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Novel aminoimidazole derived proline organocatalysts for aldol reactions

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ABSTRACT

A series of L-proline amides with 2-aminoimidazole have been synthesized and found to be highly efficient organocatalysts for aldol reactions when an appropriate acid was added to control and activate the acceptor carbonyl group. Under optimized reaction conditions, high yields (over 80%) and high selectivities (ee 98%, de 98/2) were obtained in intermolecular aldol reaction even with only 1 equiv of ketone. Likewise, these systems also can catalyze intramolecular aldol reactions with good results.

1. Introduction

Although there has been an impressive development in asymmetric aldol reactions using organocatalysts like proline and proline analogues, there are still some limitations, such as high catalyst loading, large excess of ketone and moderate yield.[1,2] In recent years, significant contributions, which mainly focus on increasing the hydrophobicity of organocatalysts have been made[2a,3] and a series of new catalysts have been described,[4] however with only limited success in decreasing the amount of catalyst and excess of ketone.[5] Moreover, very often the synthesis of new catalysts is tedious and problematic.[4a,b] Therefore, practical and efficient new organocatalysts remain in high demand.

The activation model for proline catalysis through enamine/iminium intermediates, as given by List,[6] has been widely accepted and has become a dominating principle for designing new organocatalysts. In the catalytic cycle, the proton from the carboxyl group plays a crucial role in the rate-determining step.[7] Furthermore, the proton can also activate the acceptor carbonyl group to promote reaction. Therefore, proline derivatives or analogues with other acidic groups in the side chain or basic groups, which can be protonated by extra acid have been evaluated in the search for effective catalysts. Successful examples for the first idea are the sulfonylcarboxamide systems of Berkessel[3d] and the tetrazole systems of Ley[3e] or our recently described proline sulfonimides.[3k] The second principle is exemplified by proline derived amines[8] or MacMillan's imidazolidinone systems.[9]

In this context we had the idea that proline derivatives like **1a**, **1b** or **1c**, **1d**, **1e**, **1f** might be potential catalysts when protonated (Fig. 1). Especially imidazole systems seemed to be very interesting, as imidazole has a bifunctional structure with Brönsted acid (acidic proton on *N*–1) and Brönsted base (imine) sites and is incorporated in many important biological molecules.[10] Amazingly enough,

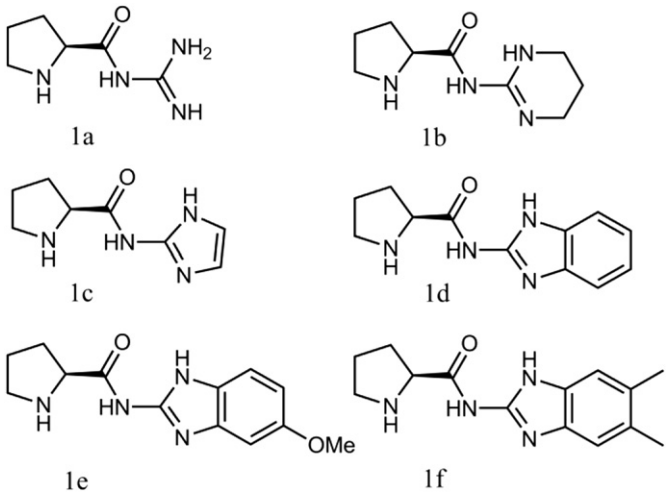

Fig. 1. The designed organocatalysts **1a**–**f**.

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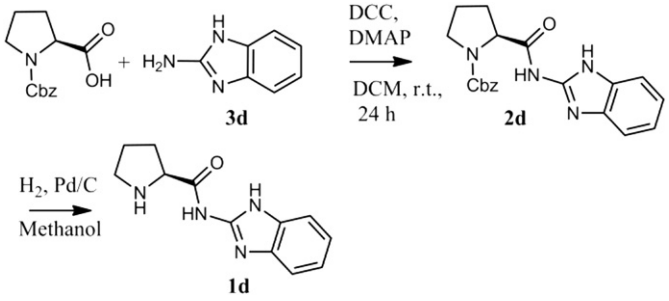
imidazole has only seldom been combined with a chiral scaffold for use as an organocatalyst, only recently a L-proline amide with 2-aminoimidazole has been introduced for an asymmetric Michael addition reaction.[11]

2. Results and discussion

In this paper for the first time, we report guanidine and aminoimidazole derivatives linked to L-proline by a stable amide bond (Fig. 1). Catalyst **1d** was synthesized as outlined in Scheme 1 with DCC and DMAP. Catalysts **1a**, **1b** and **1c**, **1e**, **1f** were prepared like **1d** from *Z*-L-proline and corresponding imidazole or guanidine derivatives in dry dichloromethane at room temperature. After reaction, the mixture was filtrated with silica gel to remove DCU and DMAP. If necessary, further purification was done by flash column chromatography. Finally, the protection group was removed with H_2, Pd/C.



Scheme 1. Synthesis of **1d**.

4-Nitrobenzaldehyde and cyclohexanone in DMSO were utilized to evaluate the catalysts **1a**–**f** (Table 1). The reaction with catalysts **1a**, **1b** gave good yield (72% and 79%) but low selectivity (7% and 5%) (entries 1 and 2, Table 1), whereas catalysts **1c**, **1d** and **1e**, **1f** gave better results in yield and selectivity. The yield with **1c** and **1d** reached 88% and 92% with enantiomeric excess (ee) 91% and 94%, respectively (entries 3 and 4, Table 1). Catalysts **1e** and **1f** gave a little higher yield and similar selectivity. It seems as if the protonated guanidine systems are less able to form hydrogen bonding to the carbonyl group than the 2-aminoimidazole systems, probably due to their higher basicity.

Besides the reaction in DMSO, we screened other solvents like DCM, THF, EtOAc, MeOH and also water with catalysts **1c**–**f**. Water is widely used as solvent in organocatalysis for its peculiar properties, but its special role is still in debate.[12] It has been reported that the selectivity of organocatalytic reactions in water is higher than that with organic solvents.[13] In our case the results show that in organic solvents, where the reaction is in a homogeneous phase, always higher yields are obtained than in heterogeneous reactions with water (Table 1). The yields of reactions with catalyst **1c**, **1d**, **1e** and **1f** in organic solvents are always above 88%, whereas the yields with water reach only 85%.

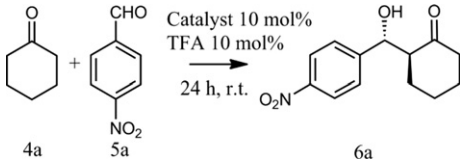
Even more importantly, we have found that the solvent has a significant effect on diastereoselectivity. The *anti*/*syn* ratio of the reaction product with **1c** in DMSO, DCM, THF, EtOAc was much lower than the obtained 90/10 and 92/8 ratio in methanol and water (entries 3, 7, 11, 15, 19, 23, Table 1). **1d** and **1e**, **1f** gave analogous results to **1c**. For the different selectivity in diverse solvents, we suspect that the added acid, which combines with the imidazole function to control and activate the carbonyl group, is more active in protic solvents. However, the yield is not obviously affected.

As the enantioselectivity of the reaction with **1c** and **1d** in protic solvents (94%, 92% in methanol and 96%, 98% in water) was generally better than in aprotic solvents and considering the advantages of water, we chose water as the solvent for further studies. In the reactions described above, the ketone was applied in excess as usual, being also a cosolvent. Using cheap and biodegradable ethyl acetate, however, excess ketone was not necessary to obtain good yields and selectivities. Considering the similarity of results between **1c**–**f**, only **1c** and **1d** were applied in the tests. With 1 equiv of cyclohexanone **1c** gave 71% yield and 94% ee (entry 27, Table 1), **1d** gave even better results (85% with 98% ee) (entry 28, Table 1).

With these promising results from reactions with 1 equiv of ketone in water and EtOAc, we screened different acids and lower catalyst loading. As in water/ethylacetate the yield with **1d** was higher than with **1c**, catalyst **1d** was chosen for the following tests (Table 2). In the search with the same amount of catalyst (10 mol %) but different acids, it was found that the selectivity of reaction is generally increased when the added acid becomes stronger in acidity. However, there is an exception—the catalysts on addition with HCl did not lead to higher selectivity. Compared with trifluoroacetic acid and trifluoromethanesulfonic acid, the selectivity of reaction with HCl is only 82% (entries 4, 5, 6, Table 2). Under these conditions quite some condensation product was detected after the reaction, as elimination takes place.

As an important result it turned out that trifluoroacetic acid is better than trifluoromethanesulfonic acid, especially with regard to

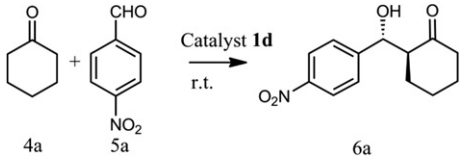
Table 1
Screening of organocatalysts for the aldol reaction[a]



Entry	Catalyst	Solvent	Yield[b] [%]	*anti*/*syn*[c]	ee [%] (*anti*)[d]
1	**1a**	DMSO	72	40/60	7
2	**1b**	DMSO	79	75/25	5
3	**1c**	DMSO	88	78/22	91
4	**1d**	DMSO	92	91/9	94
5	**1e**	DMSO	93	89/11	94
6	**1f**	DMSO	93	92/8	92
7	**1c**	DCM	93	88/12	82
8	**1d**	DCM	94	76/24	86
9	**1e**	DCM	95	80/20	88
10	**1f**	DCM	94	84/16	88
11	**1c**	THF	95	77/23	72
12	**1d**	THF	94	81/19	67
13	**1e**	THF	91	85/15	65
14	**1f**	THF	93	78/22	72
15	**1c**	EtOAc	96	70/30	77
16	**1d**	EtOAc	96	83/17	78
17	**1e**	EtOAc	94	75/25	72
18	**1f**	EtOAc	96	78/22	83
19	**1c**	MeOH	90	90/10	94
20	**1d**	MeOH	92	95/5	92
21	**1e**	MeOH	90	90/10	92
22	**1f**	MeOH	91	94/6	90
23	**1c**	H_2O	78	92/8	96
24	**1d**	H_2O	85	96/4	98
25	**1e**	H_2O	81	91/9	96
26	**1f**	H_2O	80	94/6	96
27	**1c**[e]	H_2O/EtOAc	71	94/6	94
28	**1d**[e]	H_2O/EtOAc	85	96/4	98

[a] The reaction was performed with **1** (0.1 mmol), TFA (0.1 mmol), **4a** (0.51 mL, 5.0 mmol) and **5a** (151 mg, 1.0 mmol), solvent (0.5 mL) at room temperature for 24 h.
[b] Combined yields of isolated diastereomers.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the anti product.
[e] Solvent is 0.25 mL H_2O and 0.25 mL EtOAc.

Table 2
Screening added acids and catalysts loading for aldol reaction[a]



Entry	Acid	Catalyst [mol %]	Reaction time [h]	Yield[b] [%]	*anti*/*syn*[c]	ee [%] (major)[d]	pH[e]
1	No	10	48	80	68/32	48	
2[f]	Succinic acid	10	24	65	85/15	69	2.44
3	AcOH	10	24	78	83/17	73	2.57
4	CF_3COOH	10	24	85	96/4	98	0.69
5	CF_3SO_2OH	10	18	88	88/12	97	0.58
6	HCl	10	18	69	84/16	82	0.54
7	CF_3COOH	5	36	83	98/2	98	0.91
8	CF_3COOH	2.5	48	82	89/11	95	1.13
9	CF_3COOH	1	72	80	87/13	95	1.44

[a] The reaction was performed with **1d**, **4a** (0.10 mL, 1.0 mmol) and **5a** (151 mg, 1.0 mmol), acid solution (0.25 mL), EtOAc (0.25 mL) at room temperature for the time corresponded in the table.
[b] Combined yields of isolated diastereomers.
[c] Determined by ^1H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the anti product.
[e] The added acid solutions were made with same mole amount of catalyst in 0.25 mL water.
[f] Succinic acid is 5 mol %.

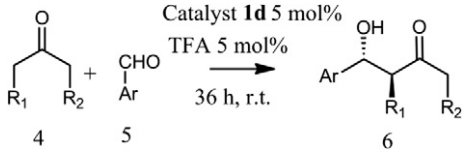
diastereoselectivity with **1d** (entries 4 and 5, Table 2). Besides this, the *anti*/*syn* ratio decreases when the catalyst loading is reduced. With 1 mol % loading, an *anti*/*syn* ratio (87/13) is obtained with excellent comparable yields of 80% and enantioselectivities of more than 95% (entries 9, Table 2).

In the following the pH in the reactions from Table 2 was investigated, in order to find a relationship between the pH of water solution and reaction selectivity. A solution of the corresponding acid in water was made and the pH of the acid solution was measured. In Table 2 it can be seen that the pH for reactions with high selectivity of product is mainly between 0.5 and 1.4. When the pH of the solution is lower than 0.5, elimination of water leading to condensation product is occurring with decrease of selectivity of the aldol addition product. When the pH of solution is higher than 1.5, the selectivity is also going down.

Finally, the optimized conditions were used to test different aldehydes and ketones. Firstly, different substituted benzaldehydes were investigated and it was found that regarding selectivity electron poor and electron rich substituted systems gave similar results, only the yields were lower with 4-chloro and 4-methoxybenzaldehyde compared to the nitro-substituted benzaldehydes. After testing different aldehydes, other ketones, namely cyclopentanone and acetone, were also investigated. Notably, in comparison to cyclohexanone, the selectivity of the reaction with the five-membered ketone and also with acetone was lower (entries 6 and 7, Table 3).

After proving that **1d** was a highly efficient catalyst for intermolecular aldol reactions, this catalyst was also tested in an intramolecular aldol reaction, namely in the final aldol reaction step in the well known Hajos–Parrish–Eder–Sauer–Wiechert process for the synthesis of **8**[14]—a valuable intermediate for steroid synthesis. 2-Methyl-2-(3-oxobutyl)-1,3-cyclohexane-dione **7**[15] was treated in different solvents with 5 mol % of catalyst **1d**. Aldol addition and condensation was accomplished in 24 h at room temperature. The enantioselectivity was highest (ee 73%) in the reaction in water (entry 4, Table 4), even better than the reported value using D-proline as a catalyst Fig. 2.

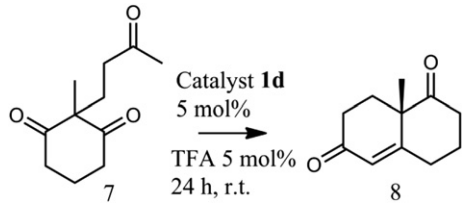
Table 3
The aldol reaction with various ketones and aldehydes[a]



Entry	Aldehyde Ar	Ketone R_1, R_2	Yield of **6** [%][b]	*anti*/*syn*[c]	ee [%] (major)[d]
1	*p*-$NO_2C_6H_4$	$-(CH_2)_3-$	**6a** 83	98/2	98
2	*o*-$NO_2C_6H_4$	$-(CH_2)_3-$	**6b** 81	95/5	96
3	*m*-$NO_2C_6H_4$	$-(CH_2)_3-$	**6c** 80	95/5	97
4	*p*-ClC_6H_4	$-(CH_2)_3-$	**6d** 63	99/1	97
5	*p*-$CH_3OC_6H_4$	$-(CH_2)_3-$	**6e** 58	97/3	96
6	*p*-$NO_2C_6H_4$	$-(CH_2)_2-$	**6f** 84	60/40	91
7	*p*-$NO_2C_6H_4$	H, H	**6g** 60		84

[a] The reaction was performed with **1d** (0.05 mmol), TFA (0.05 mmol), **4** (1.0 mmol) and **5** (151 mg, 1.0 mmol), solvent (in 0.25 mL H_2O and 0.25 mL EtOAc) at room temperature for 36 h.
[b] Combined yields of isolated diastereomers.
[c] Determined by ^1H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the anti product.

Table 4
Intramolecular aldol reaction catalyzed by catalyst **1d**[a]



Entry	Solvent	Yield[b] [%]	ee [%](major)[c]
1	THF	95	65
2	DMSO	96	67
3	Methanol	97	71
4	H_2O	93	73

[a] The reaction was performed with **1d** (0.05 mmol), TFA (0.05 mmol), **7** (1.0 mmol) and solvent (0.5 mL) at room temperature for 24 h.
[b] Yield is after purification.
[c] Determined by chiral-phase HPLC analysis.

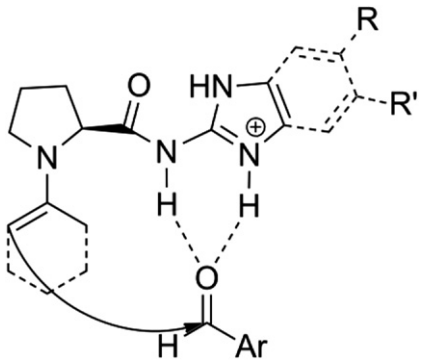


Fig. 2. The proposed transition state with organocatalysts **1c**–**f**.

3. Conclusion

In summary, an easy approach to a series of highly efficient chiral aminoimidazole catalysts in only two steps has been established and the effect of solvent and added acid on the selectivity of aldol reactions has been examined. Especially, the amides from L-proline with 2-aminobenzimidazole have been found to be effective

organocatalysts for aldol reactions in water. After protonation, these efficient catalysts may form active H-bond, with which the carbonyl group can be activated and the stereoselectivity can be controlled. It has also been found that the selectivity of reaction is greatly determined by the added acid. The reaction with catalyst **1d** and trifluoroacetic acid gives highly selective reactions in test reactions of cyclohexanone and substituted benzaldehydes (de 98/2, ee 98%) and good yields without using excess of ketone. These catalysts can be expected to be also suited for other organocatalytic reactions, in which activation of the acceptor carbonyl group is needed.

4. Experimental section

4.1. General information

Chemicals were purchased from commercial suppliers and used without further purification. Solvents were either purchased from commercial suppliers or purified by standard techniques. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using silica gel 60 F_{254} aluminium precoated plates from Merck (0.25 mm) and compounds were visualized by irradiation with UV light and/or by treatment with a Ninhydrin solution followed by heating. The pH of acid solutions was measured with Mettler DL25 with buffer standards of pH 4.01±0.02 and pH 7.00. Flash column chromatography was performed on silica gel (MN Kieselgel 60 M, 0.04–0.063 mm, 230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DPX 400 MHz spectrometer or Bruker Avance DPX 600 MHz spectrometer. Chemical shifts were reported in ppm (parts per millions) according to residual solvent signals of $CDCl_3$ (^{1}H NMR; δ=7.26 ppm, ^{13}C NMR; δ=77.0 ppm), DMSO-d_6 (^{1}H NMR; δ=2.50 ppm, ^{13}C NMR; δ=39.43 ppm) and CD_3OD (^{1}H NMR; δ=3.30 ppm, ^{13}C NMR; δ=49.0 ppm). All spectra were acquired and processed using Bruker TOPSPIN (1.3) or MestRenova. Optical rotations were measured on a PerkinElmer 241 polarimeter. High resolution mass analysis was measured on a micrOTOF series 168 instrument. Chiral HPLC studies were carried out on a Merck-Hitachi LaChrom instrument (Autosampler LaChrom L-7200, Pump LaChrom L-7100, detector LaChrom L-7490).

4.2. Synthesis of catalysts 1a–f

*4.2.1. (S)-Benzyl-2-(N-(benzyloxycarbonyl) carbamimidoylcarbamoyl) pyrrolidine-1-carboxylate (**2a**).* *N*-Cbz-guanidine was synthesized following a literature report.[16]

To a solution of *N*-carbobenzyloxy-L-proline (2.49 g, 10.0 mmol, 1.0 equiv) and *N*-Cbz-guanidine (2.21 g, 11.0 mmol, 1.1 equiv) in CH_2Cl_2 (30.0 mL) *N*,*N*′-dicyclohexylcarbo-diimide (2.26 g, 11.0 mmol, 1.1 equiv) and 4-dimethylamino pyridine (1.34 g, 11.0 mmol) were added at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min at 0 °C, then stirred at room temperature for 24 h. The reaction mixture was fast filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexylurea. Further purification was through flash column chromatography (Methanol/DCM=1:15) to give product (3.77 g, 89%). ^{1}H NMR (400 MHz, $CHCl_3$-*d*): δ 7.42–7.20 (10H, m), 5.23–5.15 (1H, m), 5.15–5.14 (2H, d, *J*=2.55 Hz), 5.14–4.99 (1H, m), 4.45–4.32 (2H, m), 3.72–3.41 (2H, m), 2.32–1.99 (2H, m), 1.99–1.82 (2H, m). ^{13}C NMR (400 MHz, $CHCl_3$-*d*): δ 171.7, 158.6, 155.9, 146.9, 136.0, 128.4, 128.4, 128.1, 128.0, 128.0, 67.6, 67.1, 61.8, 47.3, 29.3, 24.4. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{22}H_{25}N_4O_5$ 425.1825, found 425.1819.

*4.2.2. (S)-N-Carbamimidoylpyrrolidine-2-carboxamide (**1a**).* To a solution of **2a** (2.12 g, 5.0 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 h under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (MeOH/DCM=1:4) to give white solid product (0.69 g, 90% yield). $[\alpha]_D^{20}$ −3.0 (*c* 0.40, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50–7.91 (1H, br), 7.72–7.50 (1H, br), 3.90–3.82 (1H, t, *J*=8.6 Hz), 3.51–3.30 (3H, m), 3.20–3.10 (1H, m), 2.08–1.80 (3H, m), 1.56–1.48 (1H, m). ^{13}C NMR (400 MHz, DMSO-d_6): δ 189.0, 177.3, 66.9, 47.9, 27.2, 26.4. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_6H_{13}N_4O$ 157.1089, found 157.1084.

*4.2.3. (S)-Benzyl-2-(pyrimidin-2-ylcarbamoyl) pyrrolidine-1-carboxylate (**2b**).* To a solution of *N*-carbobenzyloxy-L-proline (2.49 g, 10.0 mmol, 1.0 equiv) and 2-aminopyrimidine (1.04 g, 11.0 mmol, 1.1 equiv) in CH_2Cl_2 (30.0 mL) *N*,*N*′-dicyclohexyl-carbodiimide (2.26 g, 11.0 mmol, 1.1 equiv) and 4-dimethylamino pyridine (1.34 g, 11.0 mmol) were added at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min at 0 °C, then stirred at room temperature for 24 h. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexylurea. Further purification was by flash column chromatography. The target product (2.37 g, 73% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, $CHCl_3$-*d*): δ 8.50–7.91 (1H, br), 8.60 (2H, d, *J*=4.85 Hz), 7.50–7.10 (5H, m), 7.00 (1H, s), 5.10 (2H, m), 4.95–4.85 (1H, s), 3.70–3.40 (2H, m), 2.40–1.90 (4H, m). ^{13}C NMR (400 MHz, $CHCl_3$-*d*): δ 158.1, 136.1, 128.2, 127.8, 127.6, 116.3, 67.2, 61.1, 46.9, 28.0, 24.1. HRMS (ESI): *m*/*z* [M+Na$^+$] calcd for $C_{17}H_{18}N_4NaO_3$ 349.1277, found 349.1271.

*4.2.4. (S)-N-(1,4,5,6-Tetrahydropyrimidin-2-yl) pyrrolidin-2-carboxamide (**1b**).* To a solution of **2b** (1.63 g, 5.0 mmol) in MeOH (20 mL) was added 10% Pd/C, followed by two drops of concentrated HCl was added to the solution. The mixture was stirred at room temperature for 14 h under an atmosphere of hydrogen. Then excess of Na_2CO_3 was added to the solution, the reaction mixture was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (MeOH/DCM=1:4) to give the product (0.89 g, 91% yield). $[\alpha]_D^{20}$ −1.5 (*c* 1.00, MeOH). ^{1}H NMR (400 MHz, Methanol-d_4): δ 4.18–4.14 (1H, m), 3.54–3.48 (2H, m), 3.44–3.36 (2H, m), 3.10–3.00 (2H, m), 2.20–2.10 (3H, m), 2.08–1.98 (2H, m), 1.65–1.58 (1H, m). ^{13}C NMR (400 MHz, Methanol-d_4): δ 191.9, 176.9, 69.3, 49.2, 40.5, 37.7, 29.1, 28.7, 27.8. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_9H_{17}N_4O$ 197.1402, found 197.1397.

*4.2.5. (S)-Benzyl-2-(1H-imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (**2c**).* To a solution of *N*-carbobenzyloxy-L-proline (2.49 g, 10.0 mmol, 1.0 equiv) and 2-aminoimidazole sulfate (2.36 g, 11.0 mmol, 1.1 equiv) in CH_2Cl_2 (30.0 mL) *N*,*N*′-dicyclohexylcarbodiimide (2.26 g, 11.0 mmol, 1.1 equiv) and 4-dimethylamino pyridine (2.68 g, 22.0 mmol) were added at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min at 0 °C, then at room temperature for 24 h. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexylurea. Further purification was done by flash column chromatography (Methanol/DCM=1:15). The target product (2.4 g, 78% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, $CHCl_3$-*d*): δ 7.46–7.08 (5H, m), 6.82 (2H, s), 5.21–4.92 (2H, m), 4.53–4.43 (1H, dd, *J*=3.62 Hz), 3.73–3.50 (2H, m), 2.42–2.22 (1H, m), 2.19–1.82 (3H, m). ^{13}C NMR (400 MHz, $CHCl_3$-*d*): δ 173.6, 156.9, 142.6, 140.4, 129.3, 128.9, 128.7, 119.2, 108.2, 68.3, 61.6, 40.1, 32.4, 24.6. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{16}H_{19}N_4O_3$ 315.1457, found 315.1452.

*4.2.6. N-1H-Imidazol-2-yl-L-prolinamide (**1c**).* To a solution of **2c** (1.57 g, 5.0 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 h under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (MeOH/DCM=1:4) to give the

product (0.74 g, 82% yield). $[\alpha]_D^{20}$ −48.6 (*c* 0.53, MeOH). ^{1}H NMR (400 MHz, Methanol-d_4): δ 6.72–6.68 (2H, d, *J*=1.82 Hz), 3.60–3.50 (1H, m), 3.00–2.90 (2H, m), 2.18–2.08 (1H, m), 1.90–1.75 (1H, m), 1.72–1.65 (2H, m). ^{13}C NMR (400 MHz, Methanol-d_4): δ 175.6, 142.8, 118.9, 118.9, 61.7, 47.9, 31.8, 26.9. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_8H_{13}N_4O$ 181. 1089, found 181.1084.

*4.2.7. (S)-Benzyl-2-(1H-benzo[d]imidazol-2-ylcarbamoyl)pyrrolidine-1-carboxylate (**2d**).* To a solution of *N*-carbobenzyloxy-L-proline (2.49 g, 10.0 mmol, 1.0 equiv) and 2-amino-1*H*-benzimidazole (1.46 g, 11.0 mmol, 1.1 equiv) in CH_2Cl_2 (30.0 mL) *N*,*N*′-dicyclohexylcarbo-diimide (2.26 g, 11.0 mmol, 1.1 equiv) and 4-dimethylamino pyridine (2.68 g, 22.0 mmol) were added at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min at 0 °C, then at room temperature for 24 h. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexylurea. Further purification was done by flash column chromatography (Methanol/DCM=1:15) to give **2d** as white solid product (3.31 g, 91% yield). ^{1}H NMR (600 MHz, $CHCl_3$-*d*): δ 7.4 89 (2H, s), 7.41–7.35 (3H, m), 7.28–7.22 (3H, m), 6.99 (1H, s), 5.29–5.27 (1H, d, *J*=12.2 Hz), 5.17–5.06 (1H, m), 4.77–4.74 (2H, d, *J*=17.6 Hz), 3.74–3.55 (2H, m), 2.18–2.12 (2H, m), 2.10–2.01 (1H, m), 1.90–1.89 (1H, m). ^{3}C NMR (600 MHz, $CHCl_3$-*d*): δ 173.9, 173.2, 155.4, 154.2, 147.5, 147.4, 136.3, 135.8, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 122.4, 122.2, 67.3, 60.7, 60.2, 47.3, 46.9, 31.4, 29.8, 24.4,23.6. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{20}H_{21}N_4O_3$ 365. 1614, found 365.1608.

*4.2.8. N-1H-Benzimidazol-2-yl-L-prolinamide (**1d**).* To a solution of **2d** (1.82 g, 5.0 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 h under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (MeOH/DCM=1: 4) to give the product (1.04 g, 91% yield) as a white solid. $[\alpha]_D^{20}$ −50.8 (*c* 0.46, MeOH). ^{1}H NMR (600 MHz, $CHCl_3$-*d*): δ 7.55–7.35 (2H, m), 7.25–7.20 (2H, m), 4.00–3.95 (1H, t, *J*=4.5 Hz), 3.15–2.95 (2H, m), 2.33–2.22 (1H, m), 2.12–2.02 (1H, m), 1.82–1.74 (2H, m). ^{13}C NMR (600 MHz, $CHCl_3$-*d*): δ 175.8, 146.2, 129.0, 128.5, 122.0, 114.5, 114.2, 60.4, 47.2, 30.8, 26.1. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{12}H_{15}N_4O$ 231. 1246, found 231.1240.

*4.2.9. (S)-Benzyl-2-(6-methoxy-1H-benzo[d]imidazol-2-ylcarbamoyl) pyrrolidine-1-carboxylate (**2e**).* 2-Amino-5-methoxy-1*H*-benzimidazole was obtained from 4-methoxybenzene-1,2-diamine following the reported operation.[17] To a solution of *N*-carbobenzyloxy-L-proline (2.49 g, 10.0 mmol, 1.0 equiv) and 2-amino-5-methoxy-1*H*-benzo[*d*]imidazole (1.79 g, 11.0 mmol, 1.1 equiv) in CH_2Cl_2 (30.0 mL) *N*,*N*′-dicyclo-hexylcarbodiimide (2.26 g, 11.0 mmol, 1.1 equiv) and 4-dimethylamino pyridine (1.34 g, 11.0 mmol, 1.1 equiv) were added at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min at 0 °C, then at room temperature for 24 h. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexylurea. Further purification was through flash column chromatography (Methanol/DCM=1:10). ^{1}H NMR (400 MHz, $CHCl_3$-*d*): δ 7.50–7.30 (4H, m), 7.20–6.80 (4H, m), 5.15–5.05 (2H, m), 4.60–4.40 (1H, m), 3.84 (3H, d, *J*=7.80 Hz), 3.72–3.48 (2H, m), 2.38–2.20 (1H, m), 2.10–1.75 (3H, m). ^{13}C NMR (400 MHz, $CHCl_3$-*d*): δ 179.3, 156.6, 154.5, 146.6, 136.7, 128.3, 128.0, 127.7, 127.4, 111.9, 66.5, 59.4, 55.7, 46.8, 30.8, 23.3. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{21}H_{23}N_4O_4$ 395.1719, found 395.1714.

*4.2.10. N-(5-Methoxy-1H-benzimidazol-2-yl)-L-prolinamide (**1e**).* To a solution of **2e** (1.97 g, 5.0 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 h under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (Methanol/DCM=1:4) to give the deprotection product (1.14 g, 88% yield). $[\alpha]_D^{20}$ −81.5 (*c* 1.10, MeOH). ^{1}H NMR (400 MHz, Methanol-d_4): δ 6.90–7.30 (1H, d, *J*=7.76 Hz), 6.54–6.52 (1H, d, *J*=2.37 Hz), 6.35 (1H, dd, *J*=2.39, 7.46 Hz), 3.50 (1H, m), 3.38 (3H, s), 2.60 (2H, m), 1.75 (1H, m), 1.50 (1H, m), 1.35 (2H, m). ^{13}C NMR (400 MHz, Methanol-d_4): δ 176.4, 157.7, 148.0, 115.3, 112.1, 108.8, 98.6, 62.0, 56.2, 47.9, 31.8, 26.9. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{13}H_{17}N_4O_2$ 261.1352, found 261.1352.

*4.2.11. (S)-Benzyl-2-(5,6-dimethyl-1H-benzo[d] imidazol-2-ylcarbamoyl)pyrrolidine-1-carboxylate (**2f**).* 2-Amino-5,6-dimethyl-1*H*-benzo[*d*]imidazole was obtained following the reported operation using 2-amino-5,6-dimethyl-1*H*-benzo[*d*]imidazole as starting material.[17] To a solution of Cbz-L-proline (2.49 g, 10.0 mmol, 1.0 equiv) and 2-amino-5,6-dimethyl-1*H*-benzo[*d*]imidazole (1.77 g, 11.0 mmol, 1.1 equiv) in CH_2Cl_2 (30.0 mL) *N*,*N*′-dicyclohexylcarbodiimide (2.26 g, 11.0 mmol, 1.1 equiv) and 4-dimethylamino pyridine (1.34 g, 11 mmol, 1.1 equiv) were added at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min at 0 °C, then at room temperature for 24 h. The reaction mixture was filtrated through silica gel pad (SiO_2 15 g) to remove dicyclohexylurea. Further purification was done by flash column chromatography (Methanol/DCM=1:20).

^{1}H NMR (600 MHz, $CHCl_3$-*d*): δ 7.46–7.32 (3H, m), 7.28–7.24 (2H, m), 7.24–7.20 (1H, m), 7.06–7.00 (1H, m), 5.80–5.60 (1H, m), 5.20–5.00 (1H, m), 4.70–4.60 (1H, m), 3.90–3.75 (2H, m), 2.40–2.32 (6H, d, *J*=12.2 Hz), 2.35–2.25 (2H, m), 2.20 (1H, m), 1.95–1.80 (1H, m). ^{13}C NMR (600 MHz, $CHCl_3$-*d*): δ 173.3, 155.5, 146. 8, 146.7, 136.3, 136.0, 131.3, 131.2, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 67.3, 67.2, 60.9, 60.5, 47.3, 46.9, 31.5, 29.9, 24.4, 23.7. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{22}H_{25}N_4O_3$ 393.1927, found 393.1921.

*4.2.12. N-(5,6-Dimethyl-1H-benzimidazol-2-yl)-L-prolinamide (**1f**).* To a solution of **2f** (1.96 g, 5.0 mmol) in MeOH (20 mL) was added 10% Pd/C. The mixture was stirred at room temperature for 14 h under an atmosphere of hydrogen. The reaction was filtered through Celite and the filtrate concentrated in vacuum. The crude product was purified by flash column chromatography (Methanol/DCM=1:4). The product (1.09 g, 84% yield) was obtained as a white solid. $[\alpha]_D^{25}$ −68.0 (*c* 1.02, $CHCl_3$). ^{1}H NMR (600 MHz, Methanol-d_4): δ 7.24 (2H, s), 3.50–3.45 (1H, dd, *J*=3.15, 7.25 Hz), 3.20 (1H, m), 2.80 (1H, m), 2.60 (1H, m), 2.30 (6H, s), 2.20 (1H, m), 2.00 (1H, m), 1.70 (2H, m). ^{13}C NMR (600 MHz, Methanol-d_4): δ 176.6, 147.9, 134.3, 132.2, 114.9, 62.1, 47.9, 31.7, 26.8, 20.2. HRMS (ESI): *m*/*z* [M+H$^+$] calcd for $C_{14}H_{19}N_4O$ 259. 1559, found 259.1553.

4.3. Typical procedure for the intermolecular aldol reaction

To a mixture of catalyst **1** (0.05 mmol) and TFA (3.7 μL 0.05 mmol) in water (0.25 mL) and EtOAc (0.25 mL), cyclohexanone (0.1 mL, 1.0 mmol) and 4-nitrobenzaldehyde (151 mg, 1.0 mmol) were added. After the reaction mixture had been stirred for 36 h, water (5 mL) was added, followed by extraction with diethyl ether. The organic phase was dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (Hexane/EtOAc) to afford the aldol product **6a**.

4.4. Procedure for the intramolecular aldol reaction

To a mixture of catalyst **1d** (0.05 mmol) and TFA (3.7 μL 0.05 mmol) in H_2O (0.25 mL) EtOAc (0.25 mL), 2-methyl-2-(3-oxobutyl)-cyclohexane-1,3-dione (0.19 g, 1.0 mmol) were added. After the mixture had been stirred for 24 h, water (5 mL) was added to the reaction mixture, followed by extraction with EtOAc. The

organic phase was dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (Hexane/EtOAc) to afford product **8**.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.09.071.

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