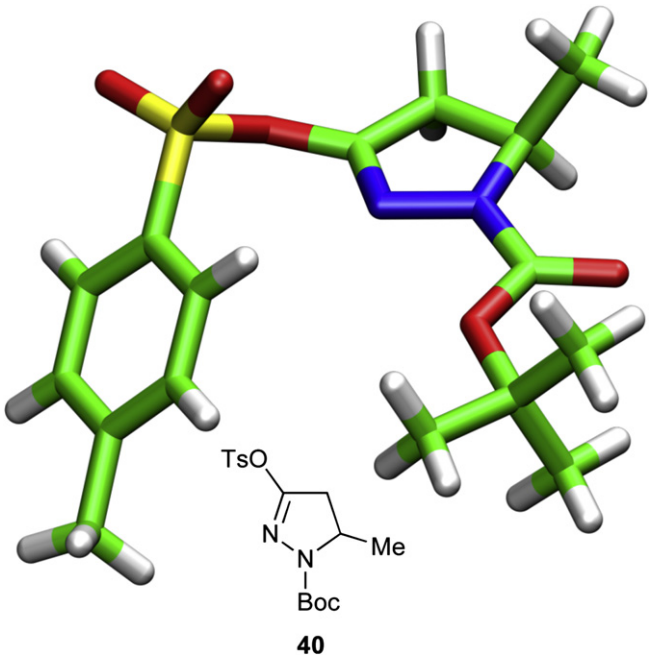
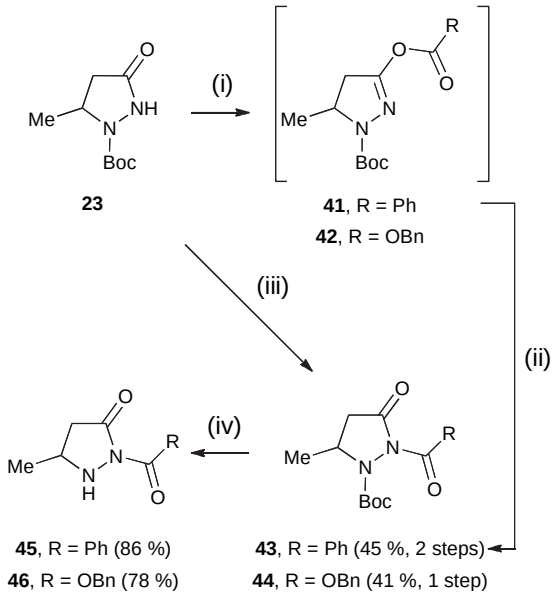


Fig. 7. Molecular representation of the X-ray crystal structure of **40**.

The incorporation of acyl or carboxyl electron withdrawing groups at N(2) was next investigated. Treatment of **23** with NEt_3 or NaH followed by benzoyl chloride gave selective O-functionalisation to give **41**. However, following the method of Vorozhtsov and co-workers,[23] refluxing *O*-benzoyl **41** in toluene resulted in rearrangement to give the desired *N*-benzoyl pyrazolidinone **43** in good yield. While treatment of **23** with NEt_3 and benzyl chloroformate again gave selective O-functionalisation to give **42**, treatment with NaH and benzyl chloroformate gave *N*-benzyloxycarbonylpyrazolidinone **44** directly. Compounds **43** and **44** were then readily deprotected to give the desired pyrazolidinones **45** and **46**, respectively (Scheme 4). The structure of **43** was unambiguously proven by X-ray crystallography (Fig. 8).



Scheme 4. Reagents and conditions: (i) NEt_3, CH_2Cl_2, then benzoyl chloride or benzyl chloroformate, −78 °C to rt; (ii) toluene, reflux; (iii) NaH, CH_2Cl_2, then benzyl chloroformate, −78 °C to rt; (iv) TFA, CH_2Cl_2, rt.

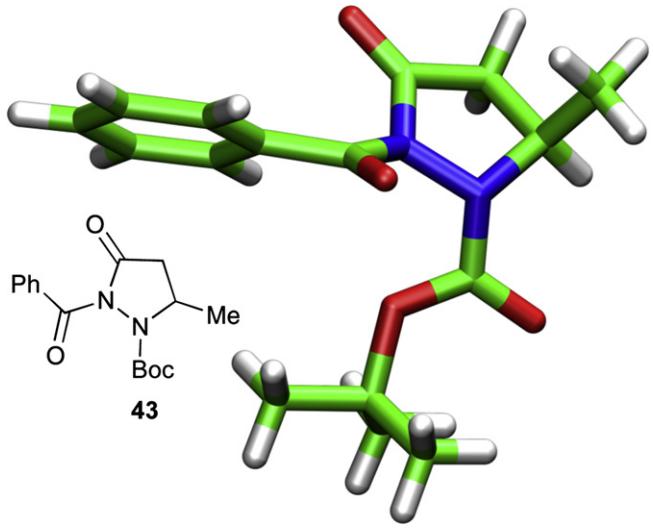
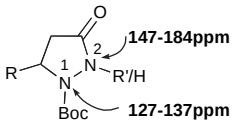


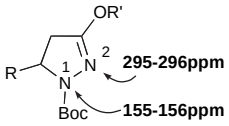
Fig. 8. Molecular representation of the X-ray crystal structure of **43**.

Given the problems with selective N-functionalisation of *N*-Boc pyrazolidinone **23**, a simple method for determining if functionalisation at either *N*- or *O*- had occurred was devised using ^{15}N NMR.[24,25] For selected compounds the values of ^{15}N chemical shifts were obtained experimentally by ^{1}H,^{15}N HMBC and also calculated at the B3LYP/6-31G* level of theory (Table 1). In the case of *N* functionalised compounds (**25**, **27**, **43** and **44**), the N(2) atom has three substituents and shows sp^3 character, while in *O*-functionalised compounds (**40** and **42**), the N(2) atom has two substituents and shows sp^2 character. This change results in *O*-functionalised compounds showing a significant downfield shift of the corresponding ^{15}N resonance relative to N-substitution by around 140 ppm, allowing the N(2) chemical shift to be used as a simple diagnostic tool. In contrast, there is no change in the hybridization of N(1) in all compounds and therefore its ^{15}N chemical shift variation is only marginal (127–156 ppm). The calculated values are slightly overestimated with an average deviation of 11.7 ppm but, nonetheless, there is good agreement between the experimental and theoretical data.

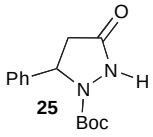
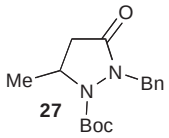
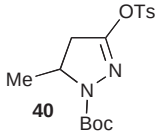
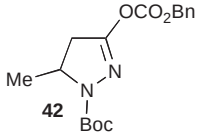
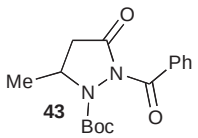
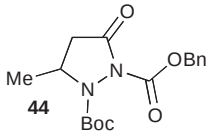
Table 1
^{15}N NMR experimental and theoretical data for selected compounds



***N*-functionalised**



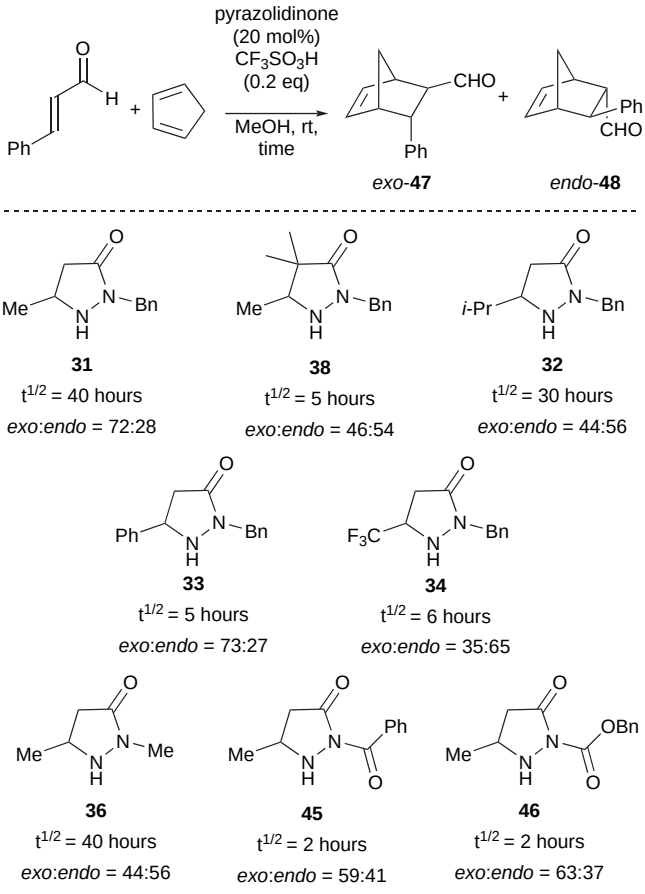
***O*-functionalised**

Compound	Experimental (ppm)		B3LYP/6-31G* (ppm)	
	N(1)	N(2)	N(1)	N(2)
 **25**	127	147	139.9	147.7
 **27**	136	156	143.8	171.6
 **40**	156	295	170.1	311.7
 **42**	155	296	165	298
 **43**	136	184	145	201.1
 **44**	137	166	146.5	183.8

2.2. Pyrazolidin-3-one catalyst testing

With a range of pyrazolidinones prepared, their efficiency in catalysis was tested using the Diels–Alder reaction of cyclopentadiene and cinnamaldehyde. Using C(5)-Me *N*-benzyl catalyst **31** and monitoring the reaction by ^{1}H NMR spectroscopy, modest levels of catalytic activity were observed using triflic acid as the

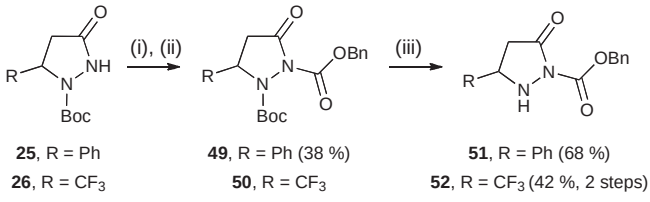
co-catalyst in H_2O (20% conversion in 24 h). Changing the reaction solvent to methanol and using either triflic acid or HCl as co-catalyst gave good conversion (>90%) although with disappointing turnover, requiring 4–5 days for high conversion. Triflic acid was selected for further studies as it gave a marginally improved rate relative to HCl.[26] Subsequent pyrazolidinone evaluation showed that the introduction of the C(4)-*gem*-dimethyl group within the catalyst architecture gave a significant increase in the rate of product formation, although with little diastereoselectivity (**38**, $t^{1/2}$=5 h) (Scheme 5). Within a series of *N*-benzyl substituted catalysts, the optimal rate was observed with either a C(5)-Ph or C(5)-CF_3 unit (**33** and **34**, $t^{1/2}$=5–6 h), consistent with the observations of Tomkinson regarding the incorporation of electron withdrawing substituents within iminium-ion catalysts leading to optimal reaction rates. Interestingly, a reversal in the diastereoselectivity of this process was observed using the C(5)-CF_3 substituted **34**, with a preference for the *endo* diastereoisomer observed. Subsequent studies probed the effect of altering the N(2)-substituent upon catalyst efficiency, with the incorporation of electron-withdrawing *N*-benzoyl or *N*-carboxybenzyl substituents leading to good catalytic efficiency (**45** and **46**, $t^{1/2}$=2 h).



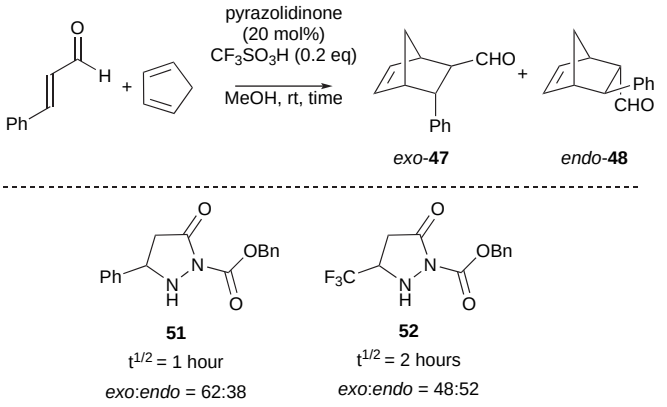
Scheme 5. Initial catalyst screening.

In an attempt to further optimise catalyst efficiencies for this model reaction, the incorporation of a C(5)-Ph or C(5)-CF_3 group, in combination with an electron-withdrawing *N*(2)-carboxybenzyl substituent, was evaluated. Following the methodology developed previously, **51** and **52** were prepared using standard methods from **25** and **26** (Scheme 6).[27]

Pyrazolidinones **51** and **52** were subsequently evaluated as catalysts for the Diels–Alder reaction, with **51** giving the best catalytic efficiency observed within this series of catalysts ($t^{1/2}$ ~1 h, Scheme 7).



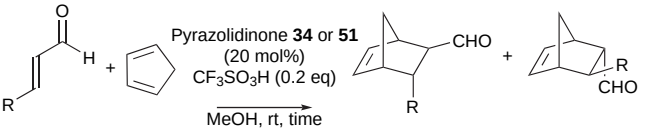
Scheme 6. Reagents and conditions: (i) NaH, CH_2Cl_2, then benzyl chloroformate, −78 °C to rt; (ii) toluene, reflux; (iii) TFA, CH_2Cl_2, rt.



Scheme 7. Optimised catalyst screening.

These reactions indicate that the incorporation of an electron-withdrawing *N*(2)-carboxybenzyl group and either a C(5)-phenyl or CF_3 unit within the pyrazolidinone template led to increased catalytic activity. The generality of the use of pyrazolidinone **51** in the organocatalytic Diels–Alder reaction was next evaluated, giving good reactivity for a series of enals with cyclopentadiene, furnishing the desired products in good isolated yields (Table 2, entries 1–4). Catalysis using pyrazolidinone **34** was also further evaluated, giving preferential *endo*-selectivity in each case (Table 2, entries 5–6). The attempted use of alternative dienes with both **51** and **34** under a range of conditions led to no product conversion.[2,14,28]

Table 2
Diels–Alder reactions promoted by pyrazolidinones **51** and **34**



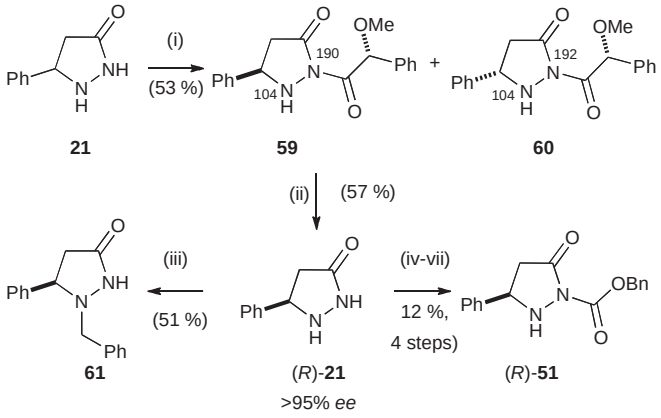
Entry	R	Catalyst	Time (h)	Yield (%)	*exo*:*endo*
1	Ph	**51**	7	89	62:38
2	4-$NO_2C_6H_4$	**51**	5	73	65:35
3	*n*-Pr	**51**	4	75	58:42
4[a]	CO_2Et	**51**	24	80	50:50
5	Ph	**34**	48	50	22:78
6	*n*-Pr	**34**	6	67	36:64

[a] Addition of 5% water.

2.3. Proof of concept: pyrazolidinone resolution and testing in enantioselective catalysis

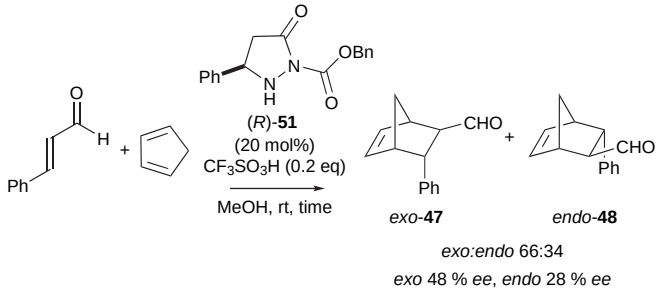
Having demonstrated that pyrazolidinone **51** shows good catalytic activity as an organocatalyst, its preparation in enantiomerically pure form was attempted in order to evaluate its ability to promote an enantioselective Diels–Alder reaction. Treatment of pyrazolidinone **21** with *O*-methyl mandelic acid under peptide coupling conditions gave the chromatographically separable

diastereoisomeric *N*(2)-acyl pyrazolidinone derivatives **59** and **60**, with N(2)-functionalisation of both diastereoisomers confirmed by ^{15}N NMR spectroscopy (Scheme 8).[29] Acid hydrolysis of **59** gave (*R*)-**21** in >95% ee, as shown by derivatisation to **61** and HPLC analysis.[30] Enantiomerically pure (*R*)-**21** was subsequently transformed to (*R*)-**51** in modest yield over four steps.



Scheme 8. Reagents and conditions: (i) EDCI·HCl, HOBt, (*R*)-*O*-methyl mandelic acid, DMF; (ii) 5 M HCl (aq), reflux; (iii) benzaldehyde, EtOH, rt, then $NaBH_4$. (iv) di-*tert* butyl dicarbonate, Na_2CO_3, dioxane/H_2O, rt; (v) NaH, CH_2Cl_2, then benzyl chloroformate, −78 °C to rt; (vi) toluene, reflux; (vii) TFA, CH_2Cl_2, rt.

Enantiomerically pure pyrazolidinone (*R*)-**51** was then evaluated as an asymmetric catalyst for the Diels–Alder reaction of cinnamaldehyde and cyclopentadiene under standard conditions, giving a 66:34 ratio of *exo*:*endo* diastereoisomers, and with modest enantioselectivities of 48% and 28%, respectively (Scheme 9).[14,31]



Scheme 9. Asymmetric evaluation of pyrazolidinone (*R*)-**51**.

3. Conclusion

In conclusion, we have outlined some structural factors that effect the catalytic activity of pyrazolidinones in the iminium-ion promoted organocatalytic Diels–Alder reaction, with the incorporation of an additional electron withdrawing substituent at N(2) and Ph substitution at C(5) resulting in optimal catalytic activity. The diastereoisomeric resolution of a model pyrazolidinone and its ability to impart modest levels of asymmetric induction in the organocatalytic Diels–Alder reaction was also evaluated. Current studies are focused upon developing alternative applications of enantiomerically pure pyrazolidinones and their derivatives in asymmetric catalysis.

4. Experimental

4.1. General

All reactions involving moisture sensitive reagents were performed under an atmosphere of argon or nitrogen using standard vacuum line techniques and with freshly distilled solvents. All glassware was flame dried and allowed to cool under vacuum.

All dried and purified solvents were obtained from a solvent purification system (MBraun, SPS-800) except for dry *N*,*N*′-dimethylformamide (DMF), which was purchased directly from Aldrich. Petrol refers to the fraction of petroleum ether boiling between 40 °C and 60 °C, dioxane refers to 1,4-dioxane, pH 7 phosphate buffer refers to a solution of sodium dihydrogen phosphate and disodium hydrogen orthophosphate and brine refers to a saturated aqueous solution of sodium chloride. Cyclopentadiene was obtained by cracking of the dimer at 170 °C, after drying over $MgSO_4$ and stored in the freezer. Catalytic runs for which isolated yields were obtained were carried out with aldehydes purified according to the guidelines of Armarego and Chai.[32] All other reagents were used directly as supplied without further purification.

Flash column chromatography was carried out according to the method of Still[33] with silica gel 60 (0.043–0.060 mm) (Merck) in the solvent system stated. Analytical thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F_{254}). TLCs were visualised either by UV fluorescence (254 nm), or by staining with basic $KMnO_4$ solution.

Melting points were recorded on an Electrothermal apparatus and are uncorrected. Microanalyses were carried out on a Carlo Erba CHNS analyser. Infrared spectra were recorded on a Perkin–Elmer Spectrum GX FT-IR Spectrometer and analysed either as thin films between NaCl plates (thin film) or KBr discs (KBr disc) as stated. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and only structurally significant peaks are quoted.

^{19}F, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (282 MHz ^{19}F, 300 MHz ^{1}H, 75 MHz ^{13}C), a Bruker Avance 400 (375 MHz ^{19}F, 400 MHz ^{1}H, 100 MHz ^{13}C) or a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer in the deuterated solvent stated. ^{13}C NMR spectra were recorded with proton decoupling. ^{15}N NMR spectra were acquired indirectly by ^{1}H, ^{15}N-HMBC experiments on a Bruker Avance 500 equipped by a 5 mm inverse tuneable double resonance probe. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to residual solvent peaks. Coupling constants, *J*, are quoted in hertz. The abbreviations s, d, dd, dt, td, q, quin, dsept and m denote singlet, doublet, doublet of doublets, doublet of triplets, triplet of doublets, quartet, quintet, doublet of septets and multiplet, respectively. The abbreviation Ar is used to denote aromatic.

Mass spectrometric (*m*/*z*) data was acquired by electrospray ionisation (ESI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility or at the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, CIMS was carried out on a Micromass Quattro II spectrometer. High resolution ESI was carried out on a Finnigan MAT 900 XLT; a Thermofisher LTQ Orbitrap XL spectrometer was used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons.

Temperatures of 0 °C were obtained using an ice/water bath and of −78 °C were obtained using a dry ice/acetone bath.

4.2. General procedure A: *O*-functionalisation of (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate 23 with triethylamine

To a solution of (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (1 equiv) in dichloromethane (0.5 M) was added triethylamine (1.1 equiv). The resulting suspension was then cooled to 0 °C and the appropriate chloride or anhydride (1.05 equiv) added. The mixture was allowed to warm to rt overnight. The

reaction was quenched with water and extracted three times with dichloromethane. The combined organic layers were washed with 0.1 M aqueous hydrochloric acid, brine, dried ($MgSO_4$), filtered and concentrated in vacuo.

4.3. General procedure B: N(2)-alkylation of Boc-protected pyrazolidin-3-one with sodium hydride

A solution of the appropriate Boc-protected pyrazolidin-3-one (1 equiv) in dichloromethane (0.5 M) was cooled to −78 °C and sodium hydride (60% dispersion in mineral oil, 1.1 equiv) added. The resulting suspension was stirred for 10 min before addition of the appropriate chloride or anhydride (1.05 equiv). The mixture was allowed to warm to rt overnight. The reaction was quenched with water and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo.

4.4. General procedure C: screening of catalysts

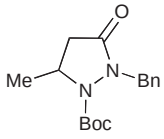
To a suspension of catalyst (20 mol %, 0.378 mmol) in methanol (2 mL) was added either concentrated hydrochloric acid solution (36% m/v, 3.60 μl, 0.378 mmol) or triflic acid (35.0 μl, 0.378 mmol). After 2 min of stirring, *trans*-cinnamaldehyde (0.240 mL, 1.89 mmol) was added, followed by a further 5 min of stirring. Cyclopentadiene (370 mg, 5.60 mmol) was then added and the resulting mixture left to stir at rt. The reaction was monitored by taking samples of the reaction mixture (0.05 mL), which were concentrated in vacuo then hydrolysed in a chloroform (1 mL), water (0.5 mL), trifluoroacetic acid (0.5 mL) mixture for 2 h. Saturated sodium hydrogen carbonate solution (10 mL) was then added and the resulting biphasic mixture extracted with chloroform (2×10 mL). The combined organic layer were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. ^{1}H NMR of the crude reaction mixture was used to establish the conversion to the products and *exo*:*endo* ratios through the integration of aldehyde peaks at: δ_H 9.93 (*exo*-**47**), 9.64 (*trans*-cinnamaldehyde) and 9.60 (*endo*-**48**), which were in accordance with previously reported literature values.[12]

4.5. General procedure D: screening of aldehyde substrates

To a suspension of catalyst **51** or **34** (20 mol %, 0.189 mmol) in methanol (1 mL) was added triflic acid (17.0 μl, 0.189 mmol). After 2 min of stirring, the appropriate aldehyde (0.950 mmol) was added, followed by a further 15 min of stirring. Cyclopentadiene (188 mg, 2.80 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 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.

4.6. Experimental data

*4.6.1. (RS)-tert-Butyl 2-benzyl-5-methyl-3-oxopyrazolidine-1-carboxylate **27**.*



27

To a solution of hydrazine hydrate (9.02 mL, 0.180 mol) in absolute ethanol (200 mL) was added ethyl crotonate **15** (21.0 mL, 0.169 mol) 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 crude (*RS*)-5-methylpyrazolidin-3-one **19** (18.1 g) as a viscous yellow oil with spectroscopic data in accordance with the literature.[19] Product was used without further purification.

δ_H (400 MHz, $CDCl_3$) 3.78–3.66 (1H, app dquin, *J* 8.7, 6.7, C(5)*H*), 2.48 (1H, dd, ABX system, J_{AB} 16.1, J_{AX} 7.1, C(4)H_AH_B), 2.12 (1H, dd, ABX system, J_{BA} 16.1, J_{BX} 8.7, C(4)H_AH_B) and 1.22 (3H, d, *J* 6.3, C(5)HCH_3).

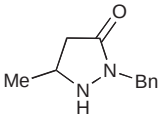
To a solution of crude (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **19** (18.1 g, 0.180 mol) in water (100 mL) were added sodium carbonate (19.1 g 0.180 mol) and dioxane (50 mL). A solution of di-*tert*-butyl dicarbonate (39.3 g, 0.240 mol) in dioxane (50 mL) was then added and the mixture stirred at rt for 1 h. The resulting suspension was filtered and the precipitate washed with chloroform. The combined organic extracts were then concentrated in vacuo to approximately 30 mL volume and partitioned between water (100 mL) and dichloromethane (100 mL). The organic extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (33.9 g) as a yellow solid with spectroscopic data in accordance with the literature.[20] Product was used without further purification.

δ_H (400 MHz, $CDCl_3$) 9.50 (1H, br s, N(2)*H*), 4.38 (1H, dqd, *J* 9.6, 6.5, 3.3, C(5)*H*), 2.92 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 9.6, C(4)H_AH_B), 2.14 (1H, dd, ABX system, J_{BA} 17.0, *J*BX 3.3, C(4)H_AH_B), 1.43 (9H, s, C(CH_3)$_3$) and 1.29 (3H, d, *J* 6.5, C(5)HCH_3).

A solution of crude (*RS*)-5-methylpyrazolidin-3-one **46** (33.9 g, 170 mmol) in DMF (125 mL) was treated with benzyl bromide (20.2 mL, 170 mmol) and potassium carbonate (23.9 g, 173 mmol) and the suspension stirred at rt for 2.5 h. The reaction mixture was partitioned between diethyl ether (150 mL) and water (250 mL) and the resultant aqueous layer washed with further diethyl ether (2×150 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography, eluting with 25% ethyl acetate in petrol to give the title compound as a colourless solid (19.9 g, 41%).

ν_{max} (KBr disc) cm^{-1} 3028 (Ar–H), 2976 (C–H), 2931 (C–H), 2871 (N–C–H), 1706 (C=O), 1690 (C=O), 1557 (Ar C=C) and 1534 (Ar C=C); mp 90–94 °C; δ_N ($CDCl_3$) 156 (*N*(2)CH_2Ph), 136 (*N*(1) Boc); δ_H (400 MHz, $CDCl_3$) 7.35–7.29 (5H, m, Ar*H*), 5.29 (1H, d, AB system, J_{AB} 14.2, CH_AH$_B$Ph), 4.42 (1H, app quin, *J* 7.2, C(5)*H*), 4.39 (1H, d, AB system, J_{BA} 14.2, C$H_A$$H_B$Ph), 2.95 (1H, dd, *J* 16.3, 8.2, C(4)H_AH_B), 1.96 (1H, d, *J* 16.3, C(4)H_AH_B), 1.56 (9H, s, C(CH_3)$_3$) and 0.65 (3H, d, *J* 6.7, C(5)HCH_3); δ_C (100 MHz, $CDCl_3$) 171.5 (*C*(3)O), 156.1 (*C*(O)O), 135.6 (*C*Ar$_{ipso}$), 129.7 (*C*Ar), 128.4 (*C*Ar), 128.1 (*C*Ar), 82.6 (*C*(CH_3)$_3$), 53.7 (*C*(5)H), 48.6 (CH_2Ph), 38.1 (*C*(4)H_2), 28.3 (C(*C*H_3)$_3$) and 19.7 (C(5)HCH_3); *m*/*z* (CI) 291.3 (100, M+H$^+$); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_3$ requires 291.1703, found 291.1705 (+0.7 ppm).

*4.6.2. (RS)-2-Benzyl-5-methylpyrazolidin-3-one **31**.*



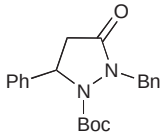
31

(*RS*)-*tert*-Butyl 2-benzyl-5-methyl-3-oxopyrazolidine-1-carboxylate **27** (2.84 g, 9.78 mmol) was stirred at rt overnight in a 1:1 mixture of trifluoroacetic acid/dichloromethane (8 mL) before being concentrated in vacuo. The resulting material was redissolved in dichloromethane (6 mL), cooled to 0 °C before treatment with

triethylamine (2.40 mL, 17.2 mmol). The resulting solution was stirred at rt for a further 15 min before being partitioned between water (40 mL) and dichloromethane (40 mL). The resultant aqueous layer was washed with dichloromethane (40 mL) and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was then purified by column chromatography, eluting with 5% methanol in ethyl acetate to give the title compound as a clear yellow oil (1.42 g, 76%).

ν_{max} (film) cm^{-1} 3202 (N–H), 3063 (Ar–H), 3031 (Ar–H), 2970 (C–H), 2925 (C–H), 2868 (N–C–H), 1678 (C=O), 1605 (Ar C=C) and 1583 (N–H bend); δ_H (300 MHz, $CDCl_3$) 7.40–7.30 (5H, m, Ar*H*), 4.70 (1H, d, AB system, J_{AB} 14.6, CH_AH$_B$Ph), 4.55 (1H, d, AB system, J_{BA} 14.6, CH$_A$$H_B$Ph), 4.10 (1H, br s, N(1)*H*), 3.69 (1H, app dquin, *J* 8.3, 6.7, C(5)*H*), 2.71 (1H, dd, ABX system, J_{AB} 16.2, J_{AX} 7.1, C(4)H_AH$_B$), 2.29 (1H, dd, ABX system, J_{BA} 16.2, J_{BX} 8.3, C(4)H$_A$$H_B$) and 1.25 (3H, d, *J* 6.4, C(5)HCH_3); δ_C (75 MHz, $CDCl_3$) 175.7 (*C*(3)O), 139.2 (*C*Ar$_{ipso}$), 132.1 (*C*Ar), 131.6 (*C*Ar), 131.1 (*C*Ar), 54.8 (*C*(5)H), 51.4 (*C*H$_2$Ph), 43.8 (*C*(4)H$_2$) and 22.1 (C(5)HCH$_3$); *m*/*z* (CI) 191.2 (100, M+H$^+$); HRMS (ESI$^+$) $C_{11}H_{15}N_2O$ requires 191.1179, found 191.1177 (−0.8 ppm).

*4.6.3. (RS) tert-Butyl 2-benzyl-3-oxo-5-phenylpyrazolidine-1-carboxylate **29**.*



29

To a solution of hydrazine hydrate (1.45 mL, 29.8 mmol) in absolute ethanol (25 mL) was added ethyl cinnamate **17** (5.00 mL, 29.8 mmol) and the resulting solution stirred at reflux overnight. The suspension was then concentrated in vacuo and redissolved in toluene (25 mL) and stirred at reflux for 3 h. The resulting solution was concentrated in vacuo to give crude (*RS*)-5-phenylpyrazolidin-3-one **21** (3.62 g) as a brown solid. Product was used without further purification. An analytical sample was taken and purified by recrystallisation in hot toluene to give the title compound as an off-white solid.

ν_{max} (KBr disc) cm^{-1} 3234 (N–H), 3191 (N–H), 3051 (Ar–H), 3019 (C–H), 1715 (C=O), 1664 (N–H bend) and 1599 (Ar C=C); mp 95–97 °C; δ_H (400 MHz, $CDCl_3$) 7.44–7.32 (5H, m, Ar*H*), 4.84 (1H, app t, *J* 8.5, C(5)*H*), 2.85 (1H, dd, ABX system, J_{AB} 16.2, J_{AX} 7.6, C(4)H_AH$_B$) and 2.76 (1H, dd, ABX system, J_{BA} 16.2, J_{BX} 9.4, C(4)H$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 176.7 (*C*(3)O), 138.4 (*C*Ar$_{ipso}$), 129.1 (*C*Ar), 128.6 (*C*Ar), 126.7 (*C*Ar), 62.0 (*C*(5)H) and 38.3 (*C*(4)H$_2$); *m*/*z* (ES) 185.0 (100, M+Na$^+$), 163.2 (100, M+H$^+$); HRMS (ESI$^+$) $C_9H_{11}N_2O$ requires 163.0866, found 163.0867 (+0.6 ppm).

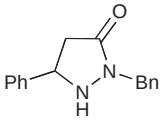
To a solution of crude (*RS*)-5-phenylpyrazolidin-3-one **21** (3.62 g, 22.3 mmol) in water (30 mL) were added sodium carbonate (2.37 g 22.3 mmol) and dioxane (10 mL). A solution of di-*tert*-butyl dicarbonate (4.90 g, 22.4 mmol) in dioxane (10 mL) was then added and the mixture stirred at rt for 3 h. The resulting suspension was filtered and the precipitate washed with chloroform. The combined organic extracts were then concentrated in vacuo to approximately 30 mL volume and partitioned between water (100 mL) and dichloromethane (75 mL). The aqueous layer was extracted with further dichloromethane (2×75 mL) and then the combined organic extracts washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude (*RS*)-*tert*-butyl 5-phenyl-3-oxopyrazolidine-1-carboxylate **25** (4.95 g) as a yellow oil. Product was used without further purification. An analytical sample was taken and purified by column chromatography, eluting with 50% dichloromethane in petrol, then 5% methanol in dichloromethane to give the title compound as a colourless solid.

ν_{max} (KBr disc) cm^{-1} 3334 (N–H), 3016 (Ar–H), 2965 (C–H), 1707 (C=O) and 1681 (C=O); mp 134–137 °C; δ_N ($CDCl_3$) 147 (*N*(1) Boc), 127 (*N*(2)H); δ_H (500 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ar*H*), 5.33 (1H, dd, *J* 10.4. 3.9, C(5)*H*), 3.30 (1H, dd, ABX system, J_{AB} 17.3, J_{AX} 10.4, C(4)H_AH$_B$), 2.63 (1H, dd, ABX system, J_{BA} 17.3, J_{BX} 3.9, C(4) H$_A$$H_B$) and 1.36 (9H, s, C(C$H_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 169.6 (*C*(3)O), 153.7 (*C*(O)O), 141.2 (*C*Ar$_{ipso}$), 129.3 (*C*Ar), 128.5 (*C*Ar), 126.1 (*C*Ar), 83.2 (*C*(CH$_3$)$_3$), 59.9 (*C*(5)H), 40.0 (*C*(4)H$_2$) and 28.5 (C(*C*H$_3$)$_3$); *m*/*z* (CI) 224.2 (100, M−C(CH$_3$)$_3$+NH$_4^+$), 263.3 (20, M+H$^+$); HRMS (ESI$^+$) $C_{14}H_{19}N_2O_3$ requires 263.1390, found 263.1392 (+0.7 ppm).

A solution of crude (*RS*)-*tert*-butyl 5-phenyl-3-oxopyrazolidine-1-carboxylate **25** (4.95 g, 18.9 mmol) in DMF (25 mL) was treated with benzyl bromide (2.25 mL, 18.9 mmol) and potassium carbonate (2.61 g, 18.9 mmol) and the suspension stirred at rt for 90 min. The reaction mixture was partitioned between diethyl ether (50 mL) and water (50 mL) and the resultant aqueous layer washed with further diethyl ether (2×50 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The material was then purified by column chromatography, eluting with 20% ethyl acetate in petrol. Chromatography was then repeated, this time eluting with 15–20% ethyl acetate in petrol to give the title compound as a yellow oil (2.63 g, 25%).

ν_{max} (film) cm^{-1} 3064 (Ar–H), 3032 (Ar–H), 2978 (C–H), 2933 (C–H), 2873 (N–C–H), 1750–1658 (2×C=O), 1604 (Ar C=C) and 1587 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 7.28–7.24 (1H, m, Ar*H*), 7.21–7.12 (5H, m, Ar*H*), 7.04 (2H, t, *J* 7.5, Ar*H*), 6.70 (2H, d, *J* 7.5, Ar*H*), 5.45 (1H, app d, *J* 9.3, C(5)*H*), 5.31 (1H, d, AB system, J_{AB} 14.2, CH_AH$_B$Ph), 4.59 (1H, d, AB system, J_{BA} 14.2, CH$_A$$H_B$Ph), 3.30 (1H, dd, *J* 16.8, 9.5, C(4)H_AH$_B$), 2.66 (1H, d, *J* 16.8, C(4)H$_A$$H_B$) and 1.56 (9H, s, C (C$H_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 170.5 (*C*(3)O), 156.7 (*C*(O)O), 139.5 (*C*Ar$_{ipso}$), 135.7 (*C*Ar$_{ipso}$), 130.1 (*C*Ar), 128.8 (*C*Ar), 128.4 (*C*Ar), 127.8 (*C*Ar), 126.1 (*C*Ar), 83.4 (*C*(CH$_3$)$_3$), 60.2 (*C*(5)H), 49.2 (*C*H$_2$Ph), 37.8 (*C* (4)H$_2$) and 28.7 (C(*C*H$_3$)$_3$); *m*/*z* (CI) 353.3 (100, M+H$^+$); HRMS (ESI$^+$) $C_{21}H_{25}N_2O_3$ requires 353.1860, found 353.1863 (+0.8 ppm).

*4.6.4. (RS)-2-Benzyl-5-phenylpyrazolidin-3-one **33**.*

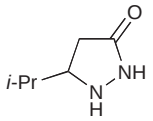


33

To a solution of (*RS*)-*tert*-butyl 2-benzyl-5-phenyl-3-oxopyrazolidine-1-carboxylate **29** (2.28 g, 6.48 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5.00 mL, 64.8 mmol) and the resulting mixture stirred at rt overnight. The excess acid was then quenched with saturated sodium hydrogen carbonate solution (150 mL) and extracted with dichloromethane (2×100 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the title compound as an off-white solid on standing (1.59 g, 97%).

ν_{max} (film) cm^{-1} 3214 (N–H), 3062 (Ar–H), 3031 (Ar–H), 2920 (C–H), 1683 (C=O), 1604 (Ar C=C) and 1560 (N–H bend); mp 60–62 °C; δ_H (400 MHz, $CDCl_3$) 7.26–7.18 (5H, m, Ar*H*), 4.62 (1H, d, AB system, J_{AB} 14.6, CH_AH$_B$Ph), 4.58 (1H, app t, *J* 8.4, C(5)*H*), 4.51 (1H, d, AB system, J_{BA} 14.6, CH$_A$$H_B$Ph), 2.87 (1H, dd, ABX system, J_{AB} 16.3, J_{AX} 7.8, C(4)H_AH$_B$) and 2.71 (1H, dd, ABX system, J_{BA} 16.3, J_{BX} 8.9, C(4)H$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 171.4 (*C*(3)O), 135.8 (*C*Ar$_{ipso}$), 135.7 (*C*Ar$_{ipso}$), 128.87 (*C*Ar), 128.85 (*C*Ar), 128.5 (*C*Ar), 128.3 (*C*Ar), 128.0 (*C*Ar), 126.5 (*C*Ar), 58.2 (*C*(5)H), 48.1 (*C*H$_2$Ph) and 39.3 (*C*(4) H$_2$); *m*/*z* (CI) 253.2 (100, M+H$^+$); HRMS (ESI$^+$) $C_{16}H_{17}N_2O$ requires 253.1335, found 253.1333 (−0.9 ppm).

*4.6.5. (RS)-5-iso-Propylpyrazolidin-3-one **20**.*

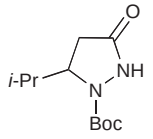


20

To a solution of *iso*-butyrlaldehyde (2.17 mL, 24.0 mmol) in dichloromethane (100 mL), cooled to 0 °C, was added ethyl (triphenylphosphoranylidene)acetate (10.0 g, 29.0 mmol) and the resulting clear yellow solution stirred at rt overnight before being concentrated in vacuo. The crude material was then passed through a plug of silica gel, eluting with 3% ethyl acetate in petrol. The resulting crude residue was then dissolved in absolute ethanol (15 mL), hydrazine hydrate (1.17 mL, 24.0 mmol) was added and the solution stirred for 1 h at rt and then at reflux for 4 h before concentration in vacuo. The crude material was purified by column chromatography, eluting with 5% methanol in dichloromethane, then flushed with 20% methanol in dichloromethane to give the product as a clear yellow oil (2.68 g, 87%).

ν_{max} (film) cm^{-1} 3401 (N–H), 3214 (N–H), 2961 (C–H), 2931 (C–H), 2874 (N–C–H) and 1683 (C=O); δ_H (300 MHz, $CDCl_3$) 3.33 (1H, app dt, *J* 9.4, 7.7, C(5)*H*), 2.43 (1H, dd, ABX system, J_{AB} 16.4, J_{AX} 7.4, C(4)H_AH_B), 2.23 (1H, dd, ABX system, J_{BA} 16.4, J_{BX} 9.4, C(4)H_AH_B), 1.67 (1H, dsept, *J* 7.9, 6.5C(5)HC*H*). 0.94 (3H, d, *J* 6.5 CH(CH_3)$_A$(CH_3)$_B$) and 0.89 (3H, d, *J* 6.5, CH(CH_3)$_A$(CH_3)$_B$); δ_C (75 MHz, $CDCl_3$) 177.6 (*C*(3)O), 65.6 (*C*(5)H), 36.6 (*C*(4)H_2), 32.5 (C(5)HCH), 19.7 (CH(CH_3)$_A$(CH_3)$_B$) and 19.6 (C(4)(CH_3)$_A$(CH_3)$_B$); *m*/*z* (CI) 129.1 (100, M+H^+); HRMS (CI) $C_6H_{13}N_2O$ requires 129.1028, found 129.1032 (+3.2 ppm).

*4.6.6. (RS)-tert-Butyl 5-iso-propyl-3-oxopyrazolidine-1-carboxylate **24**.*

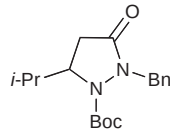


24

To a solution of (*RS*)-5-*iso*-propylpyrazolidin-3-one **20** (578 mg, 4.51 mmol) in water (6 mL) were added sodium carbonate (503 mg, 4.75 mmol) and dioxane (3 mL). A solution of di-*tert*-butyl dicarbonate (1.02 g, 4.67 mmol) in dioxane (3 mL) was then added and the mixture stirred at rt overnight. TLC analysis showed incomplete reaction. Hence, more sodium carbonate (240 mg, 2.26 mmol) and di-*tert*-butyl dicarbonate (490 mg, 2.24 mmol) in dioxane (1 mL) were added and the mixture stirred for a further 3 h. The resulting suspension was then filtered and the precipitate washed with chloroform. The combined organic extracts were then concentrated in vacuo to approximately 5 mL volume and partitioned between water (40 mL) and dichloromethane (40 mL). The aqueous layer was washed with further dichloromethane (240 mL) and then the combined organic extracts washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography, eluting with 2% methanol in dichloromethane to give the product as an off-white solid (530 mg, 51%).

ν_{max} (film) cm^{-1} 3171 (N–H), 3072 (N–H), 2970 (C–H), 2933 (C–H), 2877 (N–C–H), 1698 (C=O) and 1676 (C=O); mp 80–81 °C; δ_H (300 MHz, $CDCl_3$) 4.13 (1H, ddd, *J* 9.8, 6.4, 2.5, C(5)*H*), 2.80 (1H, dd, ABX system, J_{AB} 17.3, J_{AX} 9.8, C(4)H_AH_B), 2.23 (1H, dd, ABX system, J_{BA} 17.3, J_{BX} 2.5, C(4)H_AH_B), 1.84 (1H, app oct, *J* 6.6, C(5)HC*H*). 1.43 (9H, s, C(CH_3)$_3$) and 0.88 (6H, d, *J* 6.8, CH(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 170.7 (*C*(3)O), 154.7 (*C*(O)O), 82.6 (*C*(CH_3)$_3$), 62.1 (*C*(5)H), 33.6 (*C*(4)H_2), 32.3 (C(5)HCH), 28.3 (C(*C*H_3)$_3$), 17.9 (CH(*C*H_3)$_A$(CH_3)$_B$) and 17.7 (C(4)(CH_3)$_A$(*C*H_3)$_B$); *m*/*z* (CI) 190.3 (100, M–C(CH_3)$_3$+NH_4^+), 229.3 (35, M+H^+); HRMS (ESI$^+$) $C_{11}H_{21}N_2O_3$ requires 229.1547, found 229.1547.

*4.6.7. (RS)-tert-Butyl 2-benzyl-5-iso-propyl-3-oxopyrazolidine-1-carboxylate **28**.*

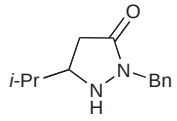


28

A solution of crude (*RS*)-*tert*-butyl 5-*iso*-propyl-3-oxopyrazolidine-1-carboxylate **24** (498 mg, 2.18 mmol) in DMF (2 mL) was treated with benzyl bromide (0.260 mL, 2.18 mmol) and potassium carbonate (301 mg, 2.18 mmol) and the suspension stirred at rt for 60 min. The reaction mixture was partitioned between diethyl ether (20 mL) and water (20 mL) and the resultant aqueous layer washed with further diethyl ether (2×20 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The material was then purified by column chromatography, eluting with 20% ethyl acetate in petrol. Chromatography was then repeated, this time eluting with 15–25% ethyl acetate in petrol to give the title compound as a crystalline yellow solid (281 mg, 41%).

ν_{max} (KBr disc) cm^{-1} 3067 (Ar–H), 3035 (Ar–H), 2971 (C–H), 2928 (C–H), 2862 (N–C–H), 1744–1661 (2×C=O), 1602 (Ar C=C) and 1586 (Ar C=C); mp 53–56 °C; δ_H (300 MHz, $CDCl_3$) 7.23 (5H, br s, Ar*H*), 5.21 (1H, d, AB system, J_{AB} 14.0, C$H_A$$H_B$Ph), 4.39 (1H, d, AB system, J_{BA} 14.0, CH$_A$$H_B$Ph), 3.76 (1H, app t, *J* 9.3, C(5)*H*), 2.78 (1H, dd, J_{AB} 16.6, 8.7, C(4)H_AH_B), 2.14 (1H, d, *J* 16.6, C(4)H$_A$$H_B$), 1.45 (9H, s, C(C$H_3$)$_3$), 0.88 (1H, dsept, *J* 10.2, 6.6, C(5)HC*H*), 0.61 (3H, d, *J* 6.6, CH(CH_3)$_A$(CH_3)$_B$) and 0.24 (3H, d, *J* 6.6, CH(CH_3)$_A$(CH_3)$_B$); δ_C (75 MHz, $CDCl_3$) 170.9 (*C*(3)O), 156.6 (*C*(O)O), 135.7 (Ar$_{ipso}$), 129.7 (*C*Ar), 128.4 (*C*Ar), 128.2 (*C*Ar), 82.4 (*C*(CH_3)$_3$), 64.1 (*C*(5)H), 48.6 (*C*H_2Ph), 34.9 (*C*(4)H_2), 30.8 (C(5)HCH), 28.3 (C(*C*H_3)$_3$), 18.5 (CH(*C*H_3)$_A$(CH_3)$_B$) and 18.3 (C(4)(CH_3)$_A$(*C*H_3)$_B$); *m*/*z* (CI) 219.3 (100, M-CO_2C(CH_3)$_3$+NH_4^+), 319.2 (60, M+H^+); HRMS (ESI$^+$) $C_{18}H_{27}N_2O_3$ requires 319.2016, found 319.2019 (–0.8 ppm).

*4.6.8. (RS)-2-Benzyl-5-iso-propylpyrazolidin-3-one **32**.*



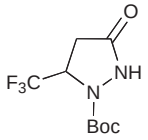
32

To a solution of (*RS*)-*tert*-butyl 2-benzyl-5-*iso*-propyl-3-oxopyrazolidine-1-carboxylate **28** (390 mg, 1.67 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.500 mL, 6.47 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.200 mL, 1.62 mmol) was added and the mixture stirred for 2 h before being concentrated in vacuo. The resulting material was partitioned between dichloromethane (50 mL) and saturated sodium hydrogen carbonate solution (50 mL). The aqueous layer was washed with dichloromethane (2×50 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The

crude material was then purified by column chromatography, eluting with 50% ethyl acetate in petrol to give the title compound as a clear yellow oil, which solidified on standing (179 mg, 67%).

ν_{max} (KBr disc) cm^{-1} 3178 (N–H), 3061 (Ar–H), 3035 (Ar–H), 2961 (C–H), 2954 (C–H), 2880 (N-C–H), 1661 (C=O), 1602 (Ar C=C) and 1560 (N–H bend); mp 53–54 °C; δ_H (400 MHz, $CDCl_3$) 7.37–7.27 (5H, m, Ar*H*), 4.64 (1H, d, AB system, J_{AB} 14.5, CH_AH_BPh), 4.52 (1H, d, AB system, J_{BA} 14.5, CH$_A$$H_B$Ph), 4.07 (1H, br s, N(1)*H*), 3.22 (1H, app q, *J* 8.1, C(5)*H*), 2.61 (1H, dd, ABX system, J_{AB} 16.4, J_{AX} 7.7, C(4)H_AH_B), 2.34 (1H, d, ABX system, J_{BA} 16.4, J_{BX} 8.7, C(4)H$_A$$H_B$), 1.61 (1H, dsept, *J* 7.8, 6.7, C(5)HC*H*), 0.91 (3H, d, *J* 6.7, CH(CH_3)$_A$(CH$_3$)$_B$) and 0.89 (3H, d, *J* 6.7, CH(CH$_3$)$_A$(CH_3)$_B$); δ_C (75 MHz, $CDCl_3$) 172.1 (*C*(3)O), 136.1 (Ar$_{ipso}$), 128.9 (*C*Ar), 128.4 (*C*Ar), 127.9 (*C*Ar), 61.3 (*C*(5)H), 48.1 (*C*H$_2$Ph), 37.0 (*C*(4)H$_2$), 32.2 (C(5)HCH) and 19.2 (CH(*C*H$_3$)$_2$); *m/z* (CI) 219.3 (100, M+H$^+$); HRMS (EI) $C_{13}H_{18}N_2O$ requires 218.1414, found 218.1413 (−0.3 ppm).

*4.6.9. (RS)-tert-Butyl 3-oxo-5-(trifluoromethyl)pyrazolidine-1-carboxylate **26**.*



26

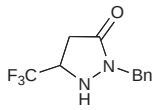
To a solution of hydrazine hydrate (1.60 mL, 32.7 mmol) in absolute ethanol (50 mL) was added ethyl 4,4,4-trifluorocrotonate **18** (4.40 mL, 29.3 mmol) and the resulting solution stirred at reflux for 3 h before concentration in vacuo to give crude (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **22** (3.35 g) as a yellow solid. Product was used without further purification. An analytical sample was taken and purified by recrystallisation in hot toluene to give the title compound as colourless plates.

ν_{max} (KBr disc) cm^{-1} 3248 (N–H), 3190 (N–H), 1694 (C=O) and 1648 (N–H bend); mp 130–132 °C; δ_F (375 MHz, CD_3OD) −81.0 (3F, d, *J* 8.2, C*F*$_3$); δ_H (300 MHz, CD_3OD) 4.18 (1H, dqd, *J* 10.3, 8.2, 2.6, C(5)*H*), 3.02 (1H, dd, ABX system, J_{AB} 17.4, J_{AX} 10.3, C(4)H_AH_B) and 2.42 (1H, dd, ABX system, J_{BA} 17.4, J_{BX} 2.6, C(4)H$_A$$H_B$); δ_C (75 MHz, CD_3OD) 174.2 (*C*(3)O), 125.2 (q, *J* 279, *C*F$_3$), 56.2 (q, *J* 31.4, *C*(5)H) and 31.0 (q, *J* 1.5, *C*(4)H$_2$); *m/z* HRMS (ESI$^+$) $C_4H_9F_3N_3O$ requires 172.0692, found 172.0688 (−2.6 ppm).

To a solution of crude (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **22** (2.62 g, 17.0 mmol) in water (20 mL) were added sodium carbonate (1.80 g, 17.0 mmol) and dioxane (10 mL). A solution of di-*tert*-butyl dicarbonate (3.70 g, 17.0 mmol) in dioxane (10 mL) was then added and the mixture stirred at rt overnight. The resulting suspension was filtered and the precipitate washed with ethyl acetate. The combined organic extracts were then concentrated in vacuo to a small volume at which point the title compound began to precipitate. This solid was collected by filtration and washed with water. The combined filtrate was cooled to 0 °C overnight to yield a second crop of the title compound, which was collected by filtration and washed with further cold water. The combined solids were dried in a desiccator to give the title compound as a colourless solid (2.64 g, 35%).

ν_{max} (film) cm^{-1} 3343 (N–H), 3010 (N–H), 2986 (C–H), 1717 (C=O) and 1697 (C=O); mp 141–144 °C; δ_F (375 MHz, $CDCl_3$) −79.3 (3F, d, *J* 6.7, C*F*$_3$); δ_H (300 MHz, $CDCl_3$) 4.89 (1H, dqd, *J* 10.6, 6.7, 2.3, C(5)*H*), 3.08 (1H, dd, ABX system, J_{AB} 17.8, J_{AX} 10.6, C(4)H_AH_B), 2.64 (1H, dd, ABX system, J_{BA} 17.8, J_{BX} 2.3, C(4)H$_A$$H_B$) and 1.52 (9H, s, C(C$H_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 168.7 (*C*(3)O), 154.0 (*C*(O)O), 124.0 (q, *J* 281, *C*F$_3$), 84.7 *C*(CH$_3$)$_3$, 56.7 (q, *J* 34.0, *C*(5)H), 30.8 (*C*(4)H$_2$) and 28.1 (C(*C*H$_3$)$_3$); *m/z* HRMS (ESI$^+$) $C_9H_{14}F_3N_2O_3$ requires 255.0951, found 255.0954 (+1.2 ppm).

*4.6.10. (RS)-2-Benzyl-5-(trifluoromethyl)pyrazolidin-3-one **34**.*



34

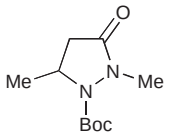
A solution of (*RS*)-*tert*-butyl 3-oxo-5-(trifluoromethyl)pyrazolidine-1-carboxylate **26** (1.00 g, 3.94 mmol) in DMF (8 mL) was treated with benzyl bromide (0.50 mL, 3.95 mmol) and potassium carbonate (544 mg, 3.95 mmol) and the suspension stirred at rt for 2 days. The reaction mixture was partitioned between diethyl ether (100 mL) and water (100 mL) and the resultant aqueous layer washed with further diethyl ether (2×100 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude (*RS*)-*tert*-butyl 2-benzyl-5-(trifluoromethyl)-3-oxopyrazolidine-1-carboxylate **30** (1.27 g) as a clear yellow oil. Product was used without further purification. An analytical sample was taken and purified by column chromatography, eluting with 15% ethyl acetate in petrol, to give the title compound as a clear oil, which became a colourless solid on standing.

ν_{max} (KBr disc) cm^{-1} 3064 (Ar–H), 3014 (Ar–H), 2985 (C–H), 1730 (C=O) and 1700 (C=O); mp 58–59 °C; δ_F (282 MHz, $CDCl_3$) −79.0 (3F, d, *J* 7.3, C*F*$_3$); δ_H (300 MHz, $CDCl_3$) 7.32–7.27 (5H, m, Ar*H*), 5.19 (1H, d, AB system, J_{AB} 14.3, CH_AH_BPh), 4.77 (1H, dqd, *J* 10.1, 7.3, 1.6, C(5)*H*), 4.58 (1H, d, AB system, J_{BA} 14.3, CH$_A$$H_B$Ph), 3.06 (1H, dd, *J* 17.5, 10.1, C(4)H_AH_B), 2.50 (1H, d, *J* 17.5, 1.6, C(4)H$_A$$H_B$) and 1.53 (9H, s, C(C$H_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 168.5 (*C*(3)O), 155.5 (*C*(O)O), 134.4 (*C*Ar$_{ipso}$), 129.8 (*C*Ar), 128.4 (*C*Ar), 128.3 (*C*Ar), 123.3 (q, *J* 281, *C*F$_3$), 84.6 (*C*(CH$_3$)$_3$), 56.9 (q, *J* 33.8, *C*(5)H), 50.0 (*C*H$_2$Ph), 30.8 (*C*(4)H$_2$) and 28.2 (C(*C*H$_3$)$_3$); *m/z* HRMS (ESI$^+$) $C_{16}H_{20}F_3N_2O_3$ requires 345.1421, found 345.1425 (+1.3 ppm).

Crude (*RS*)-*tert*-butyl 2-benzyl-5-(trifluoromethyl)-3-oxopyrazolidine-1-carboxylate **30** (1.04 g, 3.02 mmol) was stirred at rt overnight in a 1:2 mixture of trifluoroacetic acid/dichloromethane (15 mL) before being concentrated in vacuo. The resulting material was partitioned between dichloromethane (100 mL) and saturated sodium hydrogen carbonate solution (100 mL). The aqueous layer was washed with dichloromethane (2×100 mL) and the combined organic layers washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was then purified by recrystallisation from diethyl ether and the minimum quantity of dichloromethane to give the title compound as a colourless solid (484 mg, 50%).

$C_{11}H_{11}F_3N_2O$ requires C, 54.1; H 4.5; N, 11.5%; found C 53.9; H, 4.3; N, 11.6%; ν_{max} (KBr disc) cm^{-1} 3219 (N–H), 3068 (Ar–H), 3029 (Ar–H), 2951 (C–H), 2916 (C–H), 1700 (C=O) and 1667 (C=O); mp 85–86 °C; δ_F (282 MHz, $CDCl_3$) −79.1 (3F, d, *J* 7.2, C*F*$_3$); δ_H (300 MHz, $CDCl_3$) 7.38–7.28 (5H, m, Ar*H*), 4.92 (1H, d, AB system, J_{AB} 14.6, CH_AH_BPh), 4.69 (1H, s, N(1)*H*), 4.25 (1H, d, AB system, J_{BA} 14.6, CH$_A$$H_B$Ph), 3.93 (1H, dqd, *J* 10.0, 7.2, 3.3, C(5)*H*), 2.96 (1H, dd, *J* 17.4, 10.0, C(4)H_AH_B) and 2.66 (1H, d, *J* 17.4, 3.3, C(4)H$_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 168.3 (*C*(3)O), 135.1 (*C*Ar$_{ipso}$), 129.0 (*C*Ar), 128.6 (*C*Ar), 128.3 (*C*Ar), 124.7 (q, *J* 279, *C*F$_3$), 54.0 (q, *J* 32.3, *C*(5)H), 48.5 (*C*H$_2$Ph) and 31.9 (*C*(4)H$_2$); *m/z* HRMS (ESI$^+$) $C_{11}H_{12}F_3N_2O$ requires 245.0896, found 245.0890 (+0.7 ppm).

*4.6.11. (RS)-tert-Butyl 2,5-dimethyl-3-oxopyrazolidine-1-carboxylate **35**.*

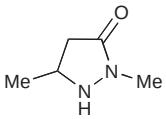


35

A solution of crude (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (2.92 g, 13.6 mmol) in DMF (30 mL) was treated with methyl iodide (2.80 mL, 45.0 mmol) and potassium carbonate (2.49 g, 18.0 mmol) and the suspension stirred at rt overnight. The reaction mixture was partitioned between diethyl ether (60 mL) and water (60 mL) and the resultant aqueous layer washed with further diethyl ether (60 mL). The combined organic layers were washed with brine (120 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The material was then purified by column chromatography, eluting with 25% ethyl acetate in petrol to give the title compound as a colourless oil with spectroscopic data in accordance with the literature (1.60 g, 53%).[20]

δ_H (300 MHz, $CDCl_3$) 4.53 (1H, app quin, *J* 7.0, C(5)*H*), 3.20 (3H, s, N(2)CH_3), 2.91 (1H, dd, *J* 16.3, 8.3, C(4)H_AH$_B$), 2.00 (1H, d, *J* 16.3, C(4)H$_A$$H_B$), 1.48 (9H, s, C(C$H_3$)$_3$) and 1.22 (3H, d, *J* 6.8, C(5)HCH_3).

4.6.12. (RS)-2,5-Dimethylpyrazolidin-3-one ***36****.*

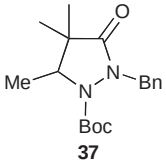


36

To a solution of (*RS*)-*tert*-butyl 2,5-dimethyl-3-oxopyrazolidine-1-carboxylate **35** (1.59 g, 7.42 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1.80 mL, 23.3 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.580 mL, 7.51 mmol) was added and the mixture stirred overnight before concentration in vacuo. The resulting material was partitioned between dichloromethane (100 mL) and saturated sodium hydrogen carbonate solution (100 mL). The aqueous layer was washed with dichloromethane (100 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the title compound as a colourless oil (145 mg). The aqueous layer was treated with triethylamine then extracted with further dichloromethane (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give further material (177 mg). The aqueous layer was then concentrated in vacuo and partitioned between 1 M sodium hydroxide solution (50 mL) and dichloromethane (80 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give further material (151 mg) (473 mg in total, 55%).

ν_{max} (film) cm^{-1} 3196 (N–H), 2969 (C–H), 2927 (C–H), 1667 (C=O), 1605 and 1597 (N–H bend); δ_H (300 MHz, $CDCl_3$) 4.12 (1H, br s, N(1)*H*), 3.66 (1H, app dquin, *J* 8.3, 6.7, C(5)*H*), 3.01 (3H, s, N(2)CH_3), 2.59 (1H, dd, ABX system, J_{AB} 16.1, J_{AX} 7.2, C(4)H_AH$_B$), 2.20 (1H, dd, ABX system, J_{BA} 16.1, J_{BX} 8.3, C(4)H$_A$$H_B$) and 1.24 (3H, d, *J* 6.4, C(5)HCH_3); δ_C (75 MHz, $CDCl_3$) 172.6 (*C*(3)O), 51.4 (*C*(5)H), 40.4 (*C*(4)H_2), 31.4 (N(2)CH_3) and 19.1 (C(5)HCH_3); *m*/*z* (CI) 115.2 (100, M+H$^+$); HRMS (ESI$^+$) $C_5H_{11}N_2O$ requires 115.0866, found 115.0865 (−0.4 ppm).

4.6.13. (RS)-tert-Butyl 2-benzyl-4,4,5-trimethyl-3-oxopyrazolidine-1-carboxylate ***37****.*

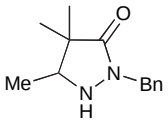


37

To a solution of (*RS*)-*tert*-butyl 2-benzyl-5-methyl-3-oxopyrazolidine-1-carboxylate **27** (268 mg, 0.923 mmol) in THF (5 mL), cooled to −78 °C, was added KHMDS (0.46 M in toluene, 10.0 mL, 4.60 mmol) and the red solution stirred for 70 min before treatment with methyl iodide (0.570 mL, 9.23 mmol). The mixture was stirred at −78 °C for 90 min, then at rt for 60 min. The reaction was then quenched with pH 7 phosphate buffer solution (20 mL), the resulting biphasic solution extracted with diethyl ether (3×15 mL) and the combined organic extracts washed with brine (30 mL) and dried ($MgSO_4$) before being filtered through a plug of silica gel and concentrated in vacuo. ^{1}H NMR showed a mixture of starting material **27**, monomethylated material and product **37** in the ratio 27:44:29 and so the crude material was redissolved in THF (5 mL), cooled to −78 °C and treated, as before, with identical amounts of KHMDS and methyl iodide. The mixture was stirred at −78 °C for 60 min before being quenched and following of the work-up procedure previously described. The crude material was purified by column chromatography, eluting with 10% ethyl acetate in petrol to give the product as a colourless oil (75 mg, 26%).

ν_{max} (film) cm^{-1} 3065 (Ar–H), 3032 (Ar–H), 2978 (C–H), 2934 (C–H), 2871 (N–C–H), 1747–1674 (2×C=O) and 1605 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 7.24–7.20 (5H, m, Ar*H*), 5.15 (1H, d, AB system, J_{AB} 14.2, CH_AH$_B$Ph), 4.31 (1H, d, AB system, J_{BA} 14.2, CH$_A$$H_B$Ph), 3.99 (1H, q, *J* 6.9, C(5)*H*), 1.48 (9H, s, C(CH_3)$_3$), 1.09 (3H, s, C(4)(CH_3)$_A$(CH$_3$)$_B$), 0.92 (3H, s, C(4)(CH$_3$)$_A$(CH_3)$_B$) and 0.42 (3H, d, *J* 6.9, C(5)HCH_3); δ_C (75 MHz, $CDCl_3$) 176.6 (*C*(3)O), 157.3 (*C*(O)O), 136.2 (*C*Ar$_{ipso}$), 130.2 (*C*Ar), 128.8 (*C*Ar), 128.5 (*C*Ar), 82.7 (*C*(CH$_3$)$_3$), 65.3 (*C*(5)H), 49.1 (*C*H$_2$Ph), 44.6 (*C*(4)(CH$_3$)$_2$), 28.7 (C(CH_3)$_3$), 24.8 (C(5)HCH_3), 18.2 (C(4)(CH_3)$_A$(CH$_3$)$_B$) and 15.8 (C(4)(CH$_3$)$_A$(CH_3)$_B$); *m*/*z* (CI) 219.2 (100, M−Boc+2H$^+$), 319.3 (60, M+H$^+$); HRMS (ESI$^+$) $C_{18}H_{27}N_2O_3$ requires 319.2016, found 319.2015 (+0.2 ppm).

4.6.14. (RS)-2-Benzyl-4,4,5-trimethylpyrazolidin-3-one ***38****.*



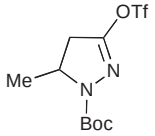
38

To a solution of (*RS*)-*tert*-butyl 2-benzyl-4,4,5-trimethyl-3-oxopyrazolidine-1-carboxylate **37** (142 mg, 0.446 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.2 mL, 2.69 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.2 mL, 2.69 mmol) was added and the mixture stirred for 2 h before being concentrated in vacuo. The resulting material was partitioned between dichloromethane (20 mL) and saturated sodium hydrogen carbonate solution (20 mL). The aqueous layer was washed with dichloromethane (2×20 mL) and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the title compound as a colourless oil (94 mg, 96%).

ν_{max} (film) cm^{-1} 3202 (N–H), 3064 (Ar–H), 3032 (Ar–H), 2969 (C–H), 2930 (C–H), 2873 (N–C–H), 1678 (C=O), 1606 (Ar C=C) and 1587 (N–H bend); δ_H (400 MHz, $CDCl_3$) 7.37–7.24 (5H, m, Ar*H*), 4.82 (1H, d, AB system, J_{AB} 14.7, CH_AH$_B$Ph), 4.34 (1H, d, AB system, J_{BA} 14.7, CH$_A$$H_B$Ph), 3.76 (1H, br s, N(1)*H*), 3.24 (1H, q, *J* 6.6, C(4)HCH_3), 1.15 (3H, s, C(4)(CH_3)$_A$(CH$_3$)$_B$), 1.06 (3H, d, *J* 6.6, C(5)HCH_3) and 0.95 (3H, s, C(4)(CH$_3$)$_A$(CH_3)$_B$); δ_C (100 MHz, $CDCl_3$) 177.7 (*C*(3)O), 136.2 (*C*Ar$_{ipso}$), 128.9 (*C*Ar), 128.2 (*C*Ar), 127.9 (*C*Ar), 61.4 (*C*(5)H), 48.1 (*C*H$_2$Ph), 43.5 (*C*(4)(CH$_3$)$_2$), 21.7 (C(4)

(CH_3)$_A$(CH_3)$_B$), 16.4 (C(4)(CH_3)$_A$(CH_3)$_B$) and 12.0 (C(5)HCH_3); *m*/*z* (ESI$^+$) 241.1 (100, M+Na$^+$); HRMS (ESI$^+$) $C_{13}H_{18}N_2ONa$ requires 241.1317, found 241.1317.

4.6.15. (RS)-tert-Butyl 3-(trifluoromethylsulfonyloxy)-5-methyl-4,5-dihydro-1H-pyrazole-1-carboxylate ***39****.*

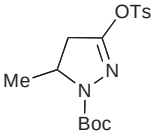


39

To a solution of (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (250 mg, 1.25 mmol) in dichloromethane (5 mL) was added triethylamine (0.700 mL, 5.00 mmol). The resulting suspension was then cooled to −78 °C and triflic anhydride (0.410 mL, 2.50 mmol) added dropwise. The reaction mixture was stirred at −78 °C for 2 h and 1:1 water/methanol added (4 mL). The reaction mixture was warmed to rt, maintained for 30 min, then diluted with diethyl ether (30 mL). The organic layer was washed with 0.1 M hydrochloric acid (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was then purified by column chromatography, eluting with 10% ethyl acetate in petrol to give the title compound as a colourless oil, which solidified on standing (176 mg, 42%).

ν_{max} (KBr disc) cm^{-1} 2990 (C–H), 2932 (C–H), 2873 (N–C–H), 1713 (C=O), 1635 (C=N) and 1572 (Ar C=C); mp 41–43 °C; δ_H (400 MHz, $CDCl_3$) 4.61 (1H, app dquin, *J* 11.3. 6.3, C(5)*H*), 3.38 (1H, dd, ABX system, J_{AB} 17.8, J_{AX} 11.3, C(4)H_AH_B), 2.70 (1H, dd, ABX system, J_{BA} 17.8, J_{BX} 5.3, C(4)H_AH_B), 1.52 (9H, s, C(CH_3)$_3$) and 1.42 (3H, d, *J* 6.3, C(5)HCH_3); δ_C (100 MHz, $CDCl_3$) 153.2 (*C*(O)O), 151.6 (*C*(4)N), 118.5 (q, *J*=321, *C*F$_3$), 82.4 (*C*(CH_3)$_3$), 56.9 (*C*(5)H), 38.7 (*C*(4)H_2), 28.4 (C(CH_3)$_3$) and 20.8 (C(5)HCH_3); *m*/*z* (CI) 132.3 (100, $SO_2CF_3^+$), 350.3 (20, M+NH_4^+); HRMS (ESI$^+$) $C_{10}H_{19}F_3N_3O_5S$ requires 350.0992, found 350.0991 (−0.3 ppm).

4.6.16. (RS)-tert-Butyl 5-methyl-3-(tosyloxy)-4,5-dihydro-1H-pyrazole-1-carboxylate ***40****.*

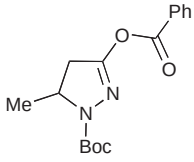


40

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (0.991 g, 4.95 mmol) triethylamine (0.800 mL, 5.74 mmol) and tosyl chloride (1.00 g, 5.25 mmol) were combined according to general procedure A. The crude material was then purified by column chromatography, eluting with 15% ethyl acetate in petrol to give the title compound as a colourless oil, which solidified on standing (810 mg, 46%).

ν_{max} (KBr disc) cm^{-1} 2987 (C–H), 2934 (C–H), 1698 (C=O), 1645 (C=N), 1596 (Ar C=C) and 1586 (Ar C=C); mp 84–86 °C; δ_N ($CDCl_3$) 295 (*N*(2)COS(O)$_2$), 156 (*N*(1)Boc); δ_H (300 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.4, Ar*H*), 7.36 (2H, d, *J* 8.4, Ar*H*), 4.46 (1H, app dquin, *J* 11.0. 6.1, C(5)*H*), 3.26 (1H, dd, ABX system, J_{AB} 17.8, J_{AX} 11.0, C(4)H_AH_B), 2.61 (1H, dd, ABX system, J_{BA} 17.8, J_{BX} 5.3, C(4)H_AH_B), 1.49 (9H, s, C(CH_3)$_3$) and 1.34 (3H, d, *J* 6.3, C(5)HCH_3); δ_C (75 MHz, $CDCl_3$) 155.0 (*C*(O)O), 151.9 (*C*(4)N), 146.3 (*C*Ar$_{ipso}$), 132.3(*C*Ar$_{para}$), 129.9 (*C*Ar), 129.3 (*C*Ar), 81.3 (*C*(CH_3)$_3$), 55.5 (*C*(5)H), 39.0 (*C*(4)H_2), 28.4 (C(CH_3)$_3$), 21.9 (CAr$_{para}$CH_3) and 20.7 (C(5)HCH_3); *m*/*z* (ESI$^+$) 372.2 (100, M+NH_4^+); HRMS (ESI$^+$) $C_{10}H_{19}F_3N_3O_5S$ requires 372.1588, found 372.1593 (+1.4 ppm).

4.6.17. (RS)-tert-Butyl 3-(benzoyloxy)-5-methyl-4,5-dihydro-1H-pyrazole-1-carboxylate ***41****.*

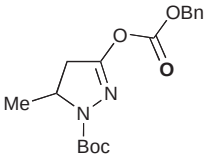


41

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (250 mg, 1.25 mmol) triethylamine (0.200 mL, 1.38 mmol) and benzoyl chloride (0.200 mL, 1.73 mmol) were combined according to general procedure A to give crude product (568 mg). Attempted purification of this material by column chromatography led to decomposition to unidentified side-products. Hence, characterisation was carried out on the crude mixture.

ν_{max} (film) cm^{-1} 3065 (Ar–H), 2979 (C–H), 2932 (C–H), 2862 (N–C–H), 1750 (C=O), 1642 (C=O) and 1601 (C=N); δ_H (300 MHz, $CDCl_3$) 8.11–8.07 (2H, m, Ar*H*), 7.56–7.45 (3H, m, Ar*H*), 4.59 (1H, app dquin, *J* 11.0. 6.0, C(5)*H*), 3.50 (1H, dd, ABX system, J_{AB} 17.6, J_{AX} 11.0, C(4)H_AH_B), 2.83 (1H, dd, ABX system, J_{BA} 17.6, J_{BX} 4.9, C(4)H_AH_B), 1.54 (9H, s, C(CH_3)$_3$) and 1.45 (3H, d, *J* 6.3, C(5)HCH_3); δ_C (100 MHz, $CDCl_3$) 163.2 (*C*(O)Ph), 157.3 (*C*(4)N), 134.6 (*C*Ar$_{ipso}$), 130.6 (*C*Ar), 130.5 (*C*Ar), 128.8 (*C*Ar), 81.5 (*C*(CH_3)$_3$), 55.8 (*C*(5)H), 38.7 (*C*(4)H_2), 28.4 (C(CH_3)$_3$) and 20.6 (C(5)HCH_3); *m*/*z* (ESI$^+$) 327.1 (100, M+Na$^+$); HRMS (ESI$^+$) $C_{16}H_{20}N_2NaO_4$ requires 327.1321, found 327.1323 (+0.6 ppm).

4.6.18. (RS)-tert-Butyl 3-(benzyloxycarbonyloxy)-5-methyl-4,5-dihydro-1H-pyrazole-1-carboxylate ***42****.*

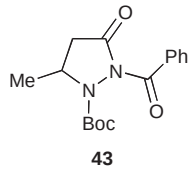


42

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (1.00 g, 5.00 mmol) triethylamine (0.800 mL, 5.74 mmol) and benzyl chloroformate (0.75 mL, 5.25 mmol) were combined according to general procedure A to give crude product (1.77 g). Attempted purification of this material by column chromatography led to decomposition and return of starting compound **23**. Hence, characterisation was carried out on the crude mixture.

ν_{max} (film) cm^{-1} 3066 (Ar–H), 3035 (Ar–H), 2978 (C–H), 2932 (C–H), 2863 (N–C–H), 1751 (C=O), 1725 (C=O), 1648 (C=N) and 1587 (Ar C=C); δ_N ($CDCl_3$) 296 (*N*(2)COC(O)), 155 (*N*(1)Boc); δ_H (300 MHz, $CDCl_3$) 7.40–7.33 (5H, m, Ar*H*), 5.23 (2H, s, CH_2Ph), 4.54 (1H, app dquin, *J* 11.1. 6.1, C(5)*H*), 3.37 (1H, dd, ABX system, J_{AB} 17.7, J_{AX} 11.1, C(4)H_AH_B), 2.68 (1H, dd, ABX system, J_{BA} 17.7, J_{BX} 5.0, C(4)H_AH_B), 1.52 (9H, s, C(CH_3)$_3$) and 1.39 (3H, d, *J* 6.3, C(5)HCH_3); δ_C (100 MHz, $CDCl_3$) 156.3 (*C*(4)N), 151.2 (O*C*(O)O), 134.1 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 128.9 (*C*Ar), 128.7 (*C*Ar), 81.6 (*C*(CH_3)$_3$), 71.2 (*C*H_2Ph), 56.0 (*C*(5)H), 38.1 (*C*(4)H_2), 28.5 (C(CH_3)$_3$) and 20.7 (C(5)HCH_3); *m*/*z* (ESI$^+$) 357.0 (100, M+Na$^+$); HRMS (ESI$^+$) $C_{17}H_{22}N_2NaO_5$ requires 357.1426, found 357.1419 (−2.1 ppm).

4.6.19. (RS)-tert-Butyl 2-benzoyl-5-methyl-3-oxopyrazolidine-1-carboxylate ***43****.*

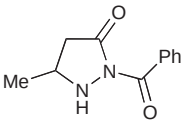


43

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (988 mg, 4.93 mmol), sodium hydride (225 mg, 5.63 mmol) and benzoyl chloride (0.60 mL, 5.24 mmol) were combined according to general procedure B. The resulting material was dissolved in toluene (15 mL) and refluxed for 5 h. The crude material was then purified by column chromatography, eluting with 25% ethyl acetate in petrol to give the title compound as a colourless solid (685 mg, 45%).

ν_{max} (KBr disc) cm^{-1} 2984 (C–H), 2932 (C–H), 2863 (N–C–H), 1759 (C=O), 1727 (C=O), 1699 (C=O) and 1596 (Ar C=C); mp 129–132 °C; δ_N ($CDCl_3$) 184 (*N*(2)C(O)), 136 (*N*(1)Boc); δ_H (300 MHz, $CDCl_3$) 7.81 (2H, dd, *J* 8.4, 1.3, ArH_{ortho}), 7.57 (1H, app tt, *J* 7.9, 1.3, ArH_{para}), 7.48–7.40 (2H, m, ArH_{meta}), 4.78 (1H, app quin, *J* 7.1, C(5)*H*), 3.14 (1H, dd, *J* 16.9, 8.3, C(4)H_AH_B), 2.28 (1H, d, *J* 16.9, C(4)H_AH_B), 1.40 (9H, s, C(CH_3)$_3$) and 1.39 (3H, d, *J* 6.4, C(5)HCH_3); δ_C (100 MHz, $CDCl_3$) 170.8 (*C*(3)O), 166.6 (*C*(O)Ph), 154.5 (*C*(O)O), 133.2 (*C*Ar$_{ipso}$), 133.1 (*C*Ar), 130.0 (*C*Ar), 128.2 (*C*Ar), 83.5 (*C*(CH_3)$_3$), 52.7 (*C*(5)H), 39.9 (*C*(4)H_2), 28.2 (C(CH_3)$_3$) and 20.4 (C(5)HCH_3); *m*/*z* (ESI^+) 139.2 (100, $H_2NC(O)Ph+NH_4^+$), 305.2 (15, $M+H^+$), 322.3 (20, $M+NH_4^+$); HRMS (ESI^+) $C_{16}H_{24}N_3O_4$ requires 322.1761, found 322.1761.

*4.6.20. (RS)-2-Benzoyl-5-methylpyrazolidin-3-one **45**.*

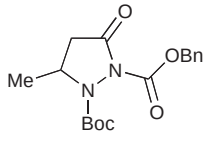


45

To a solution of (*RS*)-*tert*-butyl 2-benzoyl-5-methyl-3-oxopyrazolidine-1-carboxylate **43** (457 mg, 1.50 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.600 mL, 8.10 mmol) and the resulting solution stirred overnight at rt before being concentrated in vacuo. The resulting material was partitioned between dichloromethane (40 mL) and saturated sodium hydrogen carbonate solution (40 mL). The aqueous layer was washed with dichloromethane (2×40 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the title compound as a clear yellow oil (263 mg, 86%).

ν_{max} (film) cm^{-1} 3224 (N–H), 3061 (Ar–H), 3029 (Ar–H), 2974 (C–H), 2931 (C–H), 2873 (N–C–H), 1757 (C=O), 1672 (C=O), 1631 (N–H bend), 1600 (Ar C=C) and 1579 (Ar C=C); δ_H (400 MHz, $CDCl_3$) 7.65 (2H, dd, *J* 8.3, 1.3, ArH_{ortho}), 7.54 (1H, app tt, *J* 7.5, 1.3, ArH_{para}), 7.45–7.39 (2H, m, ArH_{meta}), 5.19 (1H, d, *J* 8.3, N(1)*H*), 3.84 (1H, app tquin, *J* 9.1, 6.4C(5)*H*), 2.85 (1H, dd, ABX system, J_{AB} 17.1, J_{AX} 6.8, C(4)H_AH_B), 2.50 (1H, dd, ABX system, J_{BA} 17.1, J_{BX} 9.5, C(4)H_AH_B) and 1.40 (3H, d, *J* 6.3, C(5)HCH_3); δ_C (100 MHz, $CDCl_3$) 171.9 (*C*(3)O), 166.7 (*C*(O)Ph), 133.1 (*C*Ar$_{ipso}$), 132.4 (*C*Ar), 129.4 (*C*Ar), 128.0 (*C*Ar), 50.2 (*C*(5)H), 42.1 (*C*(4)H_2) and 18.8 (C(5)HCH_3); *m*/*z* (CI) 205.1 (100, $M+H^+$); HRMS (CI) $C_{11}H_{13}N_2O_2$ requires 205.0977, found 205.0978 (+0.5 ppm).

*4.6.21. (RS)-1-Benzyl 2-tert-butyl 3-methyl-5-oxopyrazolidine-1,2-dicarboxylate **44**.*

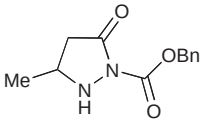


44

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **23** (1.01 g, 5.04 mmol), sodium hydride (220 mg, 5.50 mmol) and benzyl chloroformate (0.75 mL, 5.25 mmol) were combined according to general procedure B. The crude material was then purified by column chromatography, eluting with 25% ethyl acetate in petrol to give the title compound as a colourless oil (684 mg, 41%).

ν_{max} (film) cm^{-1} 3066 (Ar–H), 3034 (Ar–H), 2979 (C–H), 2933 (C–H), 2874 (N–C–H), 1799 (C=O), 1751 (C=O), 1728 (C=O) and 1587 (Ar C=C); δ_N ($CDCl_3$) 166 (*N*(2)CO_2Bn), 137 (*N*(1)Boc); δ_H (300 MHz, $CDCl_3$) 7.45–7.28 (5H, m, Ar*H*), 5.36 (1H, d, AB system, J_{AB} 12.3, CH_AH_BPh), 5.26 (1H, d, AB system, J_{BA} 12.3, CH_AH_BPh), 4.42 (1H, app quin, *J* 7.0, C(5)*H*), 2.97 (1H, dd, *J* 17.1, 8.0, C(4)H_AH_B), 1.96 (1H, d, *J* 17.1, C(4)H_AH_B), 1.38 (9H, s, C(CH_3)$_3$) and 1.31 (3H, d, *J* 6.8, C(5)HCH_3); δ_C (75 MHz, $CDCl_3$) 169.9 (*C*(3)O), 155.8 (N(1)*C*(O)O), 149.7 (N(2)*C*(O)O), 135.0 (*C*Ar$_{ipso}$), 128.7 (*C*Ar), 128.6 (*C*Ar), 128.4 (*C*Ar), 83.6 (*C*(CH_3)$_3$), 68.9 (*C*H_2Ph), 53.6 (*C*(5)H), 39.6 (*C*(4)H_2), 28.0 (C(*C*H_3)$_3$) and 19.9 (C(5)HCH_3); *m*/*z* (CI) 235.1 (100, M–Boc+$2H^+$), 352.2 (96, $M+NH_4^+$); HRMS (ESI^+) $C_{17}H_{26}N_3O_5$ requires 352.1867, found 352.1872 (+1.4 ppm).

*4.6.22. (RS)-Benzyl 3-methyl-5-oxopyrazolidine-1-carboxylate **46**.*

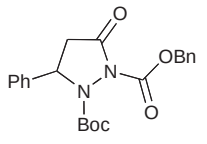


46

To a solution of (*RS*)-1-benzyl 2-*tert*-butyl 3-methyl-5-oxopyrazolidine-1,2-dicarboxylate **44** (560 mg, 1.67 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.600 mL, 8.09 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.120 mL, 1.62 mmol) was added and the mixture stirred for 4 h before being concentrated in vacuo. The resulting material was partitioned between dichloromethane (30 mL) and saturated sodium hydrogen carbonate solution (30 mL). The aqueous layer was washed with dichloromethane (2×30 mL) and the combined organic layers washed with brine (90 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was then purified by column chromatography, eluting with ethyl acetate to give the title compound as a colourless oil (304 mg, 78%).

ν_{max} (film) cm^{-1} 3234 (N–H), 2972 (C–H), 2927 (C–H), 1783 (C=O), 1729 (C=O), 1638 (N–H bend) and 1583 (Ar C=C); δ_H (300 MHz, $CDCl_3$) 7.47–7.42 (2H, m, Ar*H*), 7.40–7.31 (3H, m, Ar*H*), 5.34 (1H, d, AB system, J_{AB} 12.3, CH_AH_BPh), 5.27 (1H, d, AB system, J_{BA} 12.3, CH_AH_BPh), 4.56 (1H, d, *J* 9.9, N(1)*H*), 3.71 (1H, app tquin, *J* 9.7, 6.5, C(5)*H*), 2.75 (1H, dd, ABX system, J_{AB} 16.9, J_{AX} 6.7, C(4)H_AH_B), 2.37 (1H, dd, ABX system, J_{BA} 16.9, J_{BX} 9.7, C(4)H_AH_B) and 1.31 (3H, d, *J* 6.4, C(5)HCH_3); δ_C (100 MHz, $CDCl_3$) 172.1 (*C*(3)O), 150.0 (N(2)*C*(O)O), 135.1 (*C*Ar$_{ipso}$), 128.7 (*C*Ar), 128.6 (*C*Ar), 128.5 (*C*Ar), 68.6 (*C*H_2Ph), 50.9 (*C*(5)H), 41.9 (*C*(4)H_2) and 18.4 (C(5)HCH_3); *m*/*z* (CI) 257.0 (100, $M+H^+$); HRMS (ESI^+) $C_{12}H_{14}N_2NaO_3$ requires 257.0902, found 257.0910 (+3.2 ppm).

*4.6.23. (RS)-1-Benzyl 2-tert-butyl 5-oxo-3-phenylpyrazolidine-1,2-dicarboxylate **49**.*



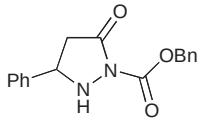
49

(*RS*)-1-Benzyl 2-*tert*-butyl 5-oxo-3-phenylpyrazolidine-1,2-dicarboxylate **25** (3.15 g, 12.1 mmol), sodium hydride (530 mg,

13.3 mmol) and benzyl chloroformate (1.81 mL, 12.7 mmol) were combined according to general procedure B. The resulting material was taken up in toluene (40 mL) and refluxed for 4 h before concentration in vacuo. The crude material was then purified by column chromatography, eluting with 15 then 25% ethyl acetate in petrol to give the title compound as a clear yellow oil, which became a colourless solid on trituration with petrol (1.83 g, 38%).

ν_{max} (KBr disc) cm^{-1} 3064 (Ar–H), 3025 (Ar–H), 2982 (C–H), 1795 (C=O), 1733 (2×C=O) and 1560 (Ar C=C); mp 112–114 °C; δ_N ($CDCl_3$) 169 (*N*(2)CO_2Bn), 133 (*N*(1)Boc); δ_H (500 MHz, $CDCl_3$) 7.44–7.28 (10H, m, Ar*H*), 5.70 (1H, d, *J* 8.6, C(5)*H*), 5.36 (1H, d, AB system, J_{AB} 12.3, C$H_A$$H_B$Ph), 5.30 (1H, d, AB system, J_{BA} 12.3, $CH_A$$H_B$Ph), 3.35 (1H, dd, *J* 17.2, 8.6, C(4)$H_A$$H_B$), 2.79 (1H, d, *J* 17.2, C(4)$H_A$$H_B$) and 1.43 (9H, s, C($CH_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 169.2 (*C*(3)O), 155.8 (N(1)*C*(O)O), 149.2 (N(2)*C*(O)O), 138.4 (*C*Ar$_{ipso}$), 134.9 (*C*Ar$_{ipso}$), 129.1 (*C*Ar), 128.7 (*C*Ar), 128.6 (*C*Ar), 128.4 (*C*Ar), 128.2 (*C*Ar), 125.6 (*C*Ar), 84.1 (*C*(CH_3)$_3$), 69.0 (*C*H_2Ph), 59.7 (*C*(5)H), 40.1 (*C*(4)H_2) and 28.0 (C(CH_3)$_3$); *m*/*z* HRMS (ESI^+) $C_{22}H_{24}N_2NaO_5$ requires 419.1577, found 419.1585 (+1.8 ppm).

*4.6.24. (RS)-Benzyl 5-oxo-3-phenylpyrazolidine-1-carboxylate **51**.*

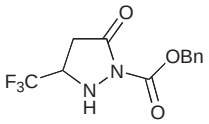


51

To a solution of (*RS*)-1-benzyl-2-*tert*-butyl 5-oxo-3-phenylpyrazolidine-1,2-dicarboxylate **49** (1.60 g, 4.04 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (1.50 mL, 19.7 mmol) and the resulting solution stirred overnight at rt before being concentrated in vacuo. The resulting material was partitioned between dichloromethane (60 mL) and saturated sodium hydrogen carbonate solution (60 mL). The aqueous layer was washed with dichloromethane (2×60 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by recrystallisation from petrol and the minimum quantity of dichloromethane to give the title compound as colourless needles (816 mg, 68%).

$C_{17}H_{16}N_2O_3$ requires C, 68.9; H 5.4; N, 9.5%; found C 68.6; H, 5.2; N, 9.5%; ν_{max} (KBr disc) cm^{-1} 3226 (N–H), 3058 (C–H), 3030 (C–H), 1739 (C=O), 1653 (N–H bend); mp 101–102 °C; δ_N ($CDCl_3$) 167 (*N*(2)CO_2Bn), 103 (*N*(1)H); δ_H (300 MHz, $CDCl_3$) 7.49–7.43 (2H, m, Ar*H*), 7.41–7.31 (8H, m, Ar*H*), 5.37 (1H, d, AB system, J_{AB} 12.2, C$H_A$$H_B$Ph), 5.31 (1H, d, AB system, J_{BA} 12.2, $CH_A$$H_B$Ph), 4.94 (1H, br s, N(1)*H*), 4.75 (1H, app t, *J* 8.2C(5)*H*), 3.05 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.3, C(4)$H_A$$H_B$) and 2.93 (1H, dd, ABX system, J_{BA} 17.0, J_{BX} 9.8, C(4)$H_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 170.7 (*C*(3)O), 149.8 (N(2)*C*(O)O), 137.3 (*C*Ar$_{ipso}$), 135.1 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 128.9 (*C*Ar), 128.8 (*C*Ar), 128.7 (*C*Ar), 128.6 (*C*Ar), 126.7 (*C*Ar), 68.7 (*C*H_2Ph), 57.9 (*C*(5)H) and 41.0 (*C*(4)H_2); *m*/*z* HRMS (ESI^+) $C_{17}H_{17}N_2O_3$ requires 297.1234, found 297.1237 (+1.1 ppm).

*4.6.25. (RS)-Benzyl 5-oxo-3-(trifluoromethyl)pyrazolidine-1-carboxylate **52**.*



52

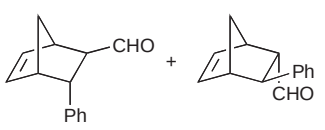
(*RS*)-1-Benzyl 2-*tert*-butyl 5-oxo-3-(trifluoromethyl)pyrazolidine-1,2-dicarboxylate **26** (619 mg, 2.43 mmol), sodium hydride (107 mg, 2.68 mmol) and benzyl chloroformate (0.400 mL, 2.55 mmol) were combined according to general procedure B with a modified work-up. In this case, the reaction was quenched with water (2 mL) and concentrated in vacuo. The resulting material was taken up in toluene (20 mL) and refluxed for 3 h before being cooled, filtered and concentrated in vacuo to give crude product (930 mg) as a yellow oil. Product was used without further purification. An analytical sample was taken and purified by column chromatography, eluting with 10% ethyl acetate in petrol to give the title compound as a colourless solid.

ν_{max} (KBr disc) cm^{-1} 3028 (C–H), 2984 (C–H), 1790 (C=O) and 1748 (C=O); mp 65–67 °C; δ_F (282 MHz, $CDCl_3$) −78.8 (3F, d, *J* 7.2, CF_3); δ_H (300 MHz, $CDCl_3$) 7.43–7.32 (5H, m, Ar*H*), 5.35 (1H, d, AB system, J_{AB} 12.3, C$H_A$$H_B$Ph), 5.30 (1H, d, AB system, J_{BA} 12.3, $CH_A$$H_B$Ph), 4.42 (1H, dqd, *J* 9.5, 7.2, 1.3, C(5)*H*), 3.14 (1H, dd, *J* 18.2, 9.5, C(4)$H_A$$H_B$), 2.77 (1H, d, *J* 18.2, 1.3, C(4)$H_A$$H_B$) and 1.38 (9H, s, C($CH_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 167.1 (*C*(3)O), 154.3 (N(1)*C*(O)O), 149.9 (N(2)*C*(O)O), 134.7 (*C*Ar$_{ipso}$), 128.8 (*C*Ar), 128.7 (*C*Ar), 128.5 (*C*Ar), 123.8 (q, *J* 281, *C*F_3), 85.4 (*C*(CH_3)$_3$), 69.4 (*C*H_2Ph), 56.2 (q, *J* 33.9, *C*(5)H), 32.2 (*C*(4)H_2) and 27.9 (C(*C*H_3)$_3$); *m*/*z* HRMS (ESI^+) $C_{17}H_{23}F_3N_3O_5$ requires 406.1584, found 406.1588 (+0.9 ppm).

A solution of crude (*RS*)-1-benzyl-2-*tert*-butyl 5-oxo-3-(trifluoromethyl)pyrazolidine-1,2-dicarboxylate **50** (890 mg, 2.29 mmol) was stirred in a 1:2 mixture of trifluoroacetic acid/dichloromethane (15 mL) overnight at rt before being concentrated in vacuo. The resulting material was partitioned between dichloromethane (100 mL) and saturated sodium hydrogen carbonate solution (100 mL). The aqueous layer was washed with dichloromethane (2×100 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by recrystallisation from diethyl ether and the minimum quantity of dichloromethane to give the title compound as colourless needles (281 mg, 42%).

ν_{max} (film) cm^{-1} 3261 (N–H), 3014 (Ar–H), 2935 (C–H), 1760 (C=O) and 1714 (C=O); mp 90–92 °C; δ_F (282 MHz, $CDCl_3$) −78.5 (3F, d, *J* 7.6, CF_3); δ_H (300 MHz, $CDCl_3$) 7.44–7.33 (5H, m, Ar*H*), 5.34 (1H, d, AB system, J_{AB} 12.3, C$H_A$$H_B$Ph), 5.32 (1H, d, *J* 7.9, N(1)*H*), 5.30 (1H, d, AB system, J_{BA} 12.3, $CH_A$$H_B$Ph), 4.13–3.98 (1H, m, C(5)*H*), 3.07 (1H, dd, ABX system, J_{AB} 18.1, J_{AX} 9.6, C(4)$H_A$$H_B$) and 2.84 (1H, dd, ABX system, J_{BA} 18.1, J_{BX} 4.1, C(4)$H_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 168.3 (*C*(3)O), 149.5 (N(2)*C*(O)O), 135.9 (*C*Ar$_{ipso}$), 128.8 (*C*Ar), 128.4 (*C*Ar), 124.1 (q, *J* 280, *C*F_3), 68.9 (*C*H_2Ph), 53.4 (q, *J* 32.6, *C*(5)H) and 33.1 (*C*(4)H_2); *m*/*z* HRMS (ESI^+) $C_{12}H_{15}F_3N_3O_3$ requires 306.1090, found 306.1066 (+2.0 ppm).

*4.6.26. exo-3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **47** and endo-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **48**.*



exo-**47** *endo*-**48**

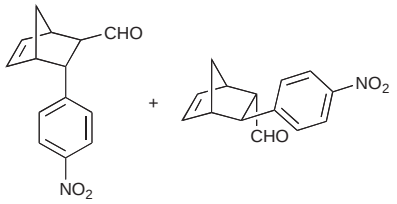
trans-Cinnamaldehyde (0.120 mL, 0.950 mmol) and catalyst **51** (56 mg, 0.190 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 5% diethyl ether in petrol to yield the title compounds as a 62:38 mixture of diastereomers, with spectroscopic data in accordance with the literature (168 mg, 89%).[12]

Compound exo-**47**: 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, CH_A=CH_B), 6.08 (1H, dd, *J* 5.8, 3.3, CH_A=CH_B), 3.73 (1H, dd, *J* 5.2, 3.4, *CH*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, C*H*$_2$).

Compound endo-**48**: 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, CH_A=CH$_B$), 6.18 (1H, dd, *J* 5.7, 2.8, CH$_A$=CH_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, CH_AH$_B$) and 1.65–1.63 (1H, m, CH$_A$$H_B$).

4.6.27. exo-3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde ***53*** *and endo-3-(4-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde* ***54***.



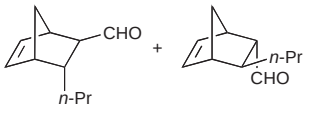
exo-**53** *endo*-**54**

4-Nitrocinnamaldehyde (168 mg, predominantly *trans*-, 0.950 mmol) and catalyst **51** (56 mg, 0.190 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 10% diethyl ether in petrol to yield the product as a 65:35 mixture of diastereomers with spectroscopic data in accordance with the literature (169 mg, 73%).[14]

Compound exo-**53**: 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, CH_A=CH$_B$), 6.05 (1H, dd, *J* 5.7, 2.8, CH$_A$=CH_B), 3.88 (1H, dd, *J* 5.0, 3.5, C*H*Ar), 3.33 (1H, br s, C*H*CH$_2$), 3.25 (1H, br s, C*H*CH$_2$), 2.62 (1H, br d, *J* 5.0, C*H*CHO) and 1.62–1.60 (2H, m, C*H*$_2$).

Compound endo-**54**: 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, CH_A=CH$_B$), 6.20 (1H, dd, *J* 5.7, 2.8, CH$_A$=CH_B), 3.43 (1H, br s, 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, C*H*$_2$).

4.6.28. exo-3-Propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde ***55*** *and endo-3-propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde* ***56***.



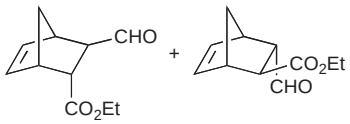
exo-**55** *endo*-**56**

trans-2-Hexen-1-al (0.110 mL, 0.950 mmol) and catalyst **51** (56 mg, 0.190 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 2.5% ethyl acetate in petrol to yield the product as a 58:42 mixture of diastereomers with spectroscopic data in accordance with the literature (117 mg, 75%).[2,34]

Compound exo-**55**: 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), 3.01 (1H, br s, C*H*CH$_2$), 2.87 (1H, br s C*H*CH$_2$), 2.28 (1H, tdd, *J* 7.6, 4.7, 3.1, C*H*CH$_2$CH$_2$), 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).

Compound endo-**56**: 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), 3.12 (1H, br s, C*H*CH$_2$), 2.66 (1H, br s, C*H*CH$_2$), 2.38 (1H, dt, *J* 4.4, 3.4, C*H*CHO), 1.72 (1H, m, C*H*CH$_2$CH$_2$), 1.77–1.06 (6H, m, CHCH_2CH, CH_2CH_2) and 0.88 (3H, t, *J* 7.2, CH_3).

4.6.29. exo-Ethyl 3-formylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde ***57*** *and endo-ethyl 3-formylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde* ***58***.



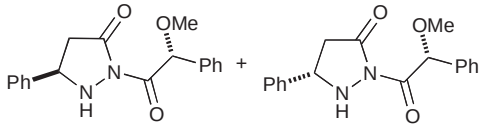
exo-**57** *endo*-**58**

Ethyl *trans*-4-oxo-2-butenoate (0.120 mL, 0.950 mmol) and catalyst **51** (56 mg, 0.190 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 15% diethyl ether in petrol to yield the product as a 50:50 mixture of diastereomers with spectroscopic data in accordance with the literature (147 mg, 80%).[10,35]

Compound exo-**57**: δ_H (300 MHz, $CDCl_3$) 9.84 (1H, d, *J* 0.9, C*H*O), 6.30 (1H, dd, *J* 5.6, 3.2, CH_A=CH$_B$), 6.13 (1H, dd, *J* 5.6, 2.8, CH$_A$=CH_B), 4.11 (2H, d, *J* 7.1, OCH_2), 3.42 (1H, dd, *J* 4.4, 3.7, C*H*CO$_2$), 3.29 (1H, br s, C*H*CH$_2$), 3.20 (1H, br s C*H*CH$_2$), 2.83–2.81 (1H, m, C*H*CHO), 1.47–1.42 (1H, m, CH_ACH$_B$), 1.36–1.11 (1H, m, CH$_A$CH_B) and 1.24 (3H, t, *J* 7.1, CH_3).

Compound endo-**58**: δ_H 9.55 (1H, d, *J* 1.2, C*H*O), 6.26 (1H, dd, *J* 5.7, 3.3, CH_A=CH$_B$), 6.09 (1H, dd, *J* 5.7, 2.6, CH$_A$=CH_B), 4.16 (2H, q, *J* 7.1, OCH_2), 3.39–3.33 (2H, m, C*H*CO$_2$ and C*H*CH$_2$), 3.20 (1H, br s C*H*CH$_2$), 2.70 (1H, ddd, *J* 4.3, 1.2, 0.5, C*H*CHO), 1.69–1.65 (1H, m, CH_ACH$_B$), 1.53–1.48 (1H, m, CH$_A$CH_B) and 1.27 (3H, t, *J* 7.1, CH_3).

4.6.30. (R)-2-((R)-2-Methoxy-2-phenylacetyl)-5-phenylpyrazolidin-3-one ***59*** *and (S)-2-((R)-2-Methoxy-2-phenylacetyl)-5-phenylpyrazolidin-3-one* ***60***.



59 **60**

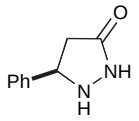
N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (14.4 g, 75.3 mmol), 1-hydroxybenzotriazole (10.2 g, 75.3 mmol) and (*R*)-*O*-methyl mandelic acid (12.5 g, 75.3 mmol) were combined in DMF (300 mL) and stirred at room temperature for 15 min. (*RS*)-5-Phenylpyrazolidin-3-one **21** (12.2 g, 75.3 mmol) 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 (500 mL) and washed with 0.1 M hydrochloric acid solution (2×500 mL), water (2×500 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography, eluting with 35% ethyl acetate in petrol to give first the title compound **60** as an amorphous yellow solid (1.17 g, 5%) and then title compound **59** as a cream solid (1.60 g, 7%). Mixed fractions (10.9 g) were also collected and subjected again to column chromatography, eluting with 25% ethyl acetate in petrol to give more compound **60** (830 mg, 4%), compound **59** (3.76 g, 16%) and 5.01 g of mixed fractions (12.4 g of compounds **59** and **60** over all fractions, 53% combined yield).

Compound **59** (lower spot): $[\alpha]_D^{20}$ −1.5 (*c* 1.0, dichloromethane); ν_{max} (KBr disc) cm^{-1} 3231 (N–H), 3025 (Ar–H), 2985 (C–H), 2934 (C–H), 1744 (C=O) and 1701 (C=O); mp 140–144 °C; δ_N ($CDCl_3$) 190 (*N*(2)C(O)), 104 (*N*(1)H); δ_H (400 MHz, $CDCl_3$) 7.52 (2H, dd, *J* 6.6, 3.2, Ar*H*), 7.38–7.34 (3H, m, Ar*H*), 7.31–7.27 (3H, m, Ar*H*), 7.23–7.21 (2H, m, Ar*H*), 5.89 (1H, s, C*H*OCH$_3$), 4.71 (1H, dd, *J* 9.3, 7.5, C(5)*H*), 3.40 (3H, s, OCH_3), 3.07 (1H, dd, ABX system, J_{AB} 17.1, J_{AX} 7.5, C(4)

H_AH_B) and 2.82 (1H, dd, ABX system, J_{BA} 17.1, J_{BX} 9.3, C(4)H_AH_B); δ_C (75 MHz, $CDCl_3$) 169.9 (N(2)*C*(O)), 167.0 (N(1)*C*(O)), 138.0 (*CAr*$_{ipso}$), 135.4 (*CAr*$_{ipso}$), 129.2 (*CAr*), 129.1 (*CAr*), 128.8 (*CAr*), 128.7 (*CAr*), 126.5 (*CAr*), 81.6 (*C*HOCH$_3$), 58.1 (*C*(5)H), 57.4 (CHO*C*H$_3$) and 41.9 (*C*(4)H$_2$); *m*/*z* HRMS (ESI$^+$) $C_{18}H_{19}N_2O_3$ requires 311.1390, found 311.1393 (+0.9 ppm).

Compound **60** (upper spot): $[\alpha]_D^{20}$ −62.6 (*c* 0.5, dichloromethane); ν_{max} (KBr disc) cm^{-1} 3246 (N–H), 3064 (Ar–H), 3025 (Ar–H), 2927 (C–H), 1750 (C=O) and 1701 (C=O); mp 43–46 °C; δ_N ($CDCl_3$) 192 (*N*(2)C(O)), 104 (*N*(1)H); δ_H (300 MHz, $CDCl_3$) 7.55–7.53 (2H, m, Ar*H*), 7.41–7.33 (8H, m, Ar*H*), 5.87 (1H, s, C*H*OCH$_3$), 4.61 (1H, app dt, *J* 10.0, 7.4, C(5)*H*), 3.40 (3H, s, OC*H*$_3$), 3.00 (1H, dd, ABX system, J_{AB} 17.1, J_{AX} 7.6, C(4)H_AH_B) and 2.93 (1H, dd, ABX system, J_{BA} 17.1, J_{BX} 10.0, C(4)H_AH_B); δ_C (75 MHz, $CDCl_3$) 170.0 (N(2)*C*(O)), 167.2 (N(1)*C*(O)), 137.5 (*CAr*$_{ipso}$), 135.7 (*CAr*$_{ipso}$), 129.2 (*CAr*), 128.9 (*CAr*), 128.8 (*CAr*), 126.7 (*CAr*), 81.7 (*C*HOCH3), 57.7 (*C*(5)H), 57.4 (CHO*C*H$_3$) and 41.7 (*C*(4)H$_2$); *m*/*z* HRMS (ESI$^+$) $C_{18}H_{19}N_2O_3$ requires 311.1390, found 311.1396 (+1.9 ppm).

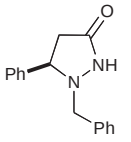
*4.6.31. (R)-5-Phenylpyrazolidin-3-one (R)-**21**.*



(*R*)-21

(*S*)-1-((*R*)-2-Hydroxy-2-phenylacetyl)-5-phenylpyrazolidin-3-one **59** (4.62 g, 14.9 mmol) was suspended in 6 M aqueous hydrochloric acid solution (40 mL) and heated to reflux for 30 min. The reaction mixture was basified with 2 M sodium hydroxide solution (150 mL) and extracted with dichloromethane (3×150 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a small quantity of the title compound (191 mg). Hence, the aqueous phase was neutralised to pH 7 with 37% hydrochloric acid solution and again extracted with dichloromethane (3×150 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a further 1.20 g of the title compound as a colourless solid, with spectroscopic data identical to (*RS*)-**21** (1.39 g, 57%). $[\alpha]_D^{20}$ −13.0 (*c* 1.0, methanol); mp 94–96 °C.

*4.6.32. (S)-1-Benzyl-5-phenylpyrazolidin-3-one (S)-**61**.*

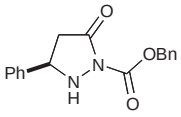


(*S*)-61

To a solution of (*S*)-5-phenylpyrazolidin-3-one (*R*)-**21** (42 mg, 0.259 mmol) in ethanol (1 mL) was added benzaldehyde (0.1 mL, 1.03 mmol) and the resulting mixture left to stir at room temperature overnight. Sodium borohydride (49 mg, 1.30 mmol) was then added and the mixture stirred for a further hour. The reaction mixture was partitioned between water (5 mL), saturated sodium hydrogen carbonate solution (5 mL) and dichloromethane (10 mL). The resulting aqueous layer was extracted with further dichloromethane (3×10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography, eluting with 40% ethyl acetate in petrol to give the title compound as a colourless solid with ^{1}H NMR in accordance with the literature[30,36] (33 mg, 51%). The compound was determined to have an enantiomeric excess of 95% by HPLC (Daicel Chiralpak AD-H 0.46 cm×25 cm), hexane/*iso*-propanol=93:7, 1.0 mL/min, 220 nm, 18.8 min (minor). Absolute configuration determined by comparison of the optical rotation to literature value.[36]

$[\alpha]_D^{20}$ +168 (*c* 0.9, dichloromethane), lit. $[\alpha]_D^{20}$ −163 ((*S*)-enantiomer, *c* 0.90, dichloromethane);[36] mp 106–109 °C; δ_H (400 MHz, $CDC1_3$) 7.48 (1H, br s, N(2)*H*), 7.40–7.37 (2H, m, Ar*H*), 7.35–7.20 (8H, m, Ar*H*), 4.15 (1H, app t, *J* 8.6, C(5)*H*), 3.95 (1H, d, AB system, J_{AB} 12.9, CH_AH$_B$Ph), 3.56 (1H, d, AB system, J_{BA} 12.9, CH$_A$$H_B$Ph), 2.90 (1H, dd, ABX system, J_{AB} 16.8, J_{AX} 8.3, C(4)H_AH_B) and 2.47 (1H, dd, ABX system, J_{BA} 16.8, J_{BX} 8.9, C(4)H_AH_B).

*4.6.33. (R)-Benzyl 5-oxo-3-phenylpyrazolidine-1-carboxylate (R)-**51**.*



(*R*)-51

Synthesised from (*R*)-**21** by identical means to those described above. $[\alpha]_D^{20}$ +22.4 (*c* 0.25, dichloromethane); mp 123–125 °C.

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Supplementary data

Spectroscopic and HPLC data is available for all products. Crystallographic data (excluding structure factors) for compounds **21**, **27**, **34**, **40** and **43** have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 772907, 772908, 772909, 772910 and 772911, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.021. These data include MOL files and InChiKeys of the most important compounds described in this article.

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27. The functionalisation of **49** and **51** was confirmed by ^{15}N NMR, see Supplementary data.
28. Catalyst **51** was found to return only starting material in the reaction of cinnamaldehyde with either isoprene or cyclohexadiene in MeOH. Changing the solvent system to MeOH:H_2O (95:5), MeCN:H_2O (95:5) or DMF:H_2O (95:5) gave no change in reactivity. Catalyst **34** also returned only starting material using both cyclohexadiene and isoprene.
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