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The synthesis and characterisation of *N*-(1-carbamoyl-1,1-dialkyl-methyl)-(*S*)-prolinamides and related pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-ones as potential enantioselective organocatalysts

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ABSTRACT

The acylation of substituted 2-aminopropanamides with (2*S*)-Boc-proline, (2*S*)-Cbz-proline and (2*S*)-Bn-proline was used to prepare substituted 1-protected *N*-(1-carbamoyl-1,1-dialkyl-methyl)-(*S*)-prolinamides (74–89%), whose subsequent deprotection gave *N*-(1-carbamoyl-1,1-dialkyl-methyl)-(*S*)-prolinamides (94–95%). The enantiomerically pure *N*-(1-carbamoyl-1,1-dialkyl-methyl)-(*S*)-prolinamides obtained were tested as organocatalysts for the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde, with yields ranging from 38% to 79% ee. The highest enantioselectivity (89% ee) was achieved by catalysis with *N*-(1-carbamoyl-cyclopentyl)-(*S*)-prolinamide (methanol, l0% HCl). By the action of sodium methoxide, Boc-*N*-(1-carbamoyl-cyclopentyl)-(*S*)-prolinamide was quantitatively cyclised to 2-(1-Boc-pyrrolidin-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one, which was accompanied by racemisation at the stereogenic centre of the proline skeleton. Alternatively, the substituted 4,4-dialkyl-2-pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-ones were prepared by oxidation of 4,4-dialkyl-2-((2*S*)-1-Boc-pyrrolidin-2-yl)-4,5-dihydro-1*H*-imidazolidin-5-ones (54–69%). In an acid medium, 2-pyrrolidin-2-yl-1,3-diazaspiro[4.4]non-1-en-4-one and (4*S*)-4-isopropyl-4-methyl-2-pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-one underwent racemisation. Conversely, the free base of (2*S*)-2-pyrrolidin-2-yl-1,3-diazaspiro[4.4]non-1-en-4-one very easily underwent oxidation to give the achiral 2-(4,5-dihydro-3*H*-pyrrol-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one.

1. Introduction

Enantioselective organocatalysis has been the focus of contemporary pure and applied research.[1] Natural (*S*)-proline and its derivatives represent a privileged group of molecules adopted as very efficient enantioselective organocatalysts in many reactions.[1] On the other hand, substituted 4,5-dihydro-1*H*-imidazol-5-ones are commonly used as mildly toxic and selective herbicides.[2] Our previous papers have dealt with the synthesis and characterisation of substituted 4,5-dihydro-1*H*-imidazol-5-ones and studied the mechanism of their formation.[3] Another possible use of 4,5-dihydro-1*H*-imidazol-5-ones is in their application as ligands forming coordination compounds with selected metal ions.[4] Some of these complexes have been successfully used as catalysts of the deallylation reactions of diallyl malonates,[4b,f] in Henry reactions,[4c,e] or in allylic oxidations.[4h] Substituted amides of (*S*)-proline, in addition to their biological activity,[5] represent highly efficient enantioselective organocatalysts of aldol reactions.[1,6] Results of recent research have also confirmed the fact that catalyst function does not necessitate the presence of the carboxylic group in the (*S*)-proline itself.[6,7] It is sufficient if the catalyst contains a group acidic enough, for example, an amide group, which can stabilise the transition state of the reaction to give the required enantiomer as the final product.[1,6,7]

The aim of this work was to prepare new derivatives of (*S*)-proline containing at least two amide functional groups in their molecule. Therefore, the aim was to modify the basic skeleton of (*S*)-proline by application of the easily available[3,4] precursors, substituted 4,5-dihydro-1*H*-imidazol-5-ones; moreover, to test the possibility of preparation of optically pure derivatives of (*S*)-proline with an attached 4,5-dihydro-1*H*-imidazol-5-one skeleton as a cyclic variant of amino acid amides. The research also included testing of the prepared optically pure derivatives as organocatalysts of the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde.

2. Results and discussion

The 1-Cbz-*N*-(1-carbamoyl-1,1-dialkyl-methyl)-(*S*)-prolinamides **1a–c**, 1-Boc-*N*-(1-carbamoyl-1,1-dialkyl-methyl)-(*S*)-prolinamides

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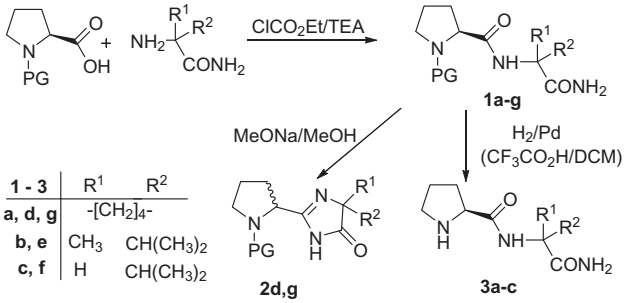
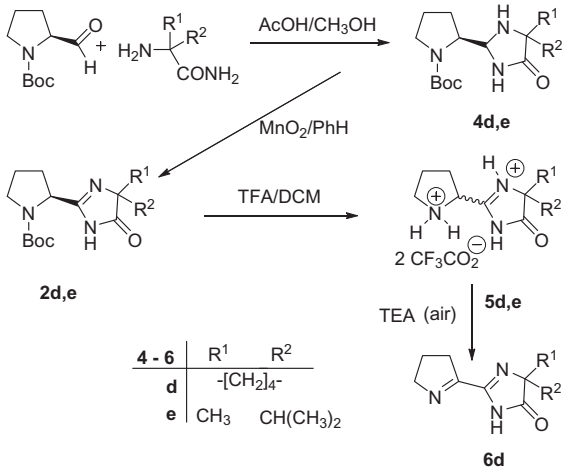
1d–**f** and (1*S*)-1-Bn-*N*-(1-carbamoyl-1,2-dimethylpropyl)-(*S*)-prolinamide **1g** were prepared by acylation of 1-aminocyclopentancarboxamide, (*S*)-2-amino-2,3-dimethylbutanamide and (*S*)-2-amino-3-methylbutanamide ((*S*)-valinamide) with activated (2*S*)-1-Boc-proline, (2*S*)-1-Cbz-proline or (2*S*)-1-Bn-proline. The activation was carried out with ethyl chloroformate, and the yields of the synthesised amides **1a**–**g** varied within the range of 74–89% (Scheme 1). In the subsequent step, 1-Boc-*N*-(1-carbamoyl-cyclopentyl)-(*S*)-prolinamide **1d** was submitted to a ring closure reaction giving the corresponding 2-(1-Boc-pyrrolidin-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one **2d**. The ring closure catalysed with sodium methoxide[3c–h] gave quantitative yields; however, the reaction was accompanied by racemisation at the stereogenous centre of the proline skeleton. Therefore, the ring closure reaction of amide **1d** to the corresponding imidazolinone **2d** was studied under various conditions with several reagents (Cs_2CO_3/toluene, $Ba(OH)_2/H_2O$, Ac_2O/AcOH, $POCl_3$/DCM and Ph_3P/CCl_4). According to Ref. 8 the application of a Cs_2CO_3/toluene system should not lead to racemisation at the proline skeleton, but in our case total or partial racemisation always took place with the use of the Cs_2CO_3/toluene system and all the basic reagents. The racemisation process was connected with the formation of a carbanion at the 2-position and its backward protonation.[8] With the other reagents, either the ring closure did not take place or the starting amide **1d** was transformed into undefinable mixtures. Amides **3a**–**c** were prepared from amides **1a**–**c** by deprotection of Cbz group (H_2/Pd/C) (92–95%), or from amides **1d**–**f** by deprotection of Boc group (CF_3COOH/DCM) (21–32%) (Scheme 1).



Scheme 1.

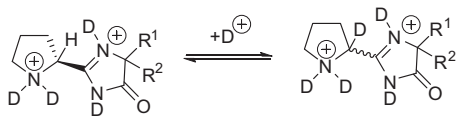
From what has been previously determined, it is obvious that the preparation of optically pure substituted 4,4-dialkyl-2-pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-ones must proceed by an alternative way that is not accompanied by racemisation. In this case, the solution was expected from the synthetic method recently described by us:[3i] synthesis of 4,4-dialkyl-2-pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-ones, which does not require the application of a strongly basic medium. Scheme 2 describes the reaction sequence of the preparation of substituted 4,4-dialkyl-2-pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-ones **5d**,**e** by oxidation of the respective imidazolidin-5-ones.

First, cyclic aminals, that is, 4,4-dialkyl-2-((2*S*)-1-Boc-pyrrolidin-2-yl)-imidazolidin-5-ones **4d**,**e** were prepared by the reaction of (2*S*)-1-Boc-prolinaldehyde with substituted 2-aminoalkanamides (66–71%). In the case of the reaction of (*S*)-2-amino-3-methylbutanamide with (2*S*)-1-Boc-prolinaldehyde, the product obtained was an equilibrium mixture of the respective Schiff base and the desired product **4c** (R^1 = H, R^2 = $CH(CH_3)_2$); however, its isolation failed. The subsequent oxidation of the cyclic aminals **4d**,**e** was performed with manganese(IV) oxide in benzene (54–69%). The obtained 4,4-dialkyl-2-(1-Boc-pyrrolidin-2-yl)-4,5-dihydro-1*H*-imidazol-5-ones **2d**,**e** were deprotected by the action of a



Scheme 2.

solution of trifluoroacetic acid in DCM. However, the isolation of optically pure 2-pyrrolidin-2-yl-1,3-diazaspiro[4.4]non-1-en-4-one **5d** and 4-isopropyl-5-methyl-2-pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-one **5e** prepared in this way was unsuccessful, which also meant that, in these cases, the synthesis was accompanied by racemisation at the stereogenous centre of the proline skeleton. ^{1}H NMR spectroscopy of compound **5d** revealed the exchange of deuterium for hydrogen atoms (Fig. 1, Scheme 3).



Scheme 3.

The figure shows a lowering of the proton signal intensity at the 2-position of the proline cycle (4.73 ppm) in the presence of CF_3COOD. This finding indicates that the hydrogen substituent at the 2-position of pyrrole nucleus was so acidified by the substitution with the 4,5-dihydro-1*H*-imidazol-5-one fragment that the protons were exchanged by excessive deuterons in the medium, resulting in racemisation.

In order to avoid a strongly acidic medium, we prepared 2-(1-benzylpyrrolidin-2-yl)-1,3-diazaspiro[4.4]non-4-one **2g** by a ring closure reaction of compound **1g** and the protecting group was removed under neutral conditions by hydrogenolysis (H_2/Pd–C). However, the free base of imidazolinone **5d** formed by hydrogenolysis or alkalisation after deprotecting the Boc group from **2d** was unstable and underwent rapid oxidation to give 2-(4,5-dihydro-3*H*-pyrrol-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one **6d** (Scheme 2). This oxidation product **6d** was not a secondary amine any longer and, therefore, could not act as an organocatalyst in aldol reactions. The described experiments showed that the promising organocatalysts of pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-one type (in contrast to the pyrrolidin-2-yl-tetrazole type[9] and pyrrolidin-2-yl-oxazoline[10]) were not stable during ordinary handling and, therefore, were not applicable in organocatalysis.

The next part of research only made use of the chiral, optically pure compounds **3a**–**c**. The studied reaction was the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone leading to 2-[hydroxy(4-nitrophenyl)methyl]cyclohexanone. This type of organocatalysis is called 'enamine catalysis' in the literature. It requires, in addition to secondary amino group, the presence of an acidic functional group in the organocatalyst molecule (e.g., CO_2H, CONHR etc.).[1,6,7] The effects of the reaction conditions upon diastereo- and

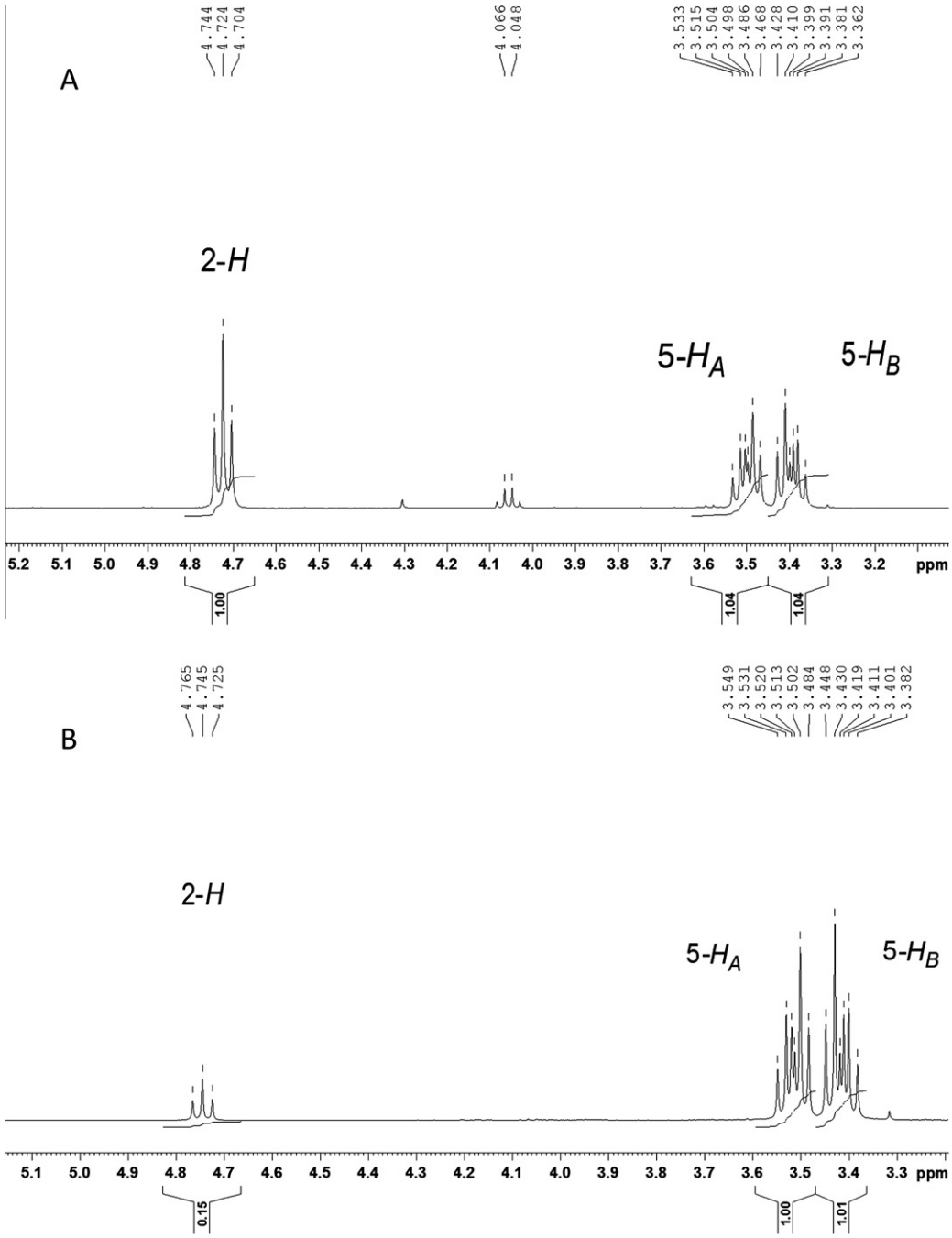


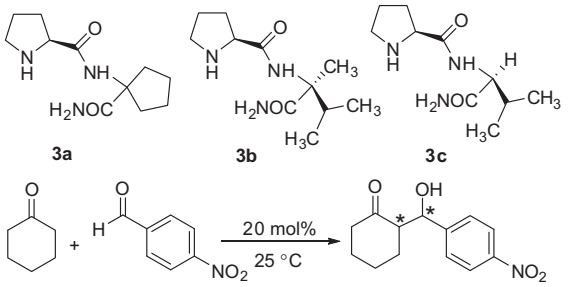
Figure 1. ^{1}H NMR spectrum of 2-pyrrolidin-2-yl-1,3-diazaspiro[4.4]non-1-en-4-one (**5d**). (a) 5% CF_3COOH in DMSO, (b) 5% CF_3COOD in DMSO.

enantioselectivity of the aldol reaction with compounds **3a**–**c** are presented in Table 1.

The molar proportion of the diastereoisomers *syn*:*anti* was determined by means of ^{1}H NMR spectroscopy. The ratio of enantiomers was determined by means of HPLC. Table 1 includes the effects of total reaction times, solvents, the acid used and acid concentration on diastereoselectivity and on ee.

The first tests used compound **3a** (entries 1–13). The starting conditions of the reaction between 4-nitrobenzaldehyde and cyclohexanone (entry 1) were set according to Ref. 6h, where the same reaction used (*S*)-*N*-(2-methyl-5-nitrophenyl)pyrrolidin-2-carboxamide as the organocatalyst and attained the diastereomeric ratio of 97:3 and 96% ee. In our case, the same conditions only led to 55% ee. In order to test the effect of acid catalysis, we carried out the reaction in DMF alone (entry 2), which resulted in a further reduction in ee. The next tests used methanol with different amounts of trifluoroacetic acid (TFA) (entries 3–5). Compared with previous cases, the optical yield was increased up to 68%, but the effect of TFA concentration was insignificant. The best result from the standpoint of both diastereoselectivity (7:93) and enantioselectivity (89% ee) was obtained with the use of hydrochloric acid (entry 6). However, this method of carrying out the process has the drawback of a slow reaction: 50% conversion was achieved only after 90 days. Further acids tested (entries 7–10) included acetic acid, benzoic acid and both *R* and *S* camphor-10-sulfonic acids. As compared with TFA and HCl, the enantioselectivity was significantly decreased, and the two optically pure camphor-10-sulfonic acids only gave the yields of 31–35% ee. The change of solvents (MeCN:

Table 1
Results of the **3a–c** catalysed aldol reaction between cyclohexanone and 4-nitrobenzaldehyde under various conditions



Entry	Catalyst	Solvent, additive	Time (days)	Yield[a] (%)	dr[a] *syn:anti*	ee[b] (%)
1	**3a**	DMF, TFA (10%)	7	60	16:84	55
2	**3a**	DMF	3	70	23:77	19
3	**3a**	MeOH, TFA (10%)	3	85	23:77	68
4	**3a**	MeOH, TFA (20%)	4	70	26:74	62
5	**3a**	MeOH, TFA (30%)	4	70	25:75	67
6	**3a**	MeOH, HCl (10%)	90	50	7:93	89
7	**3a**	MeOH, AcOH (10%)	3	80	25:75	19
8	**3a**	MeOH, PhCOOH (10%)	3	80	21:79	30
9	**3a**	MeOH, (*S*)-CSA (10%)	7	18	17:83	31
10	**3a**	MeOH, (*R*)-CSA (10%)	7	20	13:87	35
11	**3a**	MeCN, TFA (10%)	4	80	28:73	65
12	**3a**	THF, TFA (10%)	4	80	28:73	60
13	**3a**	H_2O, TFA (10%)	4	75	10:90	2
14	**3b**	MeOH, TFA (10%)	3	80	18:82	38
15	**3c**	MeOH, TFA (10%)	3	75	21:79	79

[a] Yield and diastereomeric excess determined by ^{1}H NMR of crude product.
[b] Enantiomeric excess determined by chiral HPLC for anti-diastereomer.

entry 11 and THF: entry 12) did not result in any distinct increase in diastereoselectivity or enantioselectivity. The application of water as the reaction medium turned out to be the least efficient (entry 13). Compounds **3b** and **3c** (entries 14 and 15) were tested under comparable conditions. As compared with compound **3a**, these organocatalysts possessed an additional stereogenous centre, which according to Ref. 11 should have led to a further increase in enantiomeric excess. However, the comparison of compound **3a** (entry 3) and **3c** (entry 15) showed a difference of only 11% ee. Comparison of compound **3b** (entry 14) and compound **3c** (entry 15) showed a reduction in ee to approximately one half due to the effect of the methyl substituent.

3. Conclusion

It was confirmed that the suggested organocatalysts of pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-one type are not stable under common conditions and thus cannot be used in organocatalysis, but their precursors, that is, *N*-(1-carbamoylcyclopentyl)-(*S*)-prolinamide **3a** and (1*S*)-*N*-(1-carbamoyl-2-methylpropyl)-(*S*)-prolinamide **3c**, appear to be suitable from the standpoint of their use in organocatalysis. These organocatalysts were successful in catalysing the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone, with yields of 68% ee and 79% ee, respectively. The optimum reaction medium appeared to be the methanol system containing 10% TFA, but the best yield was achieved with the use of the system of methanol containing 10% HCl. This reaction gave a high diastereoselectivity (7:93) and enantioselectivity (89% ee), but the reaction was distinctly slow. The described findings show that the abovementioned compounds **3a** and **3c** possess a high catalytic potential and can find applications in the catalysis of other reactions in the future.[12]

4. Experimental

If not stated otherwise, the starting substances were purchased from Sigma–Aldrich. The melting point temperatures have not been corrected. Abbreviations: Bn, benzyl; Boc, *tert*-butyloxycarbonyl; Cbz, benzyloxycarbonyl; DCM, dichloromethane; DMF, *N,N*-dimethylformamide; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TsOH, 4-toluenesulfonic acid. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 instrument (400.13 MHz for ^{1}H, and 100.61 MHz for ^{13}C). Chemical shifts δ were referenced to the solvent residual peak (2.50 ppm ^{1}H, 39.43 ppm ^{13}C for DMSO-d_6, and 7.26 ppm ^{1}H, 77.00 ppm ^{13}C for $CDCl_3$). The mass spectra were measured with a set of Agilent Technologies (gas chromatograph 6890N with mass detector 5973 Network; the samples were dissolved in DCM or acetone). The elemental microanalysis was carried out using a FISONS Instruments EA 1108 CHN apparatus. The optical rotation was measured on a Perkin–Elmer 341 instrument; the concentration *c* was given in g/100 ml.

4.1. General procedure for the synthesis of protected (*S*)-prolinamides 1a–g

To a solution of protected proline (10 mmol) and triethylamine (1.40 ml; 10 mmol) in dry DCM (30 ml), ethyl chloroformate was added dropwise (0.95 ml; 10 mmol) in dry DCM (10 ml). After 30 min, aminoamide (10 mmol) in dry DCM (10 ml) was added to the mixture and the solution was stirred for 5 h. The organic layer was washed with water and aqueous sodium bicarbonate, dried over sodium sulfate and concentrated in vacuo. The residue was crystallised from the appropriate solvents.

4.1.1. 1-Cbz-*N*-(1-carbamoyl-cyclopentyl)-(*S*)-prolinamide 1a

Yield: 86%; mp: 158–159 °C (ethyl acetate/hexane); $[\alpha]_D^{20} = -72.2$ (*c* 1, CH_3OH); ^{1}H NMR of two rotamers (400 MHz, DMSO-d_6): δ 8.24 (s, 1H, NH), 8.04 (s, 1H, NH), 7.34–7.31 (m, 10H, 2 × Ar), 6.91–6.89 (m, 2H, NH_2), 6.85 (s, 1H, NH_2), 6.60 (s, 1H, NH_2), 5.12–4.92 (m, 4H, 2 × CH_2), 4.27–4.24 (m, 2H, 2 × CH), 4.19–4.165 (m, 2H, 2 × CH), 3.48–3.33 (m, 4H, 2 × CH_2), 2.18–2.02 (m, 4H), 2.00–1.71 (m, 12H), 1.69–1.42 (m, 8H); ^{13}C NMR

(100 MHz, DMSO-d_6): δ 176.1, 175.5, 171.8, 154.3, 153.7, 136.8, 136.7, 128.4, 128.2, 127.8, 127.6, 127.5, 127.2, 66.1, 65.8, 59.9, 59.0, 47.1, 46.6, 37.1, 36.3, 35.4, 30.9, 29.5, 24.2, 24.1, 23.9. Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.52; H, 6.95; N, 11.72.

4.1.2. 1-Cbz-*N*-((1*S*)-1-carbamoyl-1,2-dimethylpropyl)-(*S*)-prolinamide 1b

Yield: 78%; mp: 67–69 °C (propan-2-ol/water); $[\alpha]_D^{20} = -54.7$ (*c* 1, CH_3OH); ^{1}H NMR of two rotamers (400 MHz, DMSO-d_6): δ 7.60–7.58 (m, 2H, 2 × NH), 7.37–7.31 (m, 10H, 2 × Ar), 7.00–6.91 (m, 4H, 2 × NH_2), 5.09–5.02 (m, 4H, 2 × CH_2), 4.34–4.32 (m, 1H, CH), 4.26–4.25 (m, 1H, CH), 3.52–3.25 (m, 4H), 2.19–1.97 (m, 4H), 1.97–1.84 (m, 2H), 1.84–1.73 (m, 4H), 1.33 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.93–075 (m, 12H, 2 × *i*Pr–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.9, 171.5, 171.0, 156.3, 153.8, 136.9, 136.8, 128.3, 128.1, 127.7, 127.4, 127.3, 127.0, 65.9, 65.7, 62.4, 62.3, 60.2, 59.4, 47.1, 46.5, 33.7, 33.6, 30.8, 29.3, 23.9, 22.9, 17.7, 17.3, 17.2, 17.1, 17.0, 16.8. Anal. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.18; H, 7.48; N, 11.67.

4.1.3. 1-Cbz-*N*-((1*S*)-1-carbamoyl-2-methylpropyl)-(*S*)-prolinamide 1c

Yield: 74%; mp: 192–193 °C (propan-2-ol/water); $[\alpha]_D^{20} = -68.3$ (*c* 1, CH_3OH); ^{1}H NMR of two rotamers (400 MHz, DMSO-d_6): δ 7.87 (d, *J* = 8.9 Hz, 1H, NH), 7.79 (d, *J* = 8.9 Hz, 1H, NH), 7.43–7.26 (m, 12H, 2 × Ar and 2 × Val-NH), 7.07 (m, 2H, Val-NH), 5.12–4.95 (m, 4H, 2 × CH_2), 4.42–4.39 (m, 2H, 2 × CH), 4.16–4.12 (m, 2H, 2 × CH), 3.52–3.31 (m, 4H), 2.19–1.73 (m, 10H), 0.88–0.74 (m, 12H, 2 × *i*Pr–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.9, 171.9, 171.6, 154.1, 153.8, 137.0, 136.9, 128.3, 128.1, 127.7, 127.4, 127.3, 127.0, 65.8, 65.7, 59.7, 59.0, 57.3, 47.1, 46.5, 31.3, 30.5, 30.4, 30.3, 29.8, 19.3, 19.1, 17.9. Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.19; H, 7.31; N, 12.01.

4.1.4. 1-Boc-*N*-(1-carbamoyl-cyclopentyl)-(*S*)-prolinamide 1d

Yield: 81%; mp: 116–118 °C (ethyl acetate/hexane); $[\alpha]_D^{20} = -68.9$ (*c* 1, CH_3OH); ^{1}H NMR of two rotamers (400 MHz, DMSO-d_6): δ 8.15 (s, 1H, NH), 7.93 (s, 1H, NH), 6.94 (br s, 2H, NH_2), 6.89 (s, 1H, NH_2), 6.64 (s, 1H, NH_2), 4.09–4.04 (m, 2H, 2 × CH), 3.34–3.23 (m, 4H, 2 × CH_2), 2.19–1.96 (m, 4H), 1.95–1.81 (m, 8H), 1.80–1.68 (m, 4H), 1.66–1.51 (m, 8H), 1.39 (s, 9H, $(CH_3)_3$C), 1.34 (s, 9H, $(CH_3)_3$C); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.7, 176.1, 172.8, 172.7, 154.6, 153.8, 79.6, 78.9, 66.6, 66.5, 60.0, 59.7, 47.2, 47.0, 37.9, 37.0, 35.9, 35.8, 31.3, 29.8, 28.6, 28.5. Anal. Calcd for $C_{16}H_{27}N_3O_4$: C, 59.06; H, 8.36; N, 12.91. Found: C, 59.11; H, 8.32; N, 12.85.

4.1.5. 1-Boc-*N*-((1*S*)-1-carbamoyl-1,2-dimethylpropyl)-(*S*)-prolinamide 1e

Yield: 83%; mp: 92–94 °C (ethyl acetate/hexane); $[\alpha]_D^{20} = -51.0$ (*c* 1, CH_3OH); ^{1}H NMR of two rotamers (400 MHz, DMSO-d_6): δ 7.53–7.47 (m, 2H, 2 × NH), 7.03–6.98 (m, 4H, 2 × NH_2), 4.14–4.13 (m, 1H, CH), 4.12–4.11 (m, 1H, CH), 3.29–3.21 (m, 4H), 2.23–2.05 (m, 4H), 1.93–1.75 (m, 6H), 1.40–1.33 (m, 24H, 2 × CH_3 and 2 × $(CH_3)_3$C), 0.87–0.81 (m, 12H, 2 × *i*Pr–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.8, 172.0, 171.0, 154.1, 153.2, 78.9, 78.2, 62.4, 62.1, 59.9, 59.5, 46.6, 46.4, 33.8, 33.5, 30.8, 30.6, 28.8, 27.9, 23.9, 22.9, 18.0, 17.2, 17.1, 17.0, 16.9, 16.8. Anal. Calcd for $C_{16}H_{29}N_3O_4$: C, 58.69; H, 8.93; N, 12.83. Found: C, 58.73; H, 8.85; N, 12.75.

4.1.6. 1-Boc-*N*-((1*S*)-1-carbamoyl-2-methylpropyl)-(*S*)-prolinamide 1f

Yield: 89%; mp: 87–90 °C (ethyl acetate/hexane); $[\alpha]_D^{20} = -74.7$ (*c* 1, CH_3OH); ^{1}H NMR of two rotamers (400 MHz, DMSO-d_6): δ 7.64–7.59 (m, 2H. NH), 7.42–7.38 (m, 2H, NH), 7.07 (s, 2H, NH), 4.23–4.21 (m, 2H, CH), 4.14–4.10 (m, 2H, CH), 3.42–3.33 (m, 2H), 3.32–3.25 (m, 2H), 2.18–2.07 (m, 1H), 2.06–1.90 (m, 3H), 1.89–1.69 (m, 6H), 1.40–1.25 (m, 18H, 2 × (CH_3)C), 0.89–0.84 (m, 12H, 2 × *i*Pr–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.8, 172.1, 171.6, 153.9, 153.3, 78.7, 78.4, 59.4, 59.3, 57.3, 57.1, 46.6, 46.5, 31.1, 30.5, 29.2, 28.0, 27.9, 23.9, 22.9, 19.3, 19.2, 18.0, 17.6. Anal. Calcd for $C_{15}H_{27}N_3O_4$: C, 57.49; H, 8.68; N, 13.41. Found: C, 57.55; H, 8.57; N, 13.49.

4.1.7. 1-Bn-*N*-((1*S*)-1-carbamoyl-1,2-dimethylpropyl)-(*S*)-prolinamide 1g

Yield: 87%; mp: 93–95 °C (ethyl acetate/hexane); $[\alpha]_D^{20} = -32.1$ (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (s, 1H, NH), 7.42–7.35 (m, 4H, Ar), 7.31–7.28 (m, 1H, Ar), 6.93 (s, 1H, NH), 6.85 (s, 1H, NH), 3.94–3.90 (m, 1H, CH_2), 3.52–3.44 (m, 2H, CH_2 and CH), 3.17–3.08 (m, 1H), 3.00–2.91 (m, 1H), 2.40–2.31 (m, 1H), 2.16–2.07 (m, 2H), 2.03–1.90 (m, 1H), 1.88–1.74 (m, 4H), 1.69–1.56 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.5, 173.0, 139.0, 128.7, 128.4, 127.2, 67.0, 35.8, 58.7, 53.4, 36.6, 35.5, 29.6, 24.0, 23.9, 23.4. Anal. Calcd for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.60; H, 8.05; N, 13.45.

4.2. General procedure for the cyclisation of protected (*S*)-prolinamides 1d,g

A mixture of **1d** or **1g** (3.1 mmol) and sodium methoxide in methanol (20 ml; 1.5 M) was refluxed for 2 h. Then, the solvent was evaporated and the residue was dissolved in water (20 ml). The aqueous solution was neutralised with concentrated HCl to pH ≈ 7 and extracted with DCM (4 × 20 ml). The solution was dried over sodium sulfate and concentrated in vacuo. The residue was crystallised from ethyl acetate/hexane.

4.2.1. (±)-2-(1-Boc-pyrrolidin-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one 2d

Yield: 92%; mp: 151–153 °C (ethyl acetate/hexane); ^{1}H NMR (400 MHz, DMSO-d_6): two conformers δ 10.28 (br s, 2H, NH), 4.54–4.47 (m, 2H, 2 × CH), 3.50–3.44 (m, 2H), 3.36–3.27 (m, 2H), 2.31–2.14 (m, 2H), 1.94–1.69 (m, 22H), 1.41–1.33 (m, 18H, 2 × $(CH_3)_3$C); ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.8, 185.5, 169.1, 153.5, 152.7, 79.1, 74.6, 74.4, 55.3, 55.0, 46.4, 36.8, 36.3, 31.3, 30.2, 27.9, 25.3, 23.9, 23.1. Anal. Calcd for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.48; H, 8.14; N, 13.73.

4.2.2. (±)-2-(1-Benzylpyrrolidin-2-yl)-1,3-diazaspiro[4.4]non-4-on 2g

Yield: 81%; mp: 140–141 °C (ethyl acetate/hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H, NH), 7.32–7.19 (m, 5H, Ar), 3.75–3.72 (m, 1H, CH_2), 3.44–3.58 (m, 2H, CH_2 and CH), 3.24–3.18 (m, 1H), 2.95–2.87 (m, 1H), 2.27–2.16 (m, 1H), 2.11–2.00 (m, 1H), 1.88–1.63 (m, 8H), 1.58–1.52 (m, 1H), 1.49–1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.2, 162.9, 138.7, 128.7, 128.0, 126.9, 76.9, 63.1, 57.7, 53.3, 36.9, 36.6, 28.9, 25.5, 25.4, 22.7. Anal. Calcd for $C_{18}H_{23}N_3O$: C, 72.70; H, 7.80; N, 14.13. Found: C, 72.71; H, 7.71; N, 14.21.

4.3. General procedure for the synthesis of *N*-(1-carbamoyl-1,1-dialkyl-methyl)-(*S*)-prolinamides 3a–c

A mixture of Cbz-protected (*S*)-prolinamide (**1a–c**) (7.5 mmol) and 5% Pd/C (250 mg) in 50 ml methanol was stirred under an atmosphere of hydrogen at room temperature for 12 h. After this time, the mixture was filtered through Celite and the product was isolated by the evaporation of methanol.

4.3.1. *N*-(1-Carbamoyl-cyclopentyl)-(*S*)-prolinamide 3a

Yield: 95%; mp: 174–176 °C; $[\alpha]_D^{20} = -45.4$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): δ 7.93 (s, 1H, NH), 6.97 (s, 1H, NH_2), 6.84 (s, 1H, NH_2), 3.47 (dd, 1H, *J* = 8.4 Hz, *J* = 5.4 Hz, CH), 2.81–2.79 (m, 2H, CH_2), 2.04–1.97 (m, 2H), 1.93–1.80 (m, 3H), 1.66–1.55 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.5, 174.0, 65.5, 60.2, 46.5, 36.2, 35.6, 30.0, 25.7, 23.7. Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.58; H, 8.54; N, 18.71.

4.3.2. *N*-((1*S*)-1-Carbamoyl-1,2-dimethylpropyl)-(*S*)-prolinamide 3b

Yield: 92%; mp: 202–205 °C; $[\alpha]_D^{20} = -48.5$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 1H, NH), 7.15 (s, 1H, NH_2), 7.06 (s, 1H, NH_2), 3.48 (dd, 1H, *J* = 8.8 Hz, *J* = 5.1 Hz, CH), 3.34 (br s, 1H, NH), 2.92–2.87 (m, 1H), 2.74–2.69 (m, 1H), 2.15–2.09 (m, 1H), 1.95–1.86 (m, 1H), 1.72–1.65 (m, 1H), 1.62–1.53 (m, 2H), 1.42 (s, 3H, CH_3), 0.85–0.81 (m, 6H, 2 × CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.9, 173.6, 61.5, 60.8, 46.5, 34.4, 30.2, 25.8, 18.1, 17.2, 17.1. Anal. Calcd for $C_{11}H_{21}N_3O_2$: C, 58.12; H, 9.31; N, 18.49. Found: C, 58.07; H, 9.26; N, 18.54.

4.3.3. *N*-((1*S*)-1-Carbamoyl-2-methylpropyl)-(*S*)-prolinamide 3c

Yield: 94%; mp: 127–130 °C; $[\alpha]_D^{20} = -54.2$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): δ 8.11 (d, 1H, *J* = 9.4 Hz, NH), 7.55 (s, 1H, NH_2), 7.12 (s, 1H, NH_2), 4.15 (dd, 1H, *J* = 9.4 Hz, *J* = 5.8 Hz, CH), 3.59 (dd, 1H, *J* = 9.0 Hz, *J* = 4.9 Hz, CH), 3.45 (br s, 1H, NH), 2.95–2.89 (m, 1H), 2.79–2.74 (m, 1H), 2.02–1.93 (m, 2H), 1.74–1.68 (m, 1H), 1.62–1.58 (m, 2H), 0.84 (d, 3H, *J* = 6.7 Hz, CH_3), 0.79 (d, 3H, *J* = 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.1, 172.9, 60.3, 56.3, 46.9, 31.4, 30.8, 26.0, 19.5, 17.6. Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.32; H, 8.98; N, 19.70. Found: C, 56.26; H, 8.88; N, 19.76.

4.4. General procedure for the synthesis of 4,4-dialkyl-2-(1-Boc-pyrrolidin-2-yl)-imidazolidin-5-ones 4d,e

A mixture of 1-aminocyclopentancarboxamide or (*S*)-2-amino-2,3-dimethylbutanamide (10 mmol) and (*S*)-*N*-Boc-prolinal (2.19 g; 11 mmol) in 30 ml methanol with one drop of acetic acid was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was crystallised from cyclohexane.

4.4.1. ((2*S*)-1-Boc-2-pyrrolidin-2-yl)-1,3-diazaspiro[4.4]nonan-4-one 4d

Yield: 71%; mp: 128–130 °C; $[\alpha]_D^{20} = -50.0$ (*c* 1, $CHCl_3$); ^1H NMR of two diastereomers (400 MHz, $CDCl_3$): δ 6.78 (br s, 1H, NH), 6.55 (br s, 1H, NH), 4.42 (d, 1H, *J* = 5.0 Hz, CH), 4.46–4.42 (m, 1H, CH), 3.89–3.85 (m, 2H, 2 × CH), 3.24–3.08 (m, 4H, 2 × CH_2), 2.27–2.11 (m, 2H), 2.10–2.03 (m, 2H), 1.95–1.67 (m, 16H), 1.44–1.43 (m, 18H, 2 × $(CH_3)_3C$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.3, 181.2, 156.2, 155.8, 154.5, 79.5, 79.4, 72.0, 70.1, 68.5, 68.3, 61.2, 59.8, 47.5, 46.9, 37.9, 37.5, 37.3, 28.1, 27.2, 36.5, 26.1, 24.8, 24.7, 24.6. Anal. Calcd for $C_{16}H_{27}N_3O_3$: C, 62.11; H, 8.80; N, 13.58. Found: C, 62.15; H, 8.86; N, 13.52.

4.4.2. (4*S*)-4-Isopropyl-4-methyl-2-((2*S*)-1-Boc-pyrrolidin-2-yl)-imidazolidin-5-one 4e

Yield: 66%; mp: 105–115 °C; $[\alpha]_D^{20} = -15.6$ (*c* 1, CH_3OH); ^1H NMR of two diastereomers (400 MHz, DMSO-d_6): δ 8.16–7.83 (m, 2H, 2 × NH), 4.68–4.43 (m, 2H, 2 × CH), 3.86–3.67 (m, 2H, 2 × CH), 3.31–3.12 (m, 2H, 2 × CH_2), 2.85–2.60 (m, 2H), 1.91–1.67 (m, 10H), 1.42–1.38 (m, 18H, 2 × $(CH_3)_3C$), 1.11–1.00 (m, 6H, 2 × CH_3), 0.85–0.79 (m, 12H, 2 × *i*Pr–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.7, 178.1, 177.6, 155.9, 154.8, 153.8, 79.0, 78.7, 78.5, 72.3, 70.0, 67.7, 63.2, 63.0, 62.9, 60.9, 60.4, 59.7, 47.5, 47.2, 46.7, 34.9, 33.5, 33.1, 28.1, 28.0, 26.1, 27.9, 24.1, 23.3, 21.7, 21.2, 17.8, 17.5, 16.3, 16.2, 16.0, 15.9. Anal. Calcd for $C_{16}H_{29}N_3O_3$: C, 61.71; H, 9.39; N, 13.49. Found: C, 61.68; H, 9.46; N, 13.52.

4.5. General procedure for the synthesis of 4,4-dialkyl-2-(1-Boc-pyrrolidin-2-yl)-4,5-dihydro-1*H*-imidazol-5-ones 2d,e

A mixture of the corresponding 2-(1-Boc-pyrollidin-2-yl)imidazolidin-5-one **4d** or **4e** (5 mmol) and activated manganese(IV) oxide (5 g; 91 mmol) in benzene (60 ml) was refluxed for 48 h. The suspension was filtered through a plug of silica gel, the filtrate was evaporated to dryness and recrystallised from ethyl acetate/hexane.

4.5.1. ((2*S*)-1-Boc-2-pyrrolidin-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one 2d

Yield: 69%; mp: 171–173 °C (ethyl acetate/hexane); $[\alpha]_D^{20} = -64.0$ (*c* 1, $CHCl_3$); ^1H NMR, ^{13}C NMR and elemental analyses are similar with racemic form of **2d**.

4.5.2. (4*S*)-4-Isopropyl-4-methyl-2-((2*S*)-1-Boc-pyrrolidin-2-yl)-4,5-dihydro-1*H*-imidazol-5-one 2e

Yield: 54%; yellow oil; $[\alpha]_D^{20} = -24.3$ (*c* 2.9, CH_3OH); ^1H NMR of two conformers (400 MHz, DMSO-d_6): δ 10.74–10.54 (m, 2H, 2 × NH), 4.50–4.38 (m, 2H, 2 × CH), 3.50–3.42 (m, 2H, 2 × CH_2), 3.34–3.23 (m, 2H, 2 × CH_2), 2.25 (m, 2H), 1.90–1.42 (m, 6H), 1.39–1.31 (m, 18H, 2 × $(CH_3)_3C$), 1.11–1.06 (m, 6H, 2 × CH_3), 0.88–0.84 (m, 6H, 2 × CH_3), 0.68–0.66 (m, 6H, 2 × CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.3, 186.9, 163.5, 162.9, 153.6, 153.2, 78.8, 78.6, 74.5, 74.0, 55.9, 55.6, 46.5, 46.4, 33.7, 31.8, 30.3, 28.0, 23.9, 22.9, 20.8, 16.6, 16.5, 16.4. Anal. Calcd for $C_{16}H_{27}N_3O_3$: C, 62.11; H, 8.80; N, 13.58. Found: C, 62.27; H, 8.95; N, 13.44.

4.6. General procedure for the synthesis of 4,4-dialkyl-2-pyrrolidin-2-yl-4,5-dihydro-1*H*-imidazol-5-ones 5d,e

To a solution of 1-Boc-protected proline derivative **2d** or **2e** (5 mmol) in DCM (5 ml) was added 1.5 ml TFA and the resulting mixture was stirred at room temperature for 2 h. Then, the product was isolated by the evaporation of solvents under reduced pressure.

4.6.1. (*S*)-2-(Pyrrolidin-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one bis(trifluoroacetate) salt 5d

Yield: 99%; colourless oil; ^1H NMR (400 MHz, CD_3CN): δ 10.32 (br s, 4H, NH_2^+ and CO*NH* and NH^+), 4.74–4.70 (m, 1H, CH), 3.53–3.42 (m, 1H, CH_2), 3.41–3.36 (m, 1H, CH_2), 2.51–2.43 (m, 1H), 2.27–2.15 (m, 1H), 2.13–2.05 (m, 2H), 2.01–1.86 (m, 8H); ^{13}C NMR (100 MHz, CD_3CN): δ 184.0, 164.2, 161.0 (q, CO, *J* = 38 Hz), 116.6 (q, CF_3, *J* = 286 Hz), 76.4, 56.8, 47.7, 37.8, 37.7, 29.2, 26.3, 26.2, 24.2, 24.2. Anal. Calcd for $C_{15}H_{19}F_6N_3O_5$: C, 41.39; H, 4.40; N, 9.64. Found: C, 41.52; H, 4.55; N, 9.40.

4.6.2. (4*S*)-4-Isopropyl-4-methyl-2-((2±)-pyrrolidin-2-yl)-4,5-dihydro-1*H*-imidazol-5-one bis(trifluoroacetate) 5e

Yield: 99%; colourless oil; $[\alpha]_D^{20} = -10.7$ (*c* 2.9, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): δ 14.12 (br s, 4H, NH_2^+ and CO*NH* and NH^+), 4.67–4.65 (m, 1H, CH), 3.44–3.42 (m, 1H, CH_2), 3.36–3.33 (m, 1H, CH_2), 2.44–2.37 (m, 1H), 2.08–2.00 (m, 3H), 1.96–1.90 (m, 1H), 1.26 (s, 3H, CH_3), 0.99–0.97 (m, 3H, CH_3), 0.83–0.79 (m, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 187.3, 187.1, 163.6, 162.6, 159.0 (q, CO, *J* = 38 Hz), 116.0 (q, CF_3, *J* = 286 Hz), 73.6, 73.4, 56.4, 56.3, 46.3, 34.7, 34.6, 29.5, 29.4, 23.7, 23.6, 20.9, 20.8, 17.0, 16.9. Anal. Calcd for $C_{15}H_{21}F_6N_3O_5$: C, 41.20; H, 4.84; N, 9.61. Found: C, 41.43; H, 5.02; N, 9.25.

4.7. 2-(4,5-Dihydro-3*H*-pyrrol-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one 6d

To a solution of **5d** (3 mmol) in chloroform (5 ml) was added TEA (1 ml; 7 mmol). A mixture was stirred 10 min and purified by column chromatography (silica gel; $CHCl_3/CH_3OH$ (10:1); R_f 0.23). Yield: 48%; colourless oil; ^1H NMR (400 MHz, DMSO-d_6): δ 11.16 (s, 1H, NH), 4.02–3.98 (m, 2H, CH_2), 2.81–2.77 (m, 2H, CH_2), 1.94–1.69 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.5, 166.7, 155.7, 78.2, 61.6, 36.7, 33.8, 25.4, 21.7. Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.55; H, 7.52; N, 20.60.

4.8. General experimental procedure for the aldol reaction

To a stirred solution of catalyst **3a–c** (0.1 mmol; 20 mol %) in appropriate solvents (2.0 ml), cyclohexanone (0.52 ml; 5 mmol) and acid were added. After 1 h, 4-nitrobenzaldehyde (75 mg, 0.5 mmol) was added and the mixture was kept for 3–7 days (Table 1, entry 6, 90 days) at room temperature. The reaction mixture was quenched by the addition of a saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3×10 ml). The organic layer was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on a silica gel using ethyl acetate/hexane (1:4) as the eluent to provide the pure aldol product. The spectroscopic data were identical with those reported in Ref. 6h. Enantiomeric excess was determined by chiral HPLC (Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH 85:15; flow rate 0.5 ml min^{-1}, λ = 254 nm; t_R (*syn*, minor) = 46.55 - min, t_R (*anti*, major) = 52.02 min; t_R (*anti*, minor) = 61.22 min; t_R (*syn*, major) = 66.47 min).

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