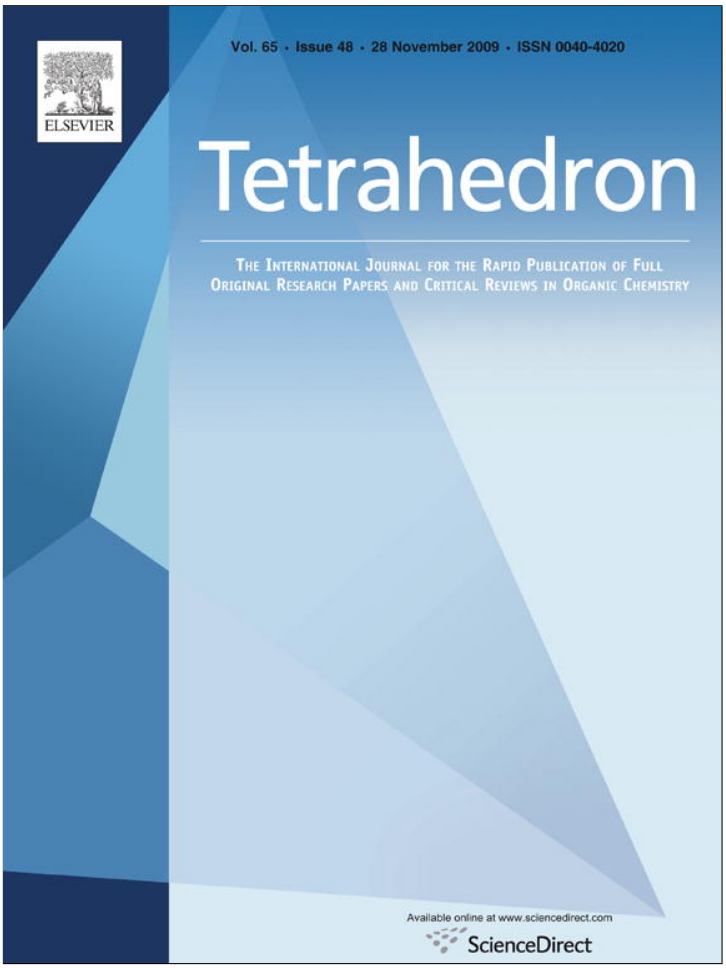

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The α-effect in cyclic secondary amines: new scaffolds for iminium ion accelerated transformations

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ABSTRACT

Five-membered secondary amine heterocycles containing an α-heteroatom were prepared and shown to be ineffective as catalysts for the iminium ion catalysed Diels–Alder reaction between cinnamaldehyde and cyclopentadiene. Their six-membered counterparts proved to be highly active catalysts. In stark contrast, the catalytic activity observed when comparing the non α-heteroatom cyclic amines proline methyl ester and methyl pipecolinate showed the five-membered ring amine was significantly more active. Concurrent density functional theoretical calculations suggest a rationale for the observed trends in reactivity, highlighting that LUMO activation through an iminium ion intermediate plays a key role in catalytic activity.

1. Introduction

Since the original report by MacMillan in 2000,[1] the use of secondary amine catalysts in cycloaddition and conjugate addition reactions of α,β-unsaturated aldehydes has provided an inspiring number of new bond-construction processes that proceed with remarkable levels of enantioselectivity.[2] The majority of work reported within this vibrant area of research has focused on the development of new methods for bond-formation, rather than understanding catalyst activity[3] and addressing the often high levels of catalyst loading. As the field matures and the number of applications expands, development will undoubtedly focus on the preparation of more active catalyst scaffolds with which to accelerate this class of transformation.

We have recently described the effects on catalyst activity of a heteroatom α- to the reactive secondary nitrogen centre, and have discovered a series of acyclic catalysts for the iminium ion catalysed Diels–Alder reaction.[4] A combination of experimental and theoretical investigations have yielded a structure–reactivity relationship between amine structure and catalyst activity for the Diels–Alder reaction, which we are adopting with the ultimate goal of developing a predictive model for future rational catalyst design.[5]

Previous synthetic investigations, as well as examination of the literature precedent, revealed two important trends relating the structure of the secondary amine and activity in the iminium ion catalysed Diels–Alder reaction. Firstly, cyclic secondary amines **3** give good levels of reactivity for these transformations. Secondly, the introduction of an *N*-methyl carbamate α- to the reactive nitrogen centre provided a catalyst **4** with the highest levels of activity to date, albeit in an achiral series. We wished to investigate if bringing together these two principal findings would lead to a further increase in catalyst activity, and set out to discover if a cyclic secondary amine incorporating an α-heteroatom (such as **5**) would provide a platform with which to generate state-of-the-art chiral catalysts for use in iminium ion catalysed transformations (Fig. 1).

2. Results and discussion

As a starting point for this investigation, we selected a series of target scaffolds **6**–**9** with which to test our original hypothesis. These fell into three distinct classes of compounds: the nature of the heteroatom (**6** and **7**); inclusion of an *endo*-cyclic electron withdrawing group (**9**); incorporation of an *exo*-cyclic electron withdrawing group (**8**) (Fig. 2).

The methods adopted to prepare these initial targets are outlined in Scheme 1.[6] Treatment of *N*-Boc hydroxylamine **10** with 1,3-dibromopropane at reflux, under phase transfer conditions allowed access to the protected precursor to our target isoxazolidine in poor but acceptable yield (17%). Removal of the Boc protecting group (89%) using HCl in diethyl ether (2 M) gave our first target **6**. The

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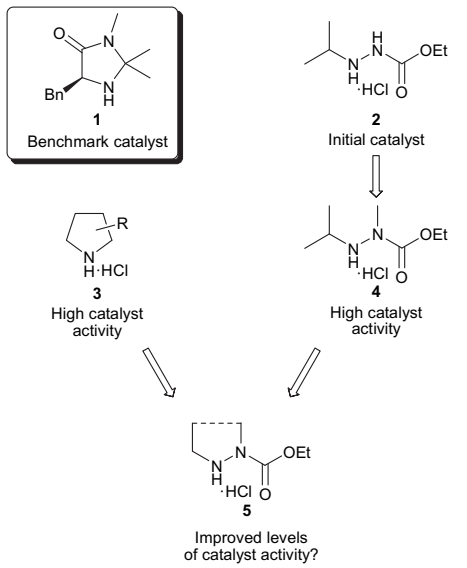


Figure 1. Design of potential catalysts.

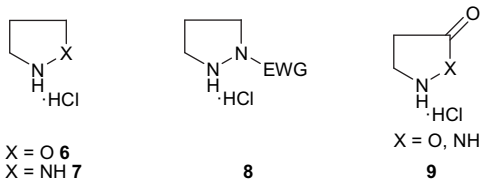
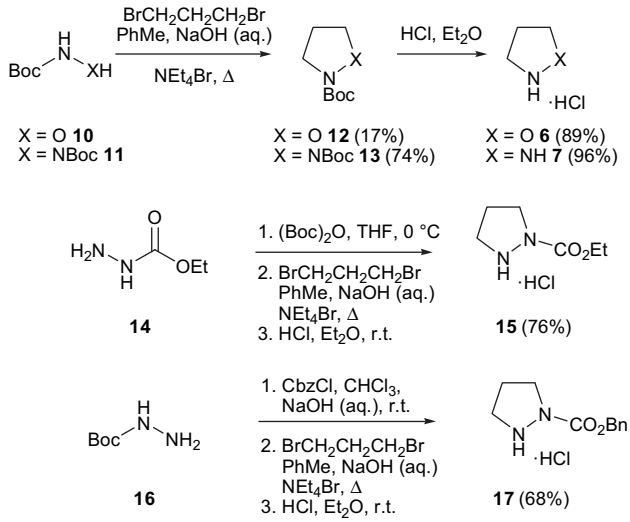


Figure 2. Initial target scaffolds.



Scheme 1. Preparation of five-membered ring hydrazides and hydroxylamines.

pyrazolidine hydrochloride **7** was prepared in an analogous procedure starting from di-Boc hydrazine **11** in a pleasing 71% overall yield. Our attention then turned to the inclusion of an electron withdrawing group on the α-nitrogen (**8**), the introduction of which had been crucial to obtaining good levels of catalyst activity within previous work on acyclic catalysts.[4] Boc protection of ethyl carbazate **14** proceeded smoothly to give the protected hydrazine in 97% yield with no purification required. This was subsequently reacted with 1,3-dibromopropane under phase transfer conditions to give the precursor to our target scaffold in 81% after purification. Finally, the Boc protecting group was removed with hydrochloric acid in diethyl ether. The hydrochloride salt **15** precipitated out of solution giving the desired catalyst in an overall yield of 76% for the three steps. Introduction of a benzyl carbamate α- to the reactive nitrogen was achieved in an analogous fashion. Cbz protection of *tert*-butyl carbazate **16** proceeded efficiently at room temperature (91%) and the resulting protected hydrazine was then submitted to a cyclisation reaction with 1,3-dibromopropane followed by removal of the Boc protecting group to give **17** as a colourless solid in an overall yield of 68% for the three steps.

Considering catalysts bearing an *endo*-cyclic electron withdrawing group encompassing the generic template **9**, it was envisaged that **18** could act as a Mannich base and therefore readily eliminate upon protonation, hence requiring preparation of a derivative such as **19** to circumvent this problem (Fig. 3). While preparing these catalysts, we became aware of a series of reports from Ogilvie showing the camphor derived hydrazide **20** to be effective for iminium ion catalysed Diels–Alder cycloaddition, the reactions proceeding with high e.e.'s.[7] The kinetics of these reactions appeared significantly slower than those observed previously with our acyclic scaffolds (e.g., **4**), such that we decided not to pursue structures such as **19** as potential catalysts.

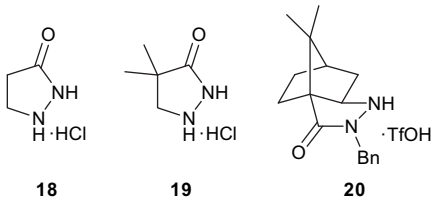
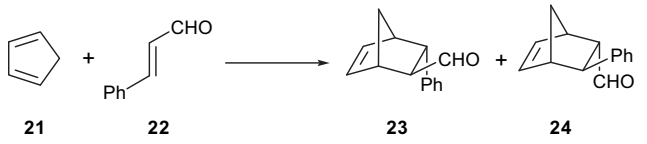


Figure 3. *Endo*-cyclic electron withdrawing groups.

Results of the Diels–Alder reaction of cinnamaldehyde **22** and cyclopentadiene **21** catalysed by the four new scaffolds (**6**, **7**, **15**, and **17**) and our previously optimised acyclic catalyst **4**[5] are shown in Table 1.

Table 1
Diels–Alder reaction of five-membered ring catalysts[a]



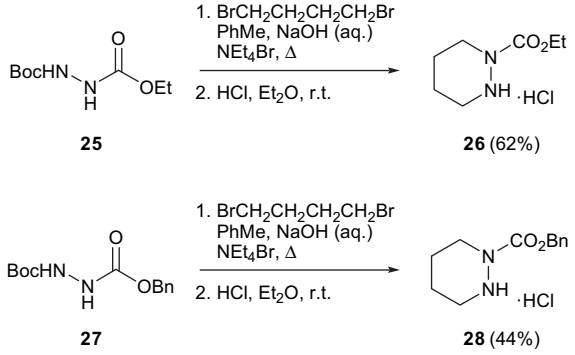
Entry	Catalyst	Time	*endo*:*exo*[c]	%Yield[b]
1	None	48	64:36	7
2	**4**	6	35:65	98
3	**6**	24	34:66	8
4	**7**	24	55:45	15
5	**15**	24	33:67	38
6	**17**	24	32:68	34

[a] All reactions carried out in methanol at 25 °C with 10 mol % catalyst as their ·HCl salts.
[b] Isolated yield of **23** & **24** after chromatography and is the average of two catalytic runs.
[c] *endo*:*exo* ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixtures.

Disappointingly, each of the five-membered cyclic secondary amines containing an α-heteroatom (entries 3–6) were substantially less active than the acyclic hydrazide **4** (entry 2) under our standard reaction conditions. Consistent with previous observations, a nitrogen α-heteroatom resulted in a more efficient catalyst when compared to its oxygen analogue (entries 3 and 4), and the introduction of the electron withdrawing group on the α-heteroatom increased reactivity further (entries 5 and 6) suggesting

a similar reactivity profile to that shown in the acyclic series. However, the level of catalytic activity was substantially less than that obtained with **4** (98% yield, 6 h). After the 24 h reaction period it was possible to isolate the catalyst (80% recovery), showing that reduced levels of activity were not due to decomposition. We conclude, therefore, that our original hypothesis of combining the α-effect with a five-membered heterocycle does not lead to the desired levels of catalyst activity for this class of transformation.

Our attention then turned to preparation of a series of six-membered rings, in order to expand the range of heterocyclic catalysts and hence draw more general structure–reactivity relations. We prepared two six-membered cyclic hydrazides **26** (62%) and **28** (44%) in an analogous manner to that adopted previously (Scheme 2).



Scheme 2. Preparation of six-membered cyclic hydrazides.

Catalysts **26** and **28** were submitted to the standard Diels–Alder reaction conditions for 6 h (Table 2). The results showed excellent yields with near quantitative results being observed for both catalysts (entries 2 and 3). *exo*:*endo* ratios were in favour of the *exo*-isomer, consistent with literature precedent for iminium ion catalysed Diels–Alder reactions of these substrates.[1] Importantly, both catalysts exhibited higher conversions when compared to the commercially available imidazolidinone **1** (entry 4) under identical reaction conditions. With near quantitative results being observed with both catalysts after six hours we examined the performance limit of **26**, altering both catalyst loading and reaction time (entries 5–8), which revealed at 10 mol % loading the reaction resulted in 90% isolated yield of the product after just 3 h, a substantial increase in reactivity over our previously described system. Recovery of **26** from the crude reaction mixture using a Varian Mega Bond Elut® SCX column resulted in 92% catalyst recovery, highlighting the stability of this class of scaffold to the reaction conditions employed.

Table 2
Diels–Alder reaction of six-membered ring catalysts[a]

Entry	Catalyst (loading)	Time	*endo*:*exo*[c]	%Yield[b]
1	**4** (10)	6	35:65	98
2	**26** (10)	6	32:68	99
3	**28** (10)	6	32:68	94
4	**1** (10)	6	39:61	87
5	**26** (1)	3	30:70	14
6	**26** (2)	3	31:69	26
7	**26** (5)	3	32:68	50
8	**26** (10)	3	32:68	90
9	**29** (10)	6	40:60	3[d]
10	**30** (10)	6	30:70	62

[a] All reactions between cyclopentadiene and cinnamaldehyde carried out in methanol at 25 °C with catalyst as ·HCl salt.
[b] Isolated yield of **23** & **24** after chromatography and is the average of two catalytic runs.
[c] *endo*:*exo* ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixtures.
[d] Conversion estimated from ^{1}H NMR spectroscopy.

The precise reason(s) behind the finding that **26** (Table 2; entry 8) was more effective than the five-membered ring counterpart **15** (Table 1; entry 5) was not apparent. Examination of methyl pipecolinate hydrochloride **29** and proline methyl ester hydrochloride **30** (Fig. 4) as catalysts within the standard Diels–Alder reaction (Table 2; entries 9 and 10) showed the five-membered ring heterocycle **30** to be significantly better (entry 10; 62%) than the six-membered ring analogue **29** (entry 9; 3%).

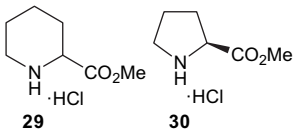


Figure 4. Cyclic catalysts without an α-heteroatom.

In the design of any chiral catalyst these important findings on reactivity should be taken into account: Catalysts that do not contain an α-heteroatom should be based upon a five-membered ring, catalysts that have an α-heteroatom should be based on a six-membered ring.

In order to try and rationalise these results we carried out a series of computational studies to examine the effects of an α-heteroatom. In recent studies,[5,8] we found that two parameters drawn from density functional theory (DFT) methods could be used to gain insight into the formation and reactivity of iminium ions. Firstly, proton affinity (PA) is related to the barrier to formation of iminium ions, since the key step in this process under acidic reaction conditions is the transfer of a proton from catalyst to substrate. Secondly, the energy of the lowest unoccupied molecular orbital of the iminium ion (E_{LUMO}) can be used to measure activation of the substrate towards Diels–Alder cycloaddition. We therefore calculated these properties for five selected amines, (**2**, **15**, **26**, **29**, and **30**) along with their iminium ion derivatives (Table 3).

Table 3
Calculated properties of amines and derived iminium ions (B3LYP/6–31+G(d,p))

Entry	Amine	PA (kJ mol^{-1})	E_{LUMO} (eV)
1	**2**	913.6	−6.41
2	**15**	911.9	−6.20
3	**26**	917.3	−6.38
4	**29**	957.1	−6.35
5	**30**	958.8	−6.35

From this data it can be concluded that introduction of an α-heteroatom on a cyclic framework significantly lowers the proton affinity of the basic nitrogen. This is the case for both five-membered (entry 2; 911.9 kJ mol^{-1} vs entry 5; 958.8 kJ mol^{-1}) and six-membered rings (entry 3; 917.3 kJ mol^{-1} vs entry 4; 957.1 kJ mol^{-1}). In the five-membered ring series introduction of the α-heteroatom substantially increases the energy level of the LUMO (entry 2; −6.2 eV vs entry 5; −6.35 eV) whereas in the six-membered ring series the energy level of the LUMO decreases (entry 3; −6.38 eV vs entry 4; −6.35 eV). This trend in E_{LUMO} is reflected within the reactivity observed with the two series of catalysts where activity is reduced on introduction of an α-heteroatom in the five-membered ring scaffold but increased in the six-membered ring series. Recent work on the iminium ion catalysed Diels–Alder reaction has shown the cycloaddition step to be rate determining.[8,9] It is therefore possible that E_{LUMO} can be adopted as a simple means for the computational evaluation of catalyst activity prior to synthesis. It is important to note these computational results do not explain the marked difference in reactivity of proline methyl ester hydrochloride (**30**) and methyl pipecolinate hydrochloride (**29**) and further investigations are clearly needed in order to develop a robust predictive model for the reactivity of secondary amines in iminium ion catalysed transformations.

3. Conclusions

In summary, we have explored the use of five- and six-membered cyclic hydrazides as novel molecular scaffolds for use in the iminium ion catalysed Diels–Alder reaction. The five-membered heterocycles performed poorly as catalysts whereas their six-membered counterparts provide an excellent basis for catalyst design. These findings are in stark contrast to catalyst scaffolds that do not bear an α-heteroatom, where five-membered cyclic secondary amines deliver significantly improved activity when compared to six-membered rings. These results provide a strong basis with which to design novel, state-of-the-art chiral scaffolds that could have applicability in catalytic asymmetric iminium ion catalysed cycloaddition and conjugate addition reactions.[10] Additionally, the catalysts described may also find applicability in the Asymmetric Counteranion-Directed Catalysis (ACDC)[11] technology recently disclosed by List where an achiral secondary amine can be coupled with a chiral anion in iminium ion activated processes. Our work in these areas will be described in due course.

4. Experimental

4.1. General

All ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DPX-400, Bruker Avance 500 or Bruker DPX-250 spectrometer, with ^{13}C spectra being recorded at 100, 125 or 62.5 MHz. Mass spectra were obtained using a Fisons VG platform II spectrometer. High resolution mass spectra were obtained by the EPSRC mass spectrometry service, Swansea. Melting points were determined on a Khofler Hot Stage Micro Melting Point Apparatus. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin–Elmer 1600 series spectrophotometer as thin films or as Nujol mulls. Thin Layer Chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected with a solution of 10% ceric sulfate in 10% sulfuric acid, followed by heating the plates. Purification of compounds was achieved by medium pressure chromatography using Merck 9385 60 silica gel.

All DFT calculations were carried out using the Gaussian03 package,[12] at the B3LYP/6–31+G(d,p) level.[13,14] E_{LUMO} was calculated with this method directly, while PA included an unscaled zero-point vibrational energy (ZPVE) correction from harmonic frequency calculation at the same level.

4.2. Isoxazolidine hydrochloride 6[6]

tert-Butyl *N*-hydroxycarbamate **10** (2.00 g, 15.0 mmol) was stirred in a solution of toluene (20 mL), sodium hydroxide (10 mL, 50% w/w) and tetraethylammonium bromide (453 mg, 2.16 mmol). 1,3-Dibromopropane (4.71 g, 22.5 mmol, 2.37 mL) was added to the slurry, which was subsequently brought to reflux for 90 min. Ethyl acetate (15 mL) was added and the mixture, which was washed with saturated sodium hydrogen carbonate solution (20 mL), water (15 mL), and brine (15 mL). The organic phase was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by chromatography eluting with acetone in light petrol (1:9) to give *tert*-butyl isoxazolidine-2-carboxylate **12** (441 mg, 17%) as a clear colourless oil; ν_{max} (Nujol)/cm^{-1} 2979, 1734, 1709; δ_H (400 MHz, $CDCl_3$) 3.84 (2H, t, *J* 7.2, CH_2CH_2ON), 3.55 (2H, t, *J* 7.2, CH_2N), 2.16 (2H, quin, *J* 7.2, CH_2CH_2N), 1.43 (9H, s, CH_3); δ_C (100 MHz, $CDCl_3$) δ_C 159.7 (C), 81.8 (C), 68.4 (CH_2), 46.8 (CH_2), 28.2(CH_3), 27.9 (CH_2); *m*/*z* (APCI): 174.7 ($M+H^+$, 8%), 118.7 (100); HRMS (ES): found $M+H^+$, 174.1128. $C_8H_{16}NO_3$ requires, 174.1125.

tert-Butyl isoxazolidine-2-carboxylate **12** (112 mg, 0.65 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 3.24 mmol, 1.62 mL) was added and the resulting solution allowed to stand until reaction was complete by TLC. The volume of liquor was reduced in vacuo and the precipitate was filtered and washed with cold ether affording the *title compound* **6** as a colourless solid (63 mg, 89%); mp (ether/chloroform) 111–112 °C; ν_{max} (Nujol)/cm^{-1} 3386, 2923, 2853, 1459, 1377, 1003; δ_H (400 MHz, d_6-DMSO) 12.48 (2H, br s, NH_2), 4.19 (2H, t, *J* 7.1, CH_2O), 3.49 (2H, t, *J* 7.1, CH_2N), 2.41 (2H, quin, *J* 7.1, CH_2CH_2N); δ_C (125 MHz, d_6-DMSO) δ_C 70.9 (CH_2), 45.5 (CH_2), 27.9 (CH_2).

4.3. Pyrazolidine hydrochloride 7

Di-*tert*-butyl hydrazodiformate **11** (5.00 g, 21.5 mmol) was stirred in a solution of toluene (50 mL), sodium hydroxide (25 mL, 50% w/w) and tetraethylammonium bromide (650 mg, 3.10 mmol). 1,3-Dibromopropane (6.50 g, 32.3 mmol, 3.27 mL) was added and the reaction was brought to reflux for 90 min. Ethyl acetate (50 mL) was added and the mixture was washed with saturated sodium hydrogen carbonate (70 mL), water (50 mL) and brine (30 mL). The organic phase was separated, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by chromatography eluting with acetone/light petrol (1:9) to give di-*tert*-butyl pyrazolidine-1,2-dicarboxylate **13** (4.33 g, 74%) as a clear colourless oil; ν_{max} (Nujol)/cm^{-1} 2928, 2853, 1704, 1489, 1422, 1156; δ_H (400 MHz, $CDCl_3$) 3.79–3.86 (2H, m, CH*H*N), 3.11–3.19 (2H, m, CH*H*N), 1.91–1.98 (2H, m, CH_2CH_2N), 1.41 (18H, s, CH_3); δ_C (100 MHz, $CDCl_3$) δ_C 156.1 (C), 81.1 (C), 46.3 (CH_2), 28.2 (CH_3), 25.7 (CH_2); *m*/*z* (APCI): 273.7 ($M+H^+$, 10%), 217.7 (10), 117.8 (100); HRMS (ES): found $M+H^+$, 273.1812. $C_{13}H_{25}N_2O_4$ requires, 273.1809.

Di-*tert*-butyl pyrazolidine-1,2-dicarboxylate **13** (200 mg, 0.73 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 1.85 mL, 3.67 mmol) was added and the resulting solution was left to stand until reaction was complete by TLC. The volume of liquor was reduced and the precipitate was filtered and washed with cold ether resulting in the *title compound* **7** as a colourless solid (95 mg, 96%); mp (ether/chloroform) 77–78 °C [lit.[6] mp 54–56 °C]; ν_{max} (Nujol)/cm^{-1} 3395, 2922, 2852, 1461, 1377; δ_H (400 MHz, d_6-DMSO) 8.89 (3H, br s, NH_2), 3.12 (4H, t, *J* 7.2, CH_2N), 2.04 (2H, quin, *J* 7.2, CH_2CH_2N); δ_C (100 MHz, d_6-DMSO) 45.8 (CH_2), 25.4 (CH_2). *m*/*z* (APCI): 73.1 ($M+H^+$, 100%); HRMS (ES): found $M-Cl^+$, 73.0773. $C_3H_9N_2$ requires, 73.0766.

4.4. Ethyl pyrazolidine-1-carboxylate hydrochloride 15

Di-*tert*-butyl dicarbonate (10.50 g, 48 mmol), in THF (90 mL), was cooled to 0 °C. Ethyl carbazate **14** (5.00 g, 48 mmol) was added. The resulting solution was stirred at 0 °C for 30 min and then allowed to warm to room temperature for a further 24 h. Removal of the solvent under reduced pressure afforded *N*′-*tert*-butyl ester ethyl carbazate (9.40 g, 96%) as a white amorphous solid with no further purification required; mp (THF) 98–99 °C [lit.[15] mp 92–93 °C]; ν_{max} (Nujol)/cm^{-1} 3282, 2926, 2852, 1740, 1712; δ_H (400 MHz, $CDCl_3$) 6.54 (1H, br s, N*H*), 6.39 (1H, br s, N*H*), 3.95 (2H, q, *J* 7.1, CH_2), 1.36 (9H, s, $C(CH_3)_3$), 1.20 (3H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 156.9 (C), 155.8 (C), 81.7 (C), 62.1 (CH_2), 28.1 (CH_3), 14.4 (CH_3); *m*/*z* (APCI): 205 ($M+H^+$, 10%), 149 (100); HRMS (ES): found $M+H^+$, 205.1183. $C_8H_{17}N_2O_4$ requires, 205.1183.

N′-*tert*-Butyl ester ethyl carbazate (2.00 g, 9.8 mmol) was stirred in a solution of toluene (20 mL), sodium hydroxide (10 mL, 50% w/w), and tetraethylammonium bromide (290 mg, 1.24 mmol). 1,3-Dibromopropane (3.07 g, 14.7 mmol, 1.55 mL) was added to the slurry, which was subsequently brought to reflux for 90 min. Ethyl acetate (15 mL) was added and the mixture, which was washed with saturated sodium hydrogen carbonate solution (20 mL), water

(15 mL) and brine (15 mL). The organic phase was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude reaction mixture was purified by chromatography eluting with acetone/light petrol (1:9) resulting in *tert*-butyl ethyl pyrazolidine-1,2-dicarboxylate (1.94 g, 81%) as a clear colourless oil; ν_{max} (Nujol)/cm^{-1} 2979, 1730, 1700, 1484, 1453, 1426, 1108; δ_H (400 MHz, $CDCl_3$) 4.03–4.22 (2H, m, CH_2N), 3.85 (2H, q, *J* 7.1, CH_2CH_3), 3.10–3.26 (2H, m, CH_2N), 1.98 (2H, quin, *J* 7.0, CH_2CH_2N), 1.42 (9H, s, CH_3), 1.23 (3H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 160.4 (C), 158.2 (C), 82.1 (C), 59.7 (CH_2), 51.2 (CH_2), 51.9 (CH_2), 34.1 (CH_2), 29.7 (CH_3), 14.2 (CH_3); *m*/*z* (APCI): 245.7 (M+H^+, 16%), 189.6 (100), 145.6 (71); HRMS (ES): found M+NH_4^+, 262.1759. $C_{11}H_{24}N_3O_4$ requires, 262.1761.

tert-Butyl ethyl pyrazolidine-1,2-dicarboxylate (100 mg, 0.40 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 1.0 mL, 2.00 mmol) was added and the reaction left to stand until complete by TLC. The volume of ether was reduced and the precipitate was filtered and washed with cold ether. The solvent was removed under reduced pressure resulting in the *title compound* **15** as a colourless solid (74 mg, 87%); mp (ether/chloroform) 129–130 °C; ν_{max} (Nujol)/cm^{-1} 2921, 1712, 1460, 1377, 1300, 1215, 1157, 1122, 1090, 1032; δ_H (400 MHz, CD_3OD) 4.30 (2H, q, *J* 7.1, CH_2CH_3), 3.74 (2H, t, *J* 7.0, CH_2N), 3.60 (2H, t, *J* 7.0, CH_2N), 2.37 (2H, quin, *J* 7.0, CH_2CH_2N), 1.34 (3H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 153.8 (C), 63.8 (CH_2), 46.3 (CH_2), 45.4 (CH_2), 24.4 (CH_2), 14.4 (CH_3); *m*/*z* (ES): 145 (M−Cl^+, 100%), 116.9 (43); HRMS (ES): found M−Cl^+, 145.0973. $C_6H_{13}N_2O_2$ requires, 145.0972.

4.5. Benzyl pyrazolidine-1-carboxylate hydrochloride 17

Benzylchloroformate (5.69 g, 33.4 mmol, 4.80 mL) was added to a vigorously stirred solution of *tert*-butyl carbazate **16** (4.41 g, 33.4 mmol), in a biphasic solution of chloroform (62 mL) and aqueous sodium hydroxide (1.8 M, 1.49 g, 37 mmol, 21 mL). The resulting solution was stirred at room temperature for 24 h. The organic layer was separated and washed with water (10 mL) and a citric acid solution (10 mL, 10% w/w). The resultant liquor was dried ($MgSO_4$) and the solvent was removed to give *N*′-*tert*-butyl ester benzyl carbazate (8.08 g, 91%) as a white solid with no further purification required; mp (chloroform/light petrol) 71–73 °C [lit.[6] mp 79–80 °C]; ν_{max} (Nujol)/cm^{-1} 3268, 2924, 1755, 1703, 1515, 1463, 1377; δ_H (400 MHz, $CDCl_3$) 7.26 (5H, br s, Ar-*H*), 6.76 (1H, br s, N*H*), 6.45 (1H, br s, N*H*), 5.07 (2H, s, CH_2), 1.38 (9H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 156.7 (C), 155.7 (C), 135.6 (C), 128.5 (CH), 128.4 (CH), 128.3(CH), 81.9 (C), 67.8 (CH_2), 28.1 (CH_3); *m*/*z* (APCI): 167.5 (M+H-Boc$^+$, 46%), 91.8 (100); HRMS (ES): found M+H^+, 267.1268. $C_{13}H_{19}N_2O_4$ requires, 267.1267.

N′-*tert*-Butyl ester benzyl carbazate (5.00 g, 18.8 mmol) was stirred in a solution of toluene (50 mL), sodium hydroxide (25 mL, 50% w/w), and tetraethylammonium bromide (650 mg, 3.10 mmol). 1,3-Dibromopropane (5.69 g, 28.2 mmol, 2.90 mL) was added and the solution was brought to reflux for 80 min. Ethyl acetate (50 mL) was added and the mixture was subsequently washed with saturated sodium hydrogen carbonate solution (70 mL), water (50 mL), and brine (30 mL). The organic phase was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure. The reaction mixture was purified by chromatography eluting with acetone/light petrol (1:9), which resulted in *tert*-butyl benzyl pyrazolidine-1,2-dicarboxylate (4.54 g, 79%) as a clear colourless oil; ν_{max} (Nujol)/cm^{-1} 2933, 1710, 1459, 1379, 1087; δ_H (500 MHz, $CDCl_3$) 7.25–7.38 (5H, m, Ar-*H*), 5.10–5.28 (2H, m, OCH_2Ar), 3.87–3.96 (2H, m, CH*H*N), 3.16–3.35 (2H, m, CH*H*N), 1.98–2.08 (2H, m, CH_2CH_2N), 1.37 (9H, s, CH_3); δ_C (60 MHz, $CDCl_3$) 156.8 (C), 156.3 (C), 136.2 (C), 128.5 (CH), 127.9 (CH), 127.0 (CH), 81.6 (C), 67.8 (CH_2), 46.7 (CH_2), 46.3 (CH_2), 28.1 (CH_3), 25.7 (CH_2); *m*/*z* (APCI): 307.3 (M+H^+, 100%); HRMS (ES): found M+H^+, 307.164. $C_{16}H_{23}N_2O_4$ requires, 307.1652.

tert-Butyl benzyl pyrazolidine-1,2-dicarboxylate (100 mg, 0.33 mmol) was dissolved in dry ether (0.5 mL). Hydrochloric acid in ether (2 M, 0.85 mL, 1.65 mmol) was added and the reaction left to stand until complete by TLC. The volume of ether was reduced and the precipitate was filtered and washed with cold ether. The solvent was removed under reduced pressure resulting in the *title compound* **17** as a colourless solid (74 mg, 94%); mp (ether/chloroform) 150–151 °C; ν_{max} (Nujol)/cm^{-1} 2927, 2854, 1721; δ_H (400 MHz, $CDCl_3$) 7.30–7.51 (5H, m, Ar-*H*), 5.22 (2H, s, CH_2Ar), 3.64 (2H, t, *J* 6.9, CH_2N), 3.42 (2H, t, *J* 6.9, CH_2N), 2.51 (2H, br s, NH_2), 2.20 (2H, quin, *J* 6.9, CH_2CH_2N); δ_C (125 MHz, d_6-DMSO) 154.7 (C), 136.0 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 68.3 (CH_2), 46.6 (CH_2), 46.4 (CH_2), 24.6 (CH_2); *m*/*z* (APCI): 207.7 (M−Cl^+, 81%); HRMS (ES): found M−Cl^+, 207.1126. $C_{11}H_{15}N_2O_2$ requires, 207.1128.

4.6. Experimental procedure for catalytic runs

trans-Cinnamaldehyde **22** (252 mg, 1.9 mmol, 0.24 mL, 1.0 equiv) was added to a solution of catalyst (10 mol %, 0.19 mmol) in methanol (2.0 mL) at 25 °C and the resulting mixture was stirred for 5 min to initiate iminium ion formation. Freshly cracked cyclopentadiene **21** (323 mg, 4.9 mmol, 0.38 mL, 2.5 equiv) was added in a single aliquot and stirring was continued for a known time. The solvent was removed under reduced pressure and the residue was hydrolysed in a chloroform (2 mL), water (1 mL) trifluoroacetic acid (1 mL) mixture over night. Saturated sodium hydrogen carbonate solution (18 mL) was added to neutralise the solution and the aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic phase was washed with water (10 mL) and dried (Na_2SO_4) prior to the removal of the volatiles under reduced pressure. ^{1}H NMR spectroscopy 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 (400 MHz, $CDCl_3$) 9.8 (*exo*) 9.65 (cinnamaldehyde) 9.53 (*endo*). The products were then purified by flash column chromatography eluting with ethyl acetate/light petroleum (1:9) resulting in a mixture of the *exo*- and *endo*- isomers of 3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **23** and **24** as a pale yellow oil. ^{1}H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values;[16] υ_{max} (liquid film)/cm^{-1} 1718, 1601, 1497; *m*/*z* (EI): 198 (M^+, 10%), 132 (89), 131 (100), 103 (52), 77 (21), 66 (54); *exo*- **23** δ_H (400 MHz, $CDCl_3$) 9.85 (1H, d, *J* 2.02, C*H*O), 7.4–7.0 (5H, m, Ar*H*), 6.27 (1H, dd, *J* 5.6 and 3.6, C*H*=CH), 6.01 (1H, dd, *J* 5.6 and 3.6, CH=C*H*), 3.66 (1H, dd, *J* 5.0 and 3.4, C*H*Ph), 3.25–3.05 (2H, m, $CHCH_2$), 2.55–2.45 (1H, m, C*H*CHO), 1.65–1.45 (2H, m, CH_2); *endo*- **24** δ_H (400 MHz, $CDCl_3$) 9.53 (1H, d, *J* 2.2, C*H*O), 7.4–7.0 (5H, m, Ar*H*), 6.36 (1H, dd, *J* 5.6 and 3.6, C*H*=CH), 6.10 (1H, dd, *J* 5.6 and 3.6, CH=C*H*), 3.3–3.2 (1H, m, C*H*Ph), 3.1–3.05 (1H, m, $CHCH_2$), 3.04–3.0 (1H, m, $CHCH_2$), 2.94–2.86 (1H, m, C*H*CHO), 1.85–1.66 (2H, m, CH_2).

4.7. *tert*-Butyl ethyl piperazine-1,2-dicarboxylate hydrochloride 26

N′-*tert*-Butyl ester ethyl carbazate (2.00 g, 9.80 mmol) was added to a stirred solution of toluene (40 mL) containing tetraethylammonium bromide (230 mg, 1.63 mmol) and 1,4-dibromobutane (3.17 g, 14.7 mmol, 1.75 mL). Aqueous sodium hydroxide (20 mL, 50% w/w) was added at ambient temperate and the reaction brought to reflux for 45 min or until the *N*′-*tert*-butyl ester ethyl carbazate was consumed. The reaction was cooled and diluted with ethyl acetate (50 mL) and washed with aqueous saturated sodium hydrogen carbonate. The organic layer was separated, washed with water (10 mL) and brine (10 mL) and subsequently dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude mixture was purified by chromatography eluting with ether/light petrol (1:1) affording *tert*-butyl ethyl piperazine-1,2-dicarboxylate (2.00 g, 79%) as a light yellow oil; δ_H (400 MHz, d_6-

DMSO) 4.20–4.10 (2H, m, OCH_2CH$_3$), 4.10–4.05 (2H, m, CHHN), 2.88 (2H, m, CHHN), 1.65–1.61 (4H, m, CH$_2$CH_2CH_2CH$_2$), 1.46 (9H, s, (CH_3)$_3$), 1.27 (3H, t, J 7.0, CH_3); δ_C (100 MHz, CDCl$_3$) 161.2 (C), 159.9 (C), 80.4 (C), 59.7 (CH$_2$), 47.2 (CH$_2$), 46.5 (CH$_2$), 29.1 (CH$_3$), 21.7 (CH$_2$), 14.1 (CH$_3$); m/z (ES): 258.0 (M+H$^+$, 68%), 231.1 (21), 185.0 (79), 157.0 (100); HRMS (ES): found M+H$^+$, 259.1581. $C_{12}H_{23}N_2O_4$ requires, 259.1580.

tert-Butyl ethyl piperazine-1,2-dicarboxylate (500 mg, 1.97 mmol) was dissolved in dry ether (1.0 mL) prior to the addition of hydrochloric acid in ether (1 M, 10 mL). The reaction was left to stand at ambient temperature until complete by TLC. The volume of liquor was reduced and the precipitate filtered and washed with cold ether affording the *title compound* **26** (294 mg, 78%) as a colourless solid; mp 147.5–148 °C; ν_{max} (Nujol)/cm^{-1} 3460, 2962, 2253, 1734, 1560, 1468, 1382, 1261; δ_H (400 MHz, d_6-DMSO) 4.32 (2H, q, J 7.1, OCH_2CH$_3$), 3.92 (2H, t, J 5.6, CH_2NCO), 3.45 (2H, t, J 5.8, CH_2NH$_2$), 2.08–2.19 (2H, m, CH_2CH$_2$NCO), 1.69–1.78 (2H, m, CH_2CH$_2$NH$_2$), 1.36 (3H, t, J 7.1, CH$_2$CH_3); δ_C (125 MHz, d_6-DMSO) 153.2 (C), 62.7 (CH$_2$), 46.0 (CH$_2$), 45.7 (CH$_2$), 24.0 (CH$_2$), 14.6 (CH$_2$), 14.3 (CH$_3$); m/z (ES): 159.1 (M−Cl$^+$, 90%) 131.0 (28), 113.0 (100); HRMS (ES): found M+H$^+$, 159.1129. $C_7H_{15}N_2O_2$ requires, 159.1128.

4.8. *tert*-Butyl benzyl piperazine-1,2-dicarboxylate hydrochloride 28

tert-Butyl benzyl piperazine-1,2-dicarboxylate was prepared under the standard reaction conditions from *N′-tert*-butyl ester benzyl carbazate **27** (2.00 g, 7.51 mmol) and 1,4-dibromobutane (2.43 g, 11.3 mmol, 1.35 mL) (1.26 g, 52%) as a colourless solid; mp 73–74 °C; ν_{max} (Nujol)/cm^{-1} 2928, 2855, 1712, 1683, 1453, 1425, 1369, 1288, 1261, 1201, 1164, 1134, 1080, 1058; δ_H (400 MHz, d_6-DMSO) 7.29–7.39 (5H, m, Ar-H), 5.05–5.29 (2H, m, CH_2Ar), 4.00–4.22 (2H, m, CHHN), 2.81–3.12 (2H, m, CHHN), 1.54–1.72 (4H, m, CH$_2$CH_2CH_2CH$_2$), 1.28–1.54 (9H, m, C(CH_3)$_3$); δ_C (125 MHz, CDCl$_3$) 154.8 (C), 154.0 (C), 136.4 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 81.2 (C), 67.5 (CH$_2$), 44.8 (CH$_2$), 40.4 (CH$_2$), 28.1 (CH$_3$), 23.8 (CH$_2$), 23.6 (CH$_2$); m/z (ES): 343 (M+Na$^+$, 20%) 265 (31), 221 (78); HRMS (ES): found M+H$^+$, 321.1803. $C_{17}H_{25}N_2O_4$ requires, 321.1809.

The hydrochloride salt was prepared under standard conditions (682 mg, 85%) as a colourless solid; mp (ether/chloroform) 146–147 °C; ν_{max} (Nujol)/cm^{-1} 3340, 2920, 1736, 1558, 1461, 1377; δ_H (400 MHz, d_6-DMSO) 11.92 (2H, br s, NH_2), 7.23–7.39 (5H, m, Ar-H), 5.52 (2H, s, CH_2Ar), 3.78–3.86 (2H, m, CH_2N), 3.38–3.42 (2H, m, CH_2N), 1.95–2.08 (2H, m, CH$_2$CH$_2$CH_2CH$_2$), 1.56–1.65 (2H, m, CH$_2$CH_2CH$_2$CH$_2$); δ_C (100 MHz, d_6-DMSO) 159.1 (C), 141.2 (C), 129.4 (CH), 128.1 (CH), 127.4 (CH), 66.8 (CH$_2$), 52.4 (CH$_2$), 49.1 (CH$_2$), 23.4 (CH$_2$), 20.8 (CH$_2$); m/z (ES): 221 (M−Cl$^+$, 100%); HRMS (ES): found M–Cl$^+$, 221.1285. $C_{12}H_{17}N_2O_2$ requires, 221.1285.

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