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Structure-reactivity relationships of L-proline derived spirolactams and α-methyl prolinamide organocatalysts in the asymmetric Michael addition reaction of aldehydes to nitroolefins.

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Graphical abstract:

Structure-reactivity relationships of L-proline derived spirolactams and α-methyl prolinamide organocatalysts in the asymmetric Michael addition reaction of aldehydes to nitroolefins.

Fintan Kelleher,* Sinead Kelly, John Watts and Vickie McKee

\[
\text{H} \quad + \quad \text{H} \quad + \quad \text{NO}_2 \quad \xrightarrow{5 \text{ mol}\% \text{ Cat}} \quad \text{NO}_2 \quad \xrightarrow{\text{DCM, RT}} \quad \text{H} \quad + \quad \text{Ar} \\
\]

70-98% yield
up to 98:2 Syn/Anti,
up to 82% e.e. (Syn)
Structure-reactivity relationships of L-proline derived spirolactams and α-methyl prolinamide organocatalysts in the asymmetric Michael addition reaction of aldehydes to nitroolefins.

Fintan Kelleher,*a John Watts,a Sinead Kellya and Vickie McKeeb

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bChemistry Department, Loughborough University, Loughborough, Leics. LE11 3TU, UK.

Abstract:
L-Proline derived spirolactams and α-methyl prolinamides act as organocatalysts for the asymmetric conjugate addition of aldehydes to nitroolefins in excellent yields, with good diastereoselectivity and enantioselectivity. Furthermore, low catalyst loadings (5 mol%) and a low aldehyde molar excess (1.5 molar equivalents) were achieved.

Keywords
Spirolactam; α-methyl prolinamide; Asymmetric Organocatalysis; Michael addition reaction.

Introduction
The field of organocatalysis has seen an explosion of interest in the last decade.1 In particular, L-proline derived compounds have found use as organocatalysts in the asymmetric Michael addition reaction of aldehydes and ketones to nitroolefins, with the products being produced in high yields, with excellent diastereo- and enantioselectivities (Figure 1).1-6 However, in many earlier cases either a large excess of the aldehyde or ketone is required (10-20 molar equivalents) or high levels of catalysts (10-25 mol%). More recently highly efficient catalyst systems for this transformation have been developed and are the benchmark for all new catalysts. Ma
was able to achieve high yields and selectivities using only 0.5 mol% of 4 and 1.5 equivalents of aldehyde in the presence of benzoic acid as an additive.\(^3\) However, Lombardo recently reported the use of the ion-tagged diphenylprolinol silyl ether 7 which achieves enantiomeric excesses of >99.5% at low catalyst loadings (0.25-5 mol%), and uses only a slight excess of aldehydes (1.2-2 molar equivalents).\(^4\) The most efficient catalyst reported to-date is the tripeptide 8 described by Wennemers.\(^5\) This catalyst is highly efficient at levels of only 0.1-0.2 mol%, even with the nitroalkene in excess, giving high yields and selectivities for a range of aldehydes and nitroalkenes. The usefulness of the products from these reactions resides in the potential for further transformation of both the nitro and carbonyl functionalities.

![Figure 1. Proline and 4-hydroxyproline derived organocatalysts.\(^1\text{-}^6\)](image)

There is an ongoing requirement for the development of new organocatalysts for this and other important chemical transformations, in order to fully understand the structure-reactivity relationships of these catalysts. Many of the reported proline-derived catalysts are conformationally flexible in nature and it was thought that the introduction of conformational constraints into the structure could lead to more specific catalysts, which might allow the use of lower amounts of aldehyde or ketone, along with the requirement for low levels of the organocatalyst (e.g. 5% or less). One way to introduce such conformational constraint would be to have, for example, the L-
proline as part of a rigid spiro fused ring system. Royer recently prepared such a rigid pyrrolidino spiro diamine (9, Figure 1) and it exhibited limited success in its ability to act as an asymmetric organocatalyst in the Michael addition reaction of aldehydes to nitroolefins, although only one set of reaction conditions was reported. Rather than having the second amino group as an exocyclic substituent, incorporation of the second nitrogen atom as part of the ring would give spirolactam and spirodiamine structures.

Results and Discussion

As part of a program to synthesise both enantiomerically pure and racemic proline-derived [4.4]-spirolactams, we recently reported our studies on their preparation by thermal intramolecular ester aminolysis methods. Diastereoisomeric spirolactams (11a and 11b) were prepared and separated chromatographically (Figure 2).

Figure 2. Synthesised spirolactam and spirodiamine organocatalysts

It was also found that the spiro diamine derivatives 13a and 13b complexed a zinc ion. Although the stereochemistry of the α-methyl benzyl substituent was known, from the choice of the starting amine, the absolute stereochemistry of the spiro centre in each of the diastereoisomers was not known. Previously, we were unable to grow crystals of sufficient quality for X-ray analysis to be obtained, so NMR spectroscopy
along with molecular modelling\textsuperscript{7c} was used to tentatively assign the stereochemistry of the \textit{SR} and \textit{RR} diastereoisomeric pair, \textbf{11a} and \textbf{11b}. Eventually crystals of sufficient quality were obtained of \textbf{11b}, by crystallisation from hexane, and an X-ray crystal structure was obtained (\textbf{Figure 3}), which confirmed the previous NMR spectroscopic and modelling assignments.\textsuperscript{7b,c}

\textbf{Figure 3.} Perspective view of \textbf{11b} showing 50\% probability ellipsoids. Hydrogen atoms omitted for clarity.

The X-ray crystal structure clearly shows the \textit{R} absolute stereochemistry at the spiro centre. As a result of this structure, the absolute stereochemistry of both diastereoisomers was now known. Treatment of \textbf{11a} and \textbf{11b} with trifluoroacetic acid gave the desired deprotected compounds \textbf{12a} and \textbf{12b}. An examination of the structures of these compounds shows that they can be considered as conformationally constrained analogues of prolinamides, an important class of organocatalysts. Therefore the investigation of the use of spirolactams \textbf{12a} and \textbf{12b} as organocatalysts in the model reaction of valeraldehyde with trans-$\beta$-nitrostyrene was undertaken (\textbf{Table 1}).

\textbf{Table 1.} Michael addition reaction of valeraldehyde to $\beta$-nitrostyrene.
The first reaction was conducted using a low molar excess of valeraldehyde (1.5 equivalents) in dichloromethane at room temperature for 72 h in the presence of 5 mol% of (S,R)-spirolactam 12a (entry 1). Product 16 was isolated in 98% yield, with a syn:anti ratio of 62:38, and the enantiomeric excess (e.e.) of the syn isomer was 66%.

Changing the solvent to chloroform or 2-propanol gave similar results, while the use of THF as solvent gave a better syn:anti ratio of 74:26 and an e.e. of 80% for the syn isomer, although the isolated yield was much reduced at 43% (entries 2, 3 and 4). DMSO gave an 80% yield, with a syn:anti ratio of 74:26, but a poor e.e. of only 25% (entry 5). For further studies, DCM was used as solvent. The effect of temperature on the outcome of the reaction was examined by running the reaction at 4 °C (entry 6). In this case, the isolated yield was reduced to 77%, while the syn:anti ratio improved to 70:30, with the syn isomer having an improved e.e. of 76%, when compared to the reaction at room temperature. Increasing the amount of valeraldehyde to 10 molar equivalents surprisingly gave a slight reduction in isolated yield to 90%, when compared to the use of 1.5 molar equivalents (98%, entry 1), but with an improved syn:anti ratio of 73:27, and an e.e. of 80% for the syn isomer (entry 7). Repeating this

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<th>Entry</th>
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<th>Temp.</th>
<th>Yield</th>
<th>Yield</th>
<th>Syn:Anti</th>
<th>ee</th>
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<td>98</td>
<td>71:29</td>
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</table>

- a Isolated yield after chromatography
- b Syn:anti ratio determined by ¹H NMR spectroscopy
- c e.e. of syn isomer determined by chiral HPLC
- d Opposite enantiomer of the syn product

The first reaction was conducted using a low molar excess of valeraldehyde (1.5 equivalents) in dichloromethane at room temperature for 72 h in the presence of 5 mol% of (S,R)-spirolactam 12a (entry 1). Product 16 was isolated in 98% yield, with a syn:anti ratio of 62:38, and the enantiomeric excess (e.e.) of the syn isomer was 66%.
reaction with 20 mol% of the catalyst, brought the isolated yield back to 98%, but unfortunately, the syn:anti ratio reduced to 64:36, with a concomitant reduction in the e.e. of the syn isomer to 72% (entry 8).

Use of the diastereoisomeric (R,R)-spirolactam 12b as catalyst, under the standard conditions, gave similar isolated yields to those obtained with 12a, with similar syn:anti ratios (Entries 9, 10 and 11). The enantiomeric excesses were also similar but, most importantly, in these cases the opposite enantiomer of the syn diastereoisomer now predominated, as shown by chiral HPLC analysis. Other groups have observed an improvement in both the diastereoisomeric ratio and the e.e. of the syn isomer on the addition of acidic additives, such as trifluoroacetic acid (TFA). Addition of 1 molar equivalent of TFA, using spirolactam 12b as catalyst, gave a reduced isolated yield, with poorer diastereoccontrol (Entry 12). All of these results show that it is the absolute stereochemistry of the spiro centre which is controlling the observed enantioselectivity, with the stereochemistry of the side-chain substituent having little effect. This is not surprising if the proposed transition state models of the reactions are considered (Figure 4).
Figure 4. Proposed transition state model for Michael addition reaction of valeraldehyde with $\beta$-nitrostyrene using spirolactam catalysts.

The syn diastereoselectivity observed is due to the “Seebach acyclic synclinal model”, in which there are favourable electrostatic interactions in the transition state between the enamine nitrogen and the nitro group. For the syn diastereoisomeric pair the Re face of the nitrostyrene can approach the enamine Re face in two different
ways (Re,Re-1 and Re,Re-2, Figure 4), depending on whether it approaches from the same, or opposite, side as the lactam carbonyl group. Similarly the Si face of the nitrostyrene can approach enamine Si face in two ways (Si,Si-1 and Si,Si-2). Of the two possible Re,Re trajectories Re,Re-2 is the much more likely because there are two destabilising steric interactions present in the Re,Re-1 trajectory, namely the less favourable enamine rotamer as well as the interaction of the nitrostyrene with the lactam carbonyl group. Neither of these interactions are present in the Re,Re-1 trajectory. Of the two possible Si,Si trajectories Si,Si-1 has the favourable enamine rotamer but a steric interaction with the lactam carbonyl, while Si,Si-2 has a steric interaction with the methylene of the lactam ring, as well as being the less favoured enamine rotamer. It is therefore not apparent which of these trajectories is more favoured. Overall, it is thus the contribution of favourable electrostatic interactions as well as the unfavourable steric interactions which controls the observed diastereoselectivity and enantioselectivity. In the case of the use of the spirolactam 12b as catalyst, with the opposite stereochemistry at the spirocentre, the transition state with the Si,Si approach of the faces of the β-nitrostyrene and the enamine would be the predominant pathway, thus giving the observed (R,S) enantiomer as the major product.

Increasing the steric bulk of the spirolactam side-chain was achieved by replacing the phenyl group with the 1-naphthyl group. The spirolactams were synthesised in an analogous manner to the phenyl substituted compounds, but (R)-(1)-(1-naphthyl)ethylamine was used in place of (R)-(1)-(1-phenylethylamine. As before the two diastereoisomeric spirolactams, 14a and 14b, were separable. Their stereochemistries were tentatively assigned by comparison of their NMR spectral data (chemical shifts and coupling constants) with the phenyl-derived compounds, as well as their relative polarities as measured by TLC analysis. Use of the Boc deprotected compounds 15a or 15b in the Michael addition reaction gave similar yields and diastereoselectivities to those of the corresponding phenyl derivatives 12a and 12b, but with slightly lower enantioselectivities (Table 1, entries 13 and 14). This confirms that the lactam side-chain is having little effect on the stereochemical outcome of the reaction.
The scope of the catalysts (12a and 12b) was examined by reacting different aldehydes and β-nitrostyrenes under the optimised conditions (Table 2). Propionaldehyde showed poor diastereo- and enantioselectivity (d.r. 62:38, e.e. 34%) and a reduced isolated yield of 77% (entry 1), while the more hindered isovaleraldehyde showed excellent diastereoselectivity (d.r. 89:11) and a hugely improved e.e. of 82% (entry 2). Unfortunately, the isolated yield was poor (22%) due to the increased steric effect of the branched aldehyde. Reaction of valeraldehyde with substituted β-nitrostyrenes show similar diastereo- and enatioselectivity to the parent β-nitrostyrene (entries 3-8). The reason for the very poor enantioselectivity of catalyst 12b (4% e.e.) with the para-methoxy substituted β-nitrostyrene (entry 6) is not known.

Table 2. Michael addition reaction of aldehydes to β-nitrostyrenes

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Reactions carried out with 1.5 molar equivalents of aldehyde.

a Isolated yield after chromatography
b Syn:anti ratio determined by 1H NMR spectroscopy
c e.e. of syn isomer determined by chiral HPLC
d Opposite enantiomer of the syn product

Many of the reported catalysts used to catalyse the Michael addition reaction of aldehydes and ketones to nitroolefins have been diamines derived from L-proline (Figure 1).1,2,6 For comparison, spirodiamines 13a and 13b were prepared, from spirolactams 12a and 12b, by removing the Boc group and reducing the lactam ring to the cyclic amine with lithium aluminium hydride.7c When 13a was used as a catalyst...
in the Michael addition reaction similar syn:anti ratios were obtained, to those when the corresponding spirolactams were used, though the isolated yield was only 85% (Table 3, entry 1).

Table 3. Michael addition reaction of valeraldehyde to β-nitrostyrene catalysed by diamines 13a and 13b.

![Chemical structure](image)

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<th>Entry</th>
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Reactions carried out in DCM at ambient temperature, for 72 hours.

a Isolated yield after chromatography
b Syn:anti ratio determined by 1H NMR spectroscopy
c e.e. of syn isomer determined by chiral HPLC
d Opposite enantiomer of the syn product

In these cases, however, the enantioselectivity was severely reduced, with the syn isomer now being obtained in close to racemic form. Increasing the amount of catalyst to 20 mol% only increased the isolated yield back to 98%, with no effect on the stereoselectivity of the reaction (entry 3). The addition of TFA or HCl as an additive, or using the epimeric spiro diamine 13b, had no effect on this outcome (entries 2, 4, 5 and 6). The selectivity of substituted pyrrolidine-based organocatalysts in the Michael addition reaction is mostly determined by the nature of the substituent in the 2-position (trans-4-hydroxy substituents also exert control). For substituents with a hydrogen bond donor present (e.g. COOH in L-proline or the N-H in prolinamides and sulfonamides), it is the attractive interaction with the nitro group of the styrene and the hydrogen bond donor which controls the facial selectivity. In the absence of such hydrogen bond donors the facial selectivity is controlled by the steric effect of
the pyrrolidine side-chain. In this study, there is no hydrogen bond donor present in the spirolactams and thus the facial selectivity is as described previously. The results with the diamines 13a and 13b can be explained by examining the transition state model of the reaction (Figure 4). In the absence of the lactam carbonyl group the Re,Re-2 and Si,Si-1 trajectories are equally likely, since there is now a methylene attached to both sides of the quaternary spiro carbon. This leads to equal steric preference for the Re,Re-2 and Si,Si-1 trajectories and thus racemic products are obtained. In this case although the spiro diamine is more conformationally flexible, the bulky nitrogen side-chain is too remote from the spiro centre to have any impact on the stereocontrol.

It would be envisaged that either breaking the lactam ring to give more conformational flexibility (17) or removal of the spiro fusion completely, to give simple prolinamides 18, might lead to improvements in the observed stereocontrol (Figure 5).

For direct comparison with the spirolactam studies it was decided to keep the α-methyl benzylamine sidechains. The synthesis of the two sets of four stereoisomers of 17 (R = Me or H) started from N-Boc-L-proline methyl ester 19 (Scheme 1).
Scheme 1: Reagents and conditions; (a) i) LiHMDS, THF, -78 °C, ii) methyl iodide, rt, 72%; (b) i) NaOH, MeOH/H₂O, reflux, ii) 1M HCl, 93%; (c) (R)-N,α-dimethylbenzyl amine, DIPEA, HATU, DMF, rt, 49%; (d) 50% TFA in DCM, rt, 88-92%; (e) (R)-α-methylbenzyl amine, DIPEA, HATU, DMF, rt, 94%; (f) 50% TFA in DCM, rt, 93-96%.

α-Methylation of 19 with methyl iodide gave the racemic α-methyl ester 20 in 72% yield, which was hydrolysed to the α-methyl carboxylic acid 21, in 93% yield. The racemic acid was then coupled, separately with R- or S-N,α-dimethylbenzylamine, using HATU as the coupling agent, to give the four N-methylated diastereoisomeric α-methyl prolinamides (22a-d). 21 was also coupled, separately, with R- or S-α-methylbenzylamine, under similar conditions, to give the four N-H stereoisomeric α-methyl prolinamides (22e-h). Removal of the Boc group in each of the eight compounds gave the free amines 17a-h. The relative stereochemistry of each compound was obtained from X-ray crystal structure data. Only one compound from each set gave crystals suitable for X-ray analysis (Figure 6).
Figure 6. X-ray structures of the cation of 17b and one of the two independent conformations of 22g. Both structures are drawn with 50% probability ellipsoids. Tosyl anion in 17b has been omitted for clarity.

Since the stereochemistry of the amine side-chain was known, from the choice of amine starting material, the absolute stereochemistry of the quaternary centre was easily obtained. The crystalline side-chain $N$-H compound was obtained as its Boc derivative 22g ($R,S$ stereochemistry) while the side-chain $N$-Me compound was obtained as its ammonium tosylate salt (17b.TsOH, $R,R$ stereochemistry).
The simple L-prolinamides 18 were prepared from L-proline by Boc protection of the proline nitrogen, to give N-Boc-L-proline 23, in almost quantitative yield, followed by separately coupling to R- or S-α-methylbenzylamine, to give the two diastereoisomeric prolinamides 24a and 24b (Scheme 2, only reaction with (R)-α-methylbenzylamine to give 24a is shown).

![Scheme 2: Reagents and conditions; (a) i) NaOH, MeOH/H2O, reflux, ii) 1M HCl, 98%; (b) (R)-α-methylbenzyl amine, DMAP, EDC, DCM, rt, 90%; (c) i) LiHMDS, THF, -78 °C, ii) methyl iodide, rt, 92%; (d) 50% TFA in DCM, rt, 86-91%.

In these cases, efficient coupling was achieved using EDC, whereas HATU was necessary in the more sterically hindered coupling reactions above. N-methylation of 24a (or 24b), with methyl iodide, gave the N-methyl prolinamide 25a (or 25b). Deprotection of 24a and 24b gave the N-H L-prolinamides 18a and 18b (R = H), while deprotection of 25a and 25b gave the N-Me L-prolinamides 18c and 18d (R = Me). Prolinamides 18a and 18b are known and have previously been described by Chimni as efficient organocatalysts, as their HBr salts, for the direct aldol reaction in water.9 Earlier Wu and Gong also described their use as enantioselective catalysts for direct aldol reactions.10

The α-methyl prolinamides 17a, 17b, 17e and 17f and simple prolinamides 18a-d were then examined as organocatalysts in the standard reaction (Table 4).

**Table 4.** Michael addition reaction of valeraldehyde to β-nitrostyrene catalysed by 17a, 17b, 17e, 17f and 18a-d.
Reactions carried out in DCM with 1.5 molar equivalents of aldehyde, at ambient temperature, for 48 hours.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17a (S,R)</td>
<td>98</td>
<td>61:39</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>17b (R,R)</td>
<td>98</td>
<td>62:38</td>
<td>59^a</td>
</tr>
<tr>
<td>3</td>
<td>17e (S,R)</td>
<td>55</td>
<td>56:44</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>17f (R,R)</td>
<td>60</td>
<td>56:44</td>
<td>59^a</td>
</tr>
<tr>
<td>5</td>
<td>18a (S,R)</td>
<td>98</td>
<td>77:23</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>18b (S,S)</td>
<td>98</td>
<td>98:2</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>18c (S,R)</td>
<td>98</td>
<td>93:7</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>18d (S,S)</td>
<td>94</td>
<td>94:6</td>
<td>65</td>
</tr>
</tbody>
</table>

a Isolated yield after chromatography
b Syn:anti ratio determined by ^1H NMR spectroscopy
c e.e. of syn isomer determined by chiral HPLC
d Opposite enantiomer of the syn product

The N-methyl-α-methyl compounds 17a and 17b gave very similar overall results to those obtained for the corresponding spirolactams 12a and 12b, with similar diastereoselectivity and a slight decrease in enantioselectivity (entries 1 and 2). It is very important to note that the major syn enantiomer (16 (R,S)) obtained for 17a is opposite to that obtained with the spirolactam 12a (Figure 2). The α-methyl N-H compounds 17e and 17f showed similar stereoselectivity, but surprisingly much reduced isolated yields of 55% and 60%. The reason for these reduced yields is not known, at present. These results clearly demonstrate that the presence of a proline α-substituent is detrimental to achieving high levels of stereocontrol. This was borne out when the α-hydrogen N-Me catalysts 18c and 18d were examined. With the removal of the α-methyl substituent the isolated yield was brought back to 94-98% with excellent diastereoselectivity (~94:6). Unfortunately, there was no observed increase in enantioselectivity (entries 7 and 8). Finally, the two N-H catalysts 18a and 18b were examined and found to give excellent isolated yields, diastereoselectivity and hugely improved enantioselectivity (71 and 81% e.e.). The diastereoselectivity for these two catalysts are quite different (77:23 and 98:2) and since both contain an N-H in the side-chain this difference is likely to be due to the overall conformation of the
side-chain (entries 5 and 6). Although 18b gave excellent yield and diastereoselectivity results, the enantiomeric excess was 81%, which is below the levels reported for many proline-derived catalysts.\textsuperscript{3-5} For this reason studies on the expansion of the scope of these catalysts in the Michael addition reaction with different aldehydes and substituted \( \beta \)-nitrostyrenes were not undertaken. The proposed transition state model, involves a steric interaction between the nitro styrene and the amide side-chain on position 2 of the pyrrolidine which destabilises the Re,Re approach for these catalysts (Figure 7), even though there is a favourable electrostatic interaction between the nitro group and the enamine nitrogen. Thus the Si,Si approach predominates where there is a favourable electrostatic interaction between the nitro group and the enamine nitrogen, but no steric interaction with the amide side-chain, thus giving the \( R,S \) enantiomer of 16 as the major enantiomer. The selectivity observed is regardless of whether the side-chain contains an \( N\)-H, as a potential hydrogen bond donor for a favourable electrostatic interaction with the nitro group, or whether it is \( N\)-methylated.
**Figure 7.** Proposed transition state model for Michael addition reaction of valeraldehyde with $\beta$-nitrostyrene using simple prolinamide catalysts 18a-d.

From these studies, it is therefore apparent that the absence of an $\alpha$-substituent and the presence of a sufficiently bulky prolinamide are necessary for the optimal simple prolinamide organocatalyst, for the Michael addition reaction of aldehydes to $\beta$-nitrostyrenes.

**Conclusions**

In conclusion, the main advantage of the spirolactam and $\alpha$-methyl prolinamide organocatalysts used in this study is that both epimers of the $\alpha$-centre can be easily synthesised from a common starting material, L-proline. It is thus possible to selectively form either enantiomer of the syn Michael addition product, in excellent yield with good stereocontrol. In the case of other proline-derived catalysts, this would only be possible by separately preparing catalysts starting with D-proline. Furthermore, the amount of catalyst required for activity is low (5 mol%), along with the requirement of only 1.5 molar equivalents of the aldehyde partner. As stated previously the presence of a trans-4-hydroxy substituent can have a considerable effect on the stereoselectivity obtained and we are also currently preparing analogues of all the synthesised organocatalysts reported here with this functionality present. Further studies on the scope of use of these new organocatalysts in the Michael addition reaction and other important asymmetric transformations are being undertaken, the results of which will be reported in due course.

**Experimental.**

TLC was performed on Merck silica gel 60F$_{254}$ plates and column chromatography was performed on Aldrich silica gel, 70-230 mesh, 60Å. $^1$H and $^{13}$C NMR ($\delta$ ppm; J Hz) spectra were recorded on a Jeol JNM-LA300 FT-NMR spectrometer using CDCl$_3$ solutions with Me$_4$Si as internal reference, unless otherwise indicated, with resolutions of 0.18 Hz and 0.01 ppm, respectively. CHCl$_3$ was used to remove last traces of ethyl acetate from some samples. The last trace of CHCl$_3$ persisted even
after prolonged heating in vacuo and in these cases was visible in NMR spectra. Infrared spectra (cm\(^{-1}\)) were recorded as KBr discs or liquid films between NaCl plates using a Nicolet Impact 410 FT-IR. Melting points were obtained on a Bibby Stuart Scientific SMP1 melting point apparatus. Microanalyses were carried out at the Microanalytical Laboratory of University College Dublin. High Resolution Mass spectra were obtained in the Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin. X-ray crystal structures were obtained in the Chemistry Department, Loughborough University, Loughborough, UK. Chiral HPLC analysis were carried out using a Shimadzu HPLC system Class-VP, incorporating a LC-10AD pump, SPD-M10AVP Diode Array Detector, Auto-injector SII-10A with a system controller SCL-10A VP, on Chiralcel OD-H and AD-H chiral columns. Polarimetry was carried out using an Optical Activity AA-55 series polarimeter at ambient temperature with a 2 dm, 1 ml cell. (±)-2-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (20) is commercially available but was synthesised (vide infra).

\textit{N-Boc-L-proline methyl ester (19).}\(^{11}\)

19 was prepared from L-proline by the method of Confalone\(^{11}\) giving 19 as a clear oil. Analytical data was in agreement with that reported. Microanalysis: Found C, 57.51; H, 8.60; N, 5.88. Calculated for C\(_{11}\)H\(_{19}\)NO\(_4\): C, 57.60; H, 8.34; N, 6.10.

(±)-\(\alpha\)-Formylmethyl \textit{N-Boc-proline methyl ester} was prepared from 19 as previously described.\(^{7c}\)

\((5S)\) and \((5R)\)-6-Oxo-7-((1’R)-naphthylethyl)-1,7-diaza-spiro[4.4]nonane-1-carboxylic acid \textit{tert}-butyl ester (14a and 14b).

Prepared from (±)-\(\alpha\)-formylmethyl \textit{N-Boc-proline methyl ester} 19 (0.65 g, 2.4 mmol) and \((R)\)-1-(1-naphthylethyl)ethylamine (0.35 ml, 2.50 mmol), using the method as previously described for 12a and 12b,\(^{7c}\) giving a yellow oil (0.75 g, 79%). The oil was purified on silica gel using 20% ethyl acetate/petroleum ether giving the two diastereoisomers.
(S,R) Diastereoisomer (14a): Yellow solid, (0.33g, 35%). R$_f$: 0.50 (60% ethyl acetate: petroleum ether). [α]$_D$: +46.66 (c = 0.75 in MeOH). M.p.: 153-155 °C. IR, (KBr)/cm$^{-1}$: 3031, 2984, 1685, 1676. $^1$H NMR (two rotamers present) δ: 8.00, 7.81, 7.50, (3 x m, 7H), 6.13 (q, 1H, J = 7.2 Hz), 3.62-3.45 (m, 3H), 3.27 & 3.08 (2 x t, 1H, J = 9.0 Hz), 2.55-2.30 (m, 2H), 2.15-2.05 (m, 2H), 1.98-1.91 (m, 2H), 1.74 (t, 3H, J = 7.3 Hz), 1.51 & 1.48 (2 x s, 9H). $^{13}$C NMR (two rotamers present) δ: 173.2, 153.6 & 153.4, 137.4, 135.6, 133.7, 128.7, 128.5, 126.0, 124.8, 124.1, 123.8, 123.7, 80.2 & 79.4, 67.6 & 67.5, 48.1 & 48.0, 46.0 & 46.2, 38.8 & 38.3, 36.8 & 36.6, 30.1 & 29.8, 24.7, 23.3 & 23.1, 16.2 & 15.8. HRMS (ESI) calculated for C$_{24}$H$_{31}$N$_2$O$_3$ [M+H]$: 395.2335. Found: 395.2336.

(R,R) Diastereoisomer (14b): Yellow oil, (0.36g, 38%). R$_f$: 0.40 (60% ethyl acetate: petroleum ether). [α]$_D$: +40.5 (c = 1 in MeOH). IR, (Thin film)/cm$^{-1}$: 3031, 2986, 1680, 1676. $^1$H NMR (two rotamers present) δ: 8.61(d, 1H, J = 8.2 Hz), 8.20 (d, 1H, J = 8.3 Hz), 7.81 & 7.50, (2 x m, 6H), 6.27 (q, 0.5H, J = 6.8 Hz), 6.06 (q, 0.5H, J = 6.8 Hz), 3.69-3.42 (m, 2H), 3.28 (m, 1H), 3.12-2.90 (m, 1H), 2.69 (t, 1H, J = 7.0 Hz), 2.41-1.67 (m, 5H), 1.63 (d, 3H, J = 7.0 Hz), 1.45 (s, 9H). $^{13}$C NMR (two rotamers present) δ: 173.5, 153.6, 136.5, 135.8, 133.2, 128.6, 128.2, 126.1, 125.0, 124.4, 123.9, 123.8, 79.8 & 79.4, 68.0 & 67.8, 48.3 & 48.1, 46.5 & 46.2, 38.7 & 38.5, 37.1 & 36.8, 29.9 & 29.8, 28.6, 22.6 & 22.2, 16.4 & 16.1. HRMS (ESI) calculated for C$_{24}$H$_{31}$N$_2$O$_3$ [M+H]$: 395.2335. Found: 395.2328.

(5S)-6-Oxo-7-((1’R)-naphthylethyl)-1,7-diaza-spiro[4.4]nonane (15a)

To a solution of 14a (0.145 g, 0.42 mmol) in DCM (0.3 ml) was added TFA (0.3 ml, 1.28 mmol), and then stirred at ambient temperature for 16 hr. The solution was then concentrated in vacuo, dissolved in H$_2$O (40 ml), and the pH adjusted to ~ 8 by adding Et$_3$N dropwise, at 0 °C. The product was then extracted with DCM (3 x 20 ml), dried over MgSO$_4$, and concentrated in vacuo yielding an oil, which was purified on silica gel using 5% MeOH:DCM, giving the product.

(S,R) Diastereoisomer (15a): yellow oil (0.77g, 90%). R$_f$: 0.5 (10% MeOH: DCM). [α]$_D$: +8.2 (c = 1.1 in MeOH). IR, (Thin film)/cm$^{-1}$: 3332, 3032, 2995, 1684. $^1$H NMR δ: 7.99-7.96 (m, 1H), 7.88-7.81 (m, 2H), 7.56-7.44 (m, 4H), 6.10 (q, 1H, J = 7.0 Hz), 3.27-3.22 (m, 1H), 3.12-3.05 (m, 1H), 2.98-2.90 (m, 1H), 2.28-2.22 (m, 1H),
1.71-1.93 (m, 7H), 1.68 (d, 3H, J = 7.1 Hz). $^{13}$C NMR $\delta$: 176.0, 135.1, 133.7, 131.6, 128.7, 128.6, 128.3, 126.8, 124.9, 124.1, 123.4, 68.1, 47.5, 46.1, 39.1, 35.3, 34.8, 26.0, 16.1. HRMS (ESI) calculated for C$_{19}$H$_{23}$N$_2$O [M+H]$^+$: 295.1810. Found: 295.1802.

**(5R)-6-Oxo-7-((1'R)-naphthylethyl)-1,7-diaza-spiro[4.4]nonane (15b)**

Was prepared from 14b in a similar manner to the preparation of 15a.

**(R,R) Diastereoisomer (15b):** yellow oil (0.78 g, 92%). $\text{R} f$: 0.3 (10% MeOH: DCM), $\lbrack \alpha \rbrack_D$: +11.0 (c = 1 in MeOH). IR, (Thin film)/cm$^{-1}$: 3335, 3030, 2994, 1685. $^1$H NMR $\delta$: 8.10-8.01 (m, 0.5H), 7.87-7.81 (m, 0.5H), 7.55-7.48 (m, 2H), 7.46-7.21 (m, 4H), 6.14 (q, 1H, J = 7.0 Hz), 3.28-3.22 (m, 1H), 3.18-3.05 (m, 1H), 2.98-2.91 (m, 1H), 2.56-2.45 (m, 1H), 2.14-1.68 (m, 7H), 1.60 (d, 3H, J = 7.1 Hz). $^{13}$C NMR $\delta$: 176.1, 135.1, 133.8, 131.5, 128.8, 128.6, 128.4, 126.8, 125.0, 124.2, 123.6, 68.4, 47.3, 46.2, 39.1, 35.2, 34.3, 25.8, 16.3. HRMS (ESI) calculated for C$_{19}$H$_{23}$N$_2$O [M+H]$^+$: 295.1810. Found: 295.1802.

**(±)-2-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (20)**

To a solution of 19 (0.5 g, 2.18 mmol) in dry THF (2 ml) at -20 °C, was added a 1.0M solution of LiHMDS in THF (3.1 ml, 3.1 mmol) slowly while keeping the temperature below -15 °C. The solution was stirred for 1.5 hr, under nitrogen, at this temperature. Methyl iodide (0.25 ml, 3.1 mmol) was added slowly at -20 °C. The solution was stirred while allowing it to warm to ambient temperature. After 18 hr the solution was quenched with a saturated aqueous solution of NH$_4$Cl (5 ml), extracted with ethyl acetate (3 x 20 ml), washed with a brine solution (3 x 10 ml) and then dried over MgSO$_4$. The resulting solution was concentrated in vacuo and was purified by column chromatography on silica gel, using 10 % ethyl acetate: petroleum ether, giving a colourless oil (0.38 g, 72 %). $\text{R} f$: 0.50 (20 % ethyl acetate: petroleum ether). IR, (Thin film)/cm$^{-1}$: 2975, 1750, 1692, 1418. $^1$H NMR (two rotamers present) $\delta$: 3.75 (s, 3H), 3.70-3.64 (m, 1H), 3.62-3.43 (m, 1H), 2.23-2.05 (m, 1H), 2.04-1.92 (m, 3H), 1.58 (s, 3H), 1.45 & 1.41 (2 x s, 9H). $^{13}$C NMR (two rotamers present) $\delta$: 175.4, 153.6, 79.9, 64.8, 52.1, 47.9, 40.1, 28.2, 23.1, 22.3.
(±)-2-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (21)
A suspension of 20 (1.25 g, 5.14 mmol) and NaOH (0.204 g, 5.1 mmol) in MeOH/H₂O (1:1, 20 ml) was heated at reflux temperature for 5 hr. The solvent was removed in vacuo, and the residue was partitioned between diethyl ether and H₂O (1:1, 20 ml). The aqueous phase was then washed with diethyl ether (3 x 10 ml), acidified to pH 3 using 1N HCl, followed by extraction with diethyl ether. The ether layer was then dried over MgSO₄ and concentrated in vacuo yielding the product (1.10 g, 93 %), which was used without further purification. R_f: 0.10 (20 % ethyl acetate: petroleum ether). M.p.: 91-94 °C. IR, (Thin film)/cm⁻¹: 2978, 1740, 1648, 1432. ¹H NMR (two rotamers present) δ: 3.62-3.42 (m, 2H), 2.60 (m, 1H), 2.45 & 2.28 (2 x m, 1H), 1.95-1.77 (m, 2H), 1.62 (s, 3H), 1.48 & 1.42 (2 x s, 9H). ¹³C NMR (two rotamers present) δ: 176.5, 152.3, 80.6, 66.8, 48.7, 38.4, 28.4, 22.8, 22.2.

2-Methyl-2-[methyl-(1-phenylethyl)-carbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (22a and 22b).
To a stirred solution of 21 (0.45 g, 1.96 mmol) in dry DMF (9 ml) was added DIPEA (0.675 ml, 3.92 mmol), followed by (R)-N-methyl-α-methylbenzyl amine (0.25 ml, 1.96 mmol) dropwise. After stirring for 5 min. the solution was cooled to 0 °C, and a solution of HATU (0.752 g, 1.98 mmol) in dry DMF (9 ml) was added slowly. After 10 min at this temperature, the solution was allowed to warm to ambient temperature and stirring was continued for 4 hr. The solution was diluted with EtOAc (200 ml), and then washed successively with 10 % HCl solution (3 x 10 ml), saturated aqueous sodium carbonate solution (3 x 10 ml), H₂O (3 x 10 ml) and brine solution (3 x 10 ml), and then dried over MgSO₄. The solution was concentrated in vacuo giving the crude product (0.65 g) which was purified by column chromatography on silica gel in 10 % ethyl acetate: petroleum ether.

(S,R) Diastereoisomer (22a): Colourless oil, (0.12 g, 18 %). R_f: 0.7 (40 % ethyl acetate: petroleum ether). [α]D: +8.18 (c = 0.55 in MeOH). IR, (Thin film)/cm⁻¹: 2976, 1686, 1678. ¹H NMR (two rotamers present) δ: 7.36-7.24 (m, 5H), 6.18-6.11 (m, 1H), 3.75-3.63 & 3.60-3.52 (2 x m, 1H), 3.38-3.30 (m, 1H), 2.61 & 2.56 (2 x s, 3H), 2.16-1.96 (m, 4H), 1.59 (s, 3H), 1.56 & 1.52 (2 x s, 3H), 1.48 (s, 9H). ¹³C NMR (two rotamers present) δ: 173.0, 152.3, 141.3, 128.5, 127.1 & 126.8, 80.3, 66.2, 51.7.
46.7, 38.1, 29.7, 28.3, 24.7, 23.8, 22.1. HRMS (ESI) calculated for C_{19}H_{29}N_{2}O_{3} [M+H]^+: 347.2335. Found: 347.2318.

(R,R) Diastereoisomer (22b): Colourless oil, (0.21 g, 31 %). Rf: 0.6 (40 % ethyl acetate: petroleum ether). [α]D: +23.9 (c = 0.67 in MeOH). IR, (Thin film)/cm⁻¹: 2972, 1680, 1678. ¹H NMR (two rotamers present) δ: 7.40-7.26 (m, 5H), 6.21-6.09 (m, 1H), 3.78-3.62 & 3.59-3.51 (2 x m, 1H), 3.36-3.23 (m, 1H), 2.65 & 2.50 (2 x s, 3H), 2.25-1.92 (m, 4H), 1.59 & 1.57 (2 x s, 3H), 1.51 & 1.42 (2 x d, J = 1.1 Hz, 3H, H), 1.25 & 1.19 (2 x s, 9H). ¹³C NMR (two rotamers present) δ: 172.8, 153.1, 141.6, 141.4, 128.6, 127.2 & 126.9, 80.1, 66.0, 51.9, 47.2 & 47.0, 38.6 & 38.2, 29.6 & 29.4, 28.7, 24.7 & 24.5, 23.8 & 23.6, 22.1 & 21.8. HRMS (ESI) calculated for C_{19}H_{29}N_{2}O_{3} [M+H]^+: 347.2335. Found: 347.2325.

The reaction was then conducted using (S)-N-methylbenzyl amine, following the method previously described, forming the (R,S) and (S,S) diastereoisomers 22c and 22d.

(R,S) Diastereoisomer (22c): Colourless oil, (0.13 g, 19 %). [α]D: -8.2 (c = 0.55 in MeOH). Analytical data is identical to that of the (S,R) diastereoisomer. HRMS (ESI) calculated for C_{19}H_{29}N_{2}O_{3} [M+H]^+: 347.2335. Found: 347.2320.

(S,S) Diastereoisomer (22d): Colourless oil, (0.24 g, 35 %). [α]D: -24 (c = 0.7 in MeOH). Analytical data is identical to that of the (R,R) diastereoisomer. HRMS (ESI) calculated for C_{19}H_{29}N_{2}O_{3} [M+H]^+: 347.2335. Found: 347.2335.

2-Methyl-pyrrolidine-2-carboxylic acid methyl-(1-phenyl-ethyl)-amide (17a-d).

To a solution of 22(a-d) (0.145 g, 0.42 mmol) in DCM (0.3 ml) was added TFA (0.3 ml, 1.28 mmol), and it was stirred at ambient temperature for 16 hr. It was then concentrated in vacuo, dissolved in H₂O (40 ml), and the pH was adjusted to ~ 8 by adding Et₃N dropwise, at 0 °C. It was then extracted with DCM (3 x 20 ml), dried over MgSO₄, and concentrated in vacuo yielding an oil, which was purified on silica gel using 5% MeOH:DCM.

23
**Diastereoisomer (17a):** Colourless oil, (0.09 g, 88 %).

R<sub>f</sub>: 0.6 (10 % MeOH: DCM). [α]<sub>D</sub>: +18 (c = 1 in MeOH). IR, (Thin film)/cm<sup>-1</sup>: 3276, 2974, 1676. ¹H NMR (two rotamers present) δ: 7.40-7.22 (m, 5H), 6.04 & 5.35 (2 x q, J = 7.0 Hz, 1H), 3.47-3.41 & 3.11-3.02 (2 x m, 2H), 2.74 (s, 3H), 2.30-1.95 (m, 4H), 1.75 & 1.70 (2 x s, 3H), 1.53 (d, J = 7.1 Hz, 3H). ¹³C NMR (two rotamers present) δ: 172.8, 139.4, 129.0, 127.7 & 127.1, 68.3, 52.7, 45.6, 36.2, 30.4, 25.6, 23.9, 15.2. HRMS (ESI) calculated for C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 247.1810. Found: 247.1821.

**Diastereoisomer (17b):** Colourless oil, (0.092 g, 89 %). R<sub>f</sub>: 0.5 (10 % MeOH: DCM). [α]<sub>D</sub>: +25 (c = 1 in MeOH). IR, (Thin film)/cm<sup>-1</sup>: 3276, 2976, 1674. ¹H NMR (two rotamers present) δ: 7.36-7.23 (m, 5H), 6.06 & 5.56 (2 x q, J = 7.1 Hz, 1H), 3.26-3.20 & 3.01-2.92 (2 x m, 2H), 2.76 & 2.70 (2 x s, 3H), 2.17-1.83 (m, 4H), 1.59 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H). ¹³C NMR (two rotamers present) δ: 174.7, 130.1, 128.6, 127.4 & 126.3, 66.9, 52.3, 46.2, 36.6, 30.4, 26.0, 25.6, 15.2. HRMS (ESI) calculated for C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 247.1810. Found: 247.1810.

**Diastereoisomer (17c):** Colourless oil, (0.095 g, 92 %). [α]<sub>D</sub>: -18 (c = 1 in MeOH). Analytical data is identical to that of the (S,R) diastereoisomer. HRMS (ESI) calculated for C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 247.1810. Found: 247.1821.

**Diastereoisomer (17d):** Colourless oil, (0.095 g, 92 %). [α]<sub>D</sub>: -26 (c = 1 in MeOH). Analytical data is identical to that of the (R,R) diastereoisomer. HRMS (ESI) calculated for C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 247.1810. Found: 247.1808.

**2-Methyl-2-(1-phenyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (22e-h).**

To a stirred solution of 21 (0.50 g, 2.18 mmol) in dry DMF (10 ml) was added DIPEA (0.75 ml, 4.36 mmol), followed by (R)-1-phenylethylamine (0.29 ml, 2.18 mmol) dropwise. After 5 min stirring, the solution was cooled to 0 °C, and a solution of HATU (0.84 g, 2.2 mmol) in dry DMF (10 ml) was added slowly. After 10 min at this temperature, the solution was allowed to warm to ambient temperature and stirring was continued for 3 hr. The solution was diluted with warm EtOAc (200 ml), and then washed successively with 10 % HCl (3 x 10 ml), saturated aqueous sodium carbonate
solution (3 x 10 ml), H₂O (3 x 10 ml) and brine solution (3 x 10 ml), and then dried over MgSO₄. The solution was concentrated in vacuo yielding a colourless oil (0.70 g), which was purified by column chromatography on silica gel in 10 % ethyl acetate: petroleum ether.

**(S,R) Diastereoisomer (22e):** White solid, (0.38 g, 52 %). R_f: 0.70 (40 % ethyl acetate: petroleum ether). M.p.: 129-132 °C. [α]D: - 18.6 (c = 0.7 in MeOH). IR, (KBr)/cm⁻¹: 3305, 2976, 1682, 1671. ¹H NMR δ: 7.82 (s(br), 1H), 7.32-7.26 (m, 5H), 5.07 (s(br), 1H), 3.52-3.25 (m(br), 2H), 2.68-2.62 (m(br), 1H), 1.67-1.70 (m(br), 2H), 1.57 (m(br), 6H), 1.47 (s, 9H). ¹³C NMR δ: 173.7, 152.5, 129.2, 128.2, 127.1, 48.2, 28.5, 22.4, 18.4. HRMS (ESI) calculated for C₁₉H₂₉N₂O₃ [M+H]^+: 333.2178. Found: 333.2174.

**(R,R) Diastereoisomer (22f):** Colourless oil, (0.30 g, 42 %). R_f: 0.60 (40 % ethyl acetate: petroleum ether). [α]D: + 3.8 (c = 0.5 in MeOH). IR, (Thin film)/cm⁻¹: 3308, 2972, 1684, 1672. ¹H NMR δ: 7.78 (s(br), 1H) 7.33-7.28 (m, 5H), 5.08 (m(br), 1H), 3.53 (m(br), 2H), 2.66 (m(br), 1H), 2.28 (m(br), 1H), 1.79 (m(br), 1H). ¹³C NMR ppm δ: 173.7, 127.4, 126.3, 125.9, 48.6, 28.2, 23.4, 22.6. HRMS (ESI) calculated for C₁₉H₂₉N₂O₃ [M+H]^+: 333.2178. Found: 333.2193.

The reaction was then conducted using (S)-(1)-phenylethyl amine, following the method previously described, forming the (R,S) and (S,S) diastereoisomers.

**(R,S) Diastereoisomer (22g):** White solid, (0.38 g, 52 %). M.p.: 128-131 °C. [α]D: + 18.5 (c = 0.7 in MeOH). Other analytical data is identical to that of 22e. HRMS (ESI) calculated for C₁₉H₂₉N₂O₃ [M+H]^+: 333.2178. Found: 333.2192.

**(S,S) Diastereoisomer (22h):** Colourless oil, (0.30 g, 42 %). [α]D: - 4.0 (c = 0.5 in MeOH). Other analytical data is identical to that of 22f. HRMS (ESI) calculated for C₁₉H₂₉N₂O₃ [M+H]^+: 333.2178. Found: 333.2180.

2-Methyl-pyrrolidine-2-carboxylic acid (1-phenyl-ethyl)-amide (17)
To a solution of 22(e-h) (0.2 g, 0.602 mmol) in DCM (0.4 ml) was added TFA (0.4 ml, 1.7 mmol), and then stirred at ambient temperature for 16 hr. The solution was then concentrated in vacuo, dissolved in H$_2$O (40 ml), and the pH adjusted to ~8 by adding Et$_3$N dropwise, at 0 °C. It was then extracted with DCM (3 x 20 ml), dried over MgSO$_4$, and concentrated in vacuo yielding an oil, which was purified on silica gel in 5% MeOH:DCM.

(S,R) Diastereoisomer (17e): Yellow solid, (0.14 g, 96 %). R$_f$: 0.2 (5 % MeOH: DCM). M.p.: 100-103 °C. [α]$_D$:$^+$ 30.5 (c = 1 in MeOH). IR, (KBr)/cm$^{-1}$: 3414, 3270, 2974, 1673. $^1$H NMR δ: 8.25 (br. s, 1H), 7.35-7.21 (m, 5H), 5.04 (q, J = 7.1 Hz, 1H), 3.08-3.03 & 2.83-2.76 (2 x m, 2H), 2.23-2.17 (m, 1H), 1.71-1.53 (m, 3H), 1.46 (d, J = 6.9 Hz, 3H), 1.43 (s, 3H). $^{13}$C NMR δ: 178.0, 144.0, 128.5, 126.9, 125.9, 66.6, 48.1, 47.4, 37.6, 26.5, 25.9, 22.3. HRMS (ESI) calculated for C$_{14}$H$_{21}$N$_2$O $[M+H]^+$: 233.1654. Found: 233.1649.

(R,R) Diastereoisomer (17f): Yellow oil, (0.13 g, 93 %). R$_f$: 0.2 (5 % MeOH: DCM). [α]$_D$$^20$: +95 (c = 1 in MeOH). IR, (Thin film)/cm$^{-1}$: 3416, 3272, 2976, 1674. $^1$H NMR δ: 8.12 (s, 1H), 7.36-7.22 (m, 5H), 5.03 (q, J = 6.9 Hz, 1H), 3.21-3.12 & 2.96-2.88 (2 x m, 2H), 2.32-2.26 (m, 1H), 1.84-1.63 (m, 3H), 1.47 (d, J = 7.0 Hz, 3H), 1.44 (s, 3H). $^{13}$C NMR δ: 175.3, 146.4, 128.6, 127.2, 126.0, 67.1, 48.5, 46.8, 37.4, 28.5, 26.1, 22.8. HRMS (ESI) calculated for C$_{14}$H$_{21}$N$_2$O $[M+H]^+$: 233.1654. Found: 233.1660.

(R,S) Diastereoisomer (17g): Yellow solid, (0.133 g, 95 %). M.p.: 106-109 °C. [α]$_D$: - 30.5 (c = 1 in MeOH). Other analytical data is identical to that of 17e diastereoisomer. HRMS (ESI) calculated for C$_{14}$H$_{21}$N$_2$O $[M+H]^+$: 233.1654. Found: 233.1652.

(S,S) Diastereoisomer (17h): Yellow oil, (0.133 g, 95 %). R$_f$: 0.2 (5 % MeOH: DCM). [α]$_D$: - 81 (c = 1 %, l = 2 dm, MeOH). Other analytical data is identical to that of 17f diastereoisomer. HRMS (ESI) calculated for C$_{14}$H$_{21}$N$_2$O $[M+H]^+$: 233.1654. Found: 233.1647.

Pyrroolidine-1,2-dicarboxylic acid 1-tert-butyl ester (23)
A suspension of N-Boc-L-proline methyl ester\(^7\) \((1.25 \text{ g, } 5.45 \text{ mmol})\) and NaOH \((0.216 \text{ g, } 5.4 \text{ mmol})\) in MeOH/H\(_2\)O \((1:1, 20 \text{ ml})\) was heated at reflux temperature for 5 hr. The solvent was removed \textit{in vacuo}, and the residue was dissolved partitioned between diethyl ether and H\(_2\)O \((1:1, 20 \text{ ml})\). The aqueous phase was then washed with diethyl ether \((3 \times 10 \text{ ml})\), acidified to pH \(~3\) using 1N HCl, and extracted with diethyl ether \((20 \text{ ml})\). The ether layer was then dried over MgSO\(_4\) and concentrated \textit{in vacuo} giving the product as a white solid \((1.15 \text{ g, } 98 \%)\). It was used without further purification. \(R_f: 0.1 \text{ (20 \% ethyl acetate: petroleum ether).}\) M.p.: 133-136 °C. IR, (KBr)/cm\(^{-1}\): 2976, 1739, 1639, 1431. \(^1\)H NMR (two rotamers present) \(\delta: 4.36-4.25 \text{ (m, 1H), 3.52-3.33 (m, 2H), 2.40-2.27 (m, 1H), 2.18-1.88 (m, 3H), 1.50 \& 1.43 (2 x s, 9H).}\) \(^{13}\)C NMR (ppm) \(\delta: 177.1, 156.7, 79.8, 67.2, 47.2, 28.3, 28.1, 23.7.\)

\(2S-(1'R-\text{Phenyl-ethylicarbamoyl})-\text{pyrrolidine-1-carboxylic acid tert-butyl ester (24a)}\)

To a stirred solution of \(23 \text{ (0.32 g, 1.50 mmol)}\) in dry DCM \((5 \text{ ml})\) was added \((R)-1\)-phenylethylamine \((0.17 \text{ ml, 1.50 mmol)}\) dropwise, followed by DMAP \((0.183 \text{ g, 1.50 mmol)}\). After 5 min stirring, the solution was cooled to 0 °C, and a solution of EDC \((0.316 \text{ g, 1.65 mmol)}\) in dry DCM \((5 \text{ ml})\) was added slowly. After 5 min at this temperature, the solution was allowed to warm to ambient temperature and stirring was continued for 16 hr. The solvent was removed \textit{in vacuo} and the resulting solid was dissolved in EtOAc \((30 \text{ ml})\). It was washed successively with H\(_2\)O \((3 \times 10 \text{ ml})\), 5 % HCl solution \((3 \times 10 \text{ ml})\), saturated aqueous sodium carbonate solution \((3 \times 10 \text{ ml})\), brine \((3 \times 10 \text{ ml})\) and then dried over MgSO\(_4\). It was concentrated \textit{in vacuo} yielding a colorless oil \((0.46 \text{ g})\), which was purified by column chromatography on silica gel in 20 % ethyl acetate: petroleum ether giving a white solid \((0.44 \text{ g, 90 \%)}\). \(R_f: 0.3 \text{ (40 \% ethyl acetate: petroleum ether). M.p.: 81-84 °C. [\(\alpha\)]D: +38.5 (c = 1 in MeOH). IR, (KBr)/cm\(^{-1}\): 3304, 2976, 1688, 1676. \(^1\)H NMR \(\delta: 7.51 \text{ (s (br), 1H), 7.31-7.22 (m, 5H), 5.10 (s (br), 1H), 4.32 (s (br), 1H), 3.34 (s (br), 2H), 2.41 (s (br), 1H), 2.13 (s (br), 1H), 1.85 (s (br), 4H), 1.45 (s, 9H).}\) \(^{13}\)C NMR \(\delta: 171.3, 155.1, 143.0, 128.6, 125.9, 47.1, 28.4.\) Some signals missing due to line broadening. HRMS (ESI) calculated for C\(_{18}\)H\(_{27}\)N\(_2\)O\(_3\) [M+H]\(^+\): 319.2222. Found: 319.2215.

\(2S-(1'S-\text{Phenyl-ethylicarbamoyl})-\text{pyrrolidine-1-carboxylic acid tert-butyl ester (24b)}\)
Prepared from 21 (0.32 g, 1.50 mmol) in a similar manner to 24a using (R)-1-phenylethylamine. The crude product was purified by column chromatography on silica gel in 20% ethyl acetate: petroleum ether giving a white solid (0.44 g, 90%). Rf: 0.2 (40% ethyl acetate: petroleum ether). M.p.: 98-101 °C. [α]D: -130 (c = 1 in MeOH). IR, (KBr)/cm⁻¹: 3305, 2977, 1688, 1675. ¹H NMR δ: 7.51 (s (br), 1H), 7.31-7.25 (m, 5H), 5.10 (s (br), 1H), 4.33 & 4.25 (2 x m, 1H), 3.35 (s (br), 2H), 2.41 (s (br), 1H), 2.12 (s (br), 1H), 1.85 (s (br), 5H), 1.46 (s, 9H). ¹³C NMR δ: 171.6, 154.1, 143.2, 130.7, 128.6, 127.1, 80.5, 48.6, 28.1. HRMS (ESI) calculated for C₁₈H₂₇N₂O₃ [M+H]⁺: 319.2022. Found: 319.2007.

2S-Pyrrolidine-2-carboxylic acid (1'R -phenyl-ethyl)-amide (18a)
To a solution of 24a (1.0 g, 3.14 mmol) in DCM (2 ml) was added TFA (2 ml, 17 mmol), and the solution was stirred at ambient temperature for 16 hr. It was then concentrated in vacuo, dissolved in H₂O (40 ml), and the pH adjusted to ~ 8 by adding Et₃N dropwise, at 0 °C. The product was then extracted with DCM (3 x 20 ml), dried over MgSO₄, and concentrated in vacuo yielding an oil, which was purified on silica gel in 5% MeOH:DCM, giving the product as a yellow oil (0.62 g, 91%). Rf: 0.5 (10% MeOH: DCM). [α]D: +21.5 (c = 1 in MeOH). IR, (Thin film)/cm⁻¹: 3412, 3263, 2976, 1672. ¹H NMR δ: 7.97 (s (br), 1H), 7.35-7.21 (m, 5H), 5.09-5.04 (m, 1H), 3.91-3.86 (m, 1H), 3.08-2.92 (m, 2H), 2.22-2.10 (m, 1H), 1.93-1.87 (m, 1H), 1.77-1.70 (m, 2H), 1.47 (d, 3H, J = 7.1 Hz). ¹³C NMR δ: 173.6, 144.8, 128.6, 127.3, 126.0, 60.3, 49.2, 48.6, 30.6, 25.9, 21.5. HRMS (ESI) calculated for C₁₃H₁₉N₂O [M+H]⁺: 219.1497. Found: 219.1498.

2S-Pyrrolidine-2-carboxylic acid (1’S-phenyl-ethyl)-amide (18b)
Prepared from 24b (1.0 g, 3.14 mmol) in a similar manner to 18a to give 18b as a yellow oil (0.64 g, 94%). Rf: 0.4 (10% MeOH: DCM). [α]D: -48 (c = 1 in MeOH). IR, (Thin film)/cm⁻¹: 3414, 3260, 2977, 1670. ¹H NMR δ: 8.08 (s (br), 1H), 7.34-7.20 (m, 5H), 5.30-5.01 (m, 1H), 4.43-4.41 (m, 1H), 3.49-3.10 (m, 2H), 2.38-2.34 (m, 1H), 1.94-1.86 (m, 3H), 1.48 (d, 3H, J = 7.2 Hz). ¹³C NMR δ: 168.8, 143.1, 128.7, 127.4, 125.8, 59.5, 50.3, 46.4, 30.2, 24.8, 22.0. HRMS (ESI) calculated for C₁₃H₁₉N₂O [M+H]⁺: 219.1497. Found: 219.1497.
2S-[Methyl-(1’R-phenyl-ethyl)-carbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (25a)

To a solution of 24a (0.5 g, 1.57 mmol) in dry THF (5 ml) at -20 °C, was added a 1.0M solution of LiHMDS in THF (1.62 ml, 1.62 mmol) slowly, while keeping the temperature below -15 °C. The solution was stirred for 30 min., under nitrogen, at this temperature. Methyl iodide (0.30 ml, 3.93 mmol) was added slowly at -20 °C. The solution was stirred while allowing it to warm to ambient temperature. After 18 hr the solution was quenched with 1N HCl (20 ml), and the majority (80%) of the solvent was removed in vacuo. The remaining suspension was diluted with diethyl ether (40 ml) and the organic phase was separated, washed with 1N HCl solution (3 x 10 ml), saturated aqueous sodium chloride solution (3 x 10 ml), then dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel in 30 % ethyl acetate: petroleum ether giving a yellow oil (0.50 g, 92 %). Rf: 0.3 (20 % ethyl acetate: petroleum ether). [α]D: +48.3 (c = 0.6 in MeOH). IR, (Thin film)/cm⁻¹: 2978, 1697, 1654. ¹H NMR (two rotamers present) δ: 7.34-7.20 (m, 5H), 6.15-6.05 (m, 1H), 5.02 & 4.60 (2 x m, 1H), 3.70-3.35 (m, 2H), 2.82 & 2.70 (2 x s, 3H), 1.95-1.88 (m, 2H), 1.65 (s, 3H), 1.48 & 1.35 (2 x s, 9H). ¹³C NMR (two rotamers present) δ: 173.6, 153.4, 140.3, 128.8, 128.2, 127.0, 56.7, 50.5, 46.8, 30.6, 29.5, 28.5, 24.4, 15.6. HRMS (ESI) calculated for C₁₉H₂₉N₂O₃ [M+H]⁺: 333.2178. Found: 333.2171.

2S-[Methyl-(1’S-phenyl-ethyl)-carbamoyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (25b)

Prepared from 24b (0.5 g, 1.57 mmol) in a similar manner to 25a. The crude product was purified by column chromatography on silica gel in 30 % ethyl acetate: petroleum ether giving a yellow oil (0.52 g, 98 %). Rf: 0.2 (20 % ethyl acetate: petroleum ether). [α]D: -102.3 (c = 0.85 in MeOH). IR, (Thin film)/cm⁻¹: 2978, 1696, 1653. ¹H NMR (two rotamers present) δ: 7.34-7.21 (m, 5H), 6.04 (m, 1H), 4.67 & 4.55 (2 x m, 1H), 3.68-3.45 (m, 2H), 2.73 & 2.68 (2 x s, 3H), 2.08-2.02 (m, 2H), 1.89-1.85 (m, 2H), 1.58 (s, 3H), 1.48 & 1.45 (2 x s, 9H). ¹³C NMR (two rotamers present) δ: 172.9, 151.3, 141.6, 128.5, 128.4, 127.2, 57.8, 50.6, 47.1, 29.2, 28.9, 28.5, 23.5, 15.2. HRMS (ESI) calculated for C₁₀H₂₀N₂O₃ [M+H]⁺: 333.2178. Found: 333.2166.
2S-Pyrrolidine-2-carboxylic acid methyl-(1’R-phenyl-ethyl)-amide (18c)
To a solution of 25a (0.3 g, 0.903 mmol) in DCM (0.6 ml) was added TFA (0.6 ml, 2.6 mmol), and the solution was stirred at ambient temperature for 16 hr. It was concentrated in vacuo, dissolved in H₂O (40 ml), and the pH was adjusted to ~8 by adding Et₃N dropwise, at 0 °C. The product was then extracted with DCM (3 x 20 ml), dried over MgSO₄, and concentrated in vacuo yielding an oil, which was purified on silica gel in 5% MeOH:DCM, giving the product as a yellow oil (0.18 g, 86%). Rf: 0.6 (10 % MeOH: DCM). [α]D: + 41 (c = 1 in MeOH). IR, (Thin film)/cm⁻¹: 3438, 2979, 1697, 1655. ¹H NMR (two rotamers present) δ: 8.10 (d (br), 1H), 7.40-7.22 (m, 5H), 5.92 (q, 1H, J = 7.1 Hz), 5.30 & 4.74, 3.98 & 3.69 (4 x m, 1H), 3.49-3.39 & 3.18-2.90 (2 x m, 2H), 2.76 & 2.71 (2 x s, 3H), 2.51-1.58 (m, 4H), 1.50 & 1.47 (2 x d, 3H, J = 7.1 Hz). ¹³C NMR (two rotamers present) δ: 172.1 & 169.3, 142.8 & 138.5, 129.1, 128.6, 127.1, 60.3 & 58.1, 52.3 & 48.4, 47.1 & 46.6, 30.6 & 29.7, 25.8 & 25.6, 22.2, 15.6. HRMS (ESI) calculated for C₁₄H₂₁N₂O [M+H]⁺: 233.1654. Found: 233.1661.

2S-Pyrrolidine-2-carboxylic acid methyl-(1’S-phenyl-ethyl)-amide (18d)
Prepared from 25b (0.3 g, 0.903 mmol) in a similar manner to 18c to give an oil, which was purified on silica gel in 5% MeOH:DCM, giving the product as a yellow solid (0.19 g, 88 %). Rf: 0.5 (10 % MeOH:DCM). M.p.: 172-175 °C. [α]D: -120 (c = 1 in MeOH). IR, (KBr)/cm⁻¹: 3436, 2980, 1698, 1650. ¹H NMR (two rotamers present) δ: 7.39-7.21 (m, 5H), 5.93 (q, 1H, J = 7.1 Hz), 5.05 & 4.84, (2 x m, 1H), 3.56-3.51 & 3.46-2.38 (2 x m, 2H), 2.69 (s, 3H), 2.54-2.47 (m, 1H), 2.21-2.14 (m, 1H), 2.08-2.00 (m, 1H), 1.88-1.82 (m, 1H), 1.55 (d, 3H, J = 7.2 Hz). ¹³C NMR (two rotamers present) δ: 169.3, 138.8, 129.3, 128.8, 127.2, 58.0, 52.4, 46.7, 29.7, 29.1, 25.3, 15.2. HRMS (ESI) calculated for C₁₄H₂₁N₂O [M+H]⁺: 233.1654. Found: 233.1655.

General procedure for the Michael Addition reaction of aldehydes and β-nitrostyrene.
To a solution of the β-nitrostyrene (0.15 g, 1 mmol) in dry DCM (1 ml) was added the relevant catalyst (0.05 mmol), followed by the aldehyde (1.5 mmol). The reaction was stirred at ambient temperature for 48 or 72 hours, under a nitrogen atmosphere. It was
then diluted with chloroform (5 ml) and treated with 1N HCl (4 ml), while stirring vigorously. The aqueous layer was extracted with chloroform and the combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel with 5% EtOAc: petroleum ether. For example, 2-propyl-4-nitro-3-phenylbutyraldehyde (16): R_f: 0.6 (20% ethyl acetate: petroleum ether). Analytical data was as reported in the literature. HPLC data: Chiralcel OD-H column; flow 1.6 ml/min using 90/10 hexane/2-propanol, syn t_r = 6.4 min (S,R) and 8.9 min (R,S), anti t_r = 7.6 min and 13.0 min.

X-Ray data
The data were collected at 150(2)K on a Bruker Apex II CCD diffractometer. The structures were solved by direct methods and refined on F² using all the reflections. All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. The H atoms bonded to nitrogen or oxygen were located from difference maps and refined with thermal parameters riding on the carrier atoms.

Crystal data for 11b. C_{20}H_{28}N_{2}O_{3}, M = 344.44. orthorhombic, a = 6.5297(9), b = 16.557(2), c = 17.425(3) Å, U = 1883.9(5) Å³, T = 150(2) K, space group P2₁2₁2₁, Z = 4, 14987 reflections measured, 1930 independent reflections (R_int = 0.0534). The final wR(F²) was 0.0949 (all data) and R1 was 0.0374 for I>2s(I). CCDC No. 687387.

Crystal data for 17b.TsOH. C_{22}H_{30}N_{2}O_{4}S, M = 418.54. orthorhombic, a = 7.8627(11), b = 12.6431(18), c = 21.679(3) Å, U = 2155.1(5) Å³, T = 150(2) K, space group P2₁2₁2₁, Z = 4, 19139 reflections measured, 4406 independent reflections (R_int = 0.0571) which were used in all calculations. The final wR(F²) was 0.0812 (all data) and R1 was 0.0397 for I>2s(I). CCDC No. 749092.

Crystal data for 22g. C_{19}H_{28}N_{2}O_{3}, M = 332.43. orthorhombic, a = 9.9790(9), b = 16.6480(15), c = 23.276(2) Å, U = 3866.9(6) Å³, T = 150(2) K, space group P2₁2₁2₁, Z = 8, (two independent molecules in the asymmetric unit), 34133 reflections measured, 4427 independent reflections (R_int = 0.0801). The final wR(F²) was 0.0820 (all data) and R1 was 0.0400 for I>2s(I). CCDC No. 749093.
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References and Notes


