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Systematic evaluation of a few proline derivatives as catalysts for a direct aldol reaction

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ABSTRACT

A series of pyrrolidine derivatives were prepared and examined as catalysts for an aldol reaction. Structural variations in these molecules involved altering the sterics at the α-position, the position of the carbonyl group, and the acidities of the hydrogen bonding sites. The effect of these factors on catalytic activity and enantioselectivity was studied. The experimental results revealed that additional sterics at the α-position were detrimental. However, no correlation was found between the catalytic activity and N–H acidity.

1. Introduction

Since the discovery of L-proline catalyzed intermolecular aldol reactions,[1] asymmetric organocatalysis has received growing attention.[2] Although the direct use of free α-amino acids[1,3] and easily accessible chiral amines[4] as catalysts is much preferable, the rather narrow applicability, unsatisfactory catalytic activities, formation of various side products and, low reaction rates restricts their generality.[5] To overcome these limitations, simple modifications of amino acids and chiral amines have become an expedient choice.[6] Therefore various primary and secondary amines have been continuously developed as new organocatalysts based on the principles of enamine, iminium and hydrogen bonding, catalysis etc.[7]

For an amine to act as an efficient catalyst,[8] Lewis or Brønsted acidic additives are needed to assist enamine formation. The enamine generated reacts readily with reactive electrophiles, which control its approach through steric interactions.[9a] However for relatively unreactive electrophiles such as aldehydes, ketones and imines, additional assistance for the catalysis is required, which is generally provided by suitably positioned hydrogen bond donors in the catalyst.[9b,c] This results in the simultaneous activation of both nucleophiles and electrophiles. If these hydrogen bonding sites are sufficiently acidic as the carboxylic acid groups of amino acids, then they also assist the enamine formation. Thus, for enantioselective enamine catalysis, the presence of a properly positioned steric bulk or a substituent carrying at least one hydrogen bonding site, is essential. A catalytic system containing all these factors together as a combination of two chiral organocatalysts, has recently been reported.[10] Although a number of bi- and polyfunctional catalysts have been already developed, the rational design and synthesis of efficient enamine catalysts still receives considerable attention.[11]

Most of the successful enamine catalysts reported for direct aldol-type reactions are based on the amide derivatives of proline or diamines with or without additional hydrogen bonding sites[12] or derivatives of 4-hydroxy proline.[13] Recently, catalysts with modifications at both sites, that are the 4-hydroxy and carboxylate groups of 4-hydroxy proline, have also been reported.[14] The strategies used for their modification mainly focus on variations in the electronic and/or steric properties of the groups in the side chains.

Despite the recently reported kinetic studies and theoretical calculations on the mechanistic investigations and the comparison of various organocatalysts for this reaction,[15] there is still a need for systematic and practical screenings of simple proline derivatives based on the transition states shown in Figure 1. Such information could explain the effect of sterics at the stereogenic center, the effect of the position of the carbonyl group in the amide containing the catalysts, and the effect of the acidities of the hydrogen bonding sites. Herein we report a series of chiral bifunctional secondary amines and their catalytic behavior in a direct aldol reaction (See Figs. 2–4).

2. Results and discussion

There are only a few reports on α,α-disubstituted pyrrolidines as catalysts for this reaction; α-methyl proline, thiazolidinium derivatives,[3a] and α-α′-disubstituted imidazolidinone.[16] It has been reported that when the reaction is catalyzed by α-methyl proline **1b**, it gives a lower yield and enantioselectivity of the aldol product than that catalyzed by L-proline (Table 1, entries 1 vs 3).[3a] To further study the effect of sterics of the α-substituent, the methyl group in **1b** was replaced by a benzyl group **1c**.[17a] A few easily accessible proline derivatives **2a**–**3b**[17b–d] with and without a substituent at the stereogenic carbon were prepared and exam-

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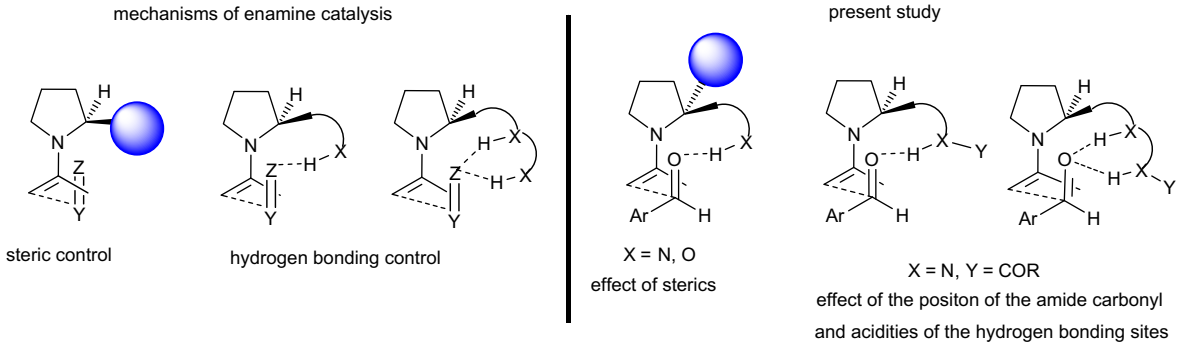


Figure 1. Transition states for enamine catalysis.

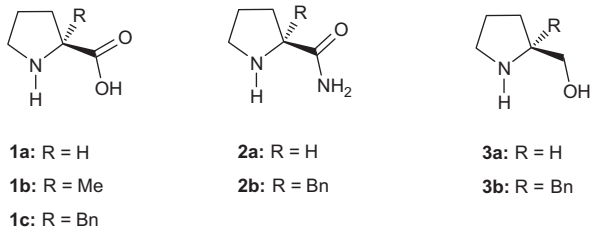


Figure 2. Selected pyrrolidine derivatives used to study the effect of sterics at the α-position.

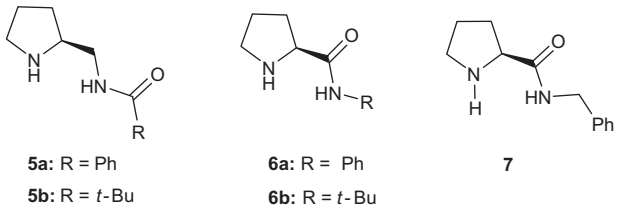


Figure 3. Selected chiral amides used to study the effect of the position of the carbonyl group.

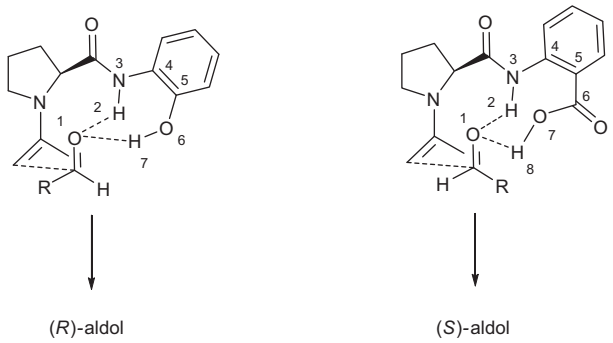


Figure 5. Stereochemical outcome and ring size of the transition state.

ined as catalysts for a direct aldol reaction. For the sake of comparison, acetone and *p*-nitrobenzaldehyde were used as substrates (See Scheme 1).

It was observed that the rate as well as enantioselectivity decreased considerably with an increase in steric hindrance from **1a**–**1c** (Table 1, entries 1, 3, and 4). However, under neat conditions, **1c** could not catalyze the reaction while **1a** gave a moderate yield and enantioselectivity (Table 1, entries 5 vs 2). To rule out the possiblility of oxazolidinone formation as the side reaction,[15d] aqueous DMF was examined as the solvent. However similar results were realized (Table 1, entry 6). Therefore, for the rest of our study, neat reaction conditions were employed. The catalytic reactivity pattern of prolinamides **2a** and **2b** was similar to proline derivatives **1a** and **1c**. Further evidence for the detrimental effect of the α-substituent was provided by the proline derivatives **3a** and **3b**. Acetone was replaced with cyclopentanone to rule out the possibility of imidazolidinone formation from the reaction with an amino alcohol. However, similar results were obtained. The reaction of cyclopentanone with benzaldehyde was catalyzed by **3a**, but not by **3b**, as can be seen in Table 1 (entries 9 and 10).

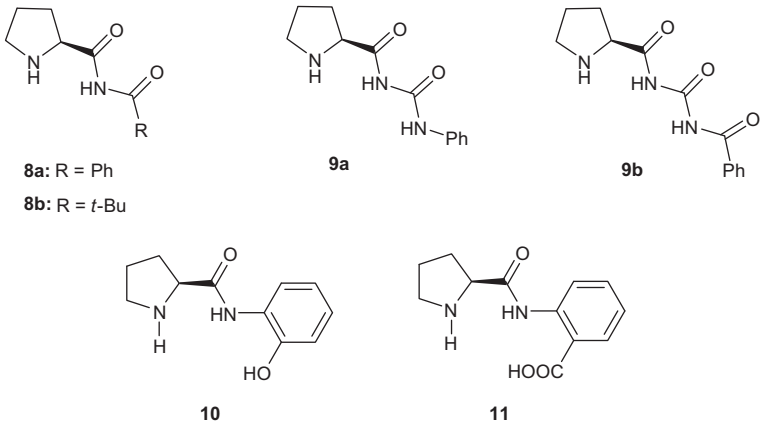


Figure 4. Organocatalysts for comparison of increased acidities and hydrogen bonding.

Table 1
Screening of pyrrolidine derivatives to study the effect of α-sterics

No	Catalyst	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1[c]	**1a**	DMSO	2	68	76
2[c]	**1a**	Neat	24	60	67
3[c]	**1b**	DMSO	2	26	61
4	**1c**	DMSO	72	57	36
5	**1c**	Neat	96	Trace	—
6	**1c**	aq DMF[d]	48	Trace	—
7[e]	**2a**	Neat	24	81	33
8	**2b**	Neat	72	Trace	—
9[f]	**3a**	Neat	15	89[g]	36[h]
10[f]	**3b**	Neat	18	No reaction	—

[a] Isolated yield of aldol product **A**.
[b] The ee of the (*R*)-enantiomer was determined by chiral HPLC analysis.
[c] Reported[3a] using 20 mol % of catalyst.
[d] 3 vol % water in DMF.
[e] Reported[18a] using 20 mol % of catalyst.
[f] Cyclopentanone and benzaldehyde were used as reactants.
[g] *syn*:*anti* (80:20).
[h] The ee of the major *syn*-diastereoisomer.

Our results indicated that in proline derivatives, substitution of the α-hydrogen with an alkyl group adversely affects the outcome of the direct aldol reaction. It retards the initial reaction of the pyrrolidine nitrogen with acetone as the bulk increases from methyl to benzyl. When the reaction was carried out with catalysts with large α-sterics, the reactivity vanishes completely under neat conditions. These results are in accordance with the theoretical calculations by Boyd et al.,[15a] which indicate that the initial complexation between proline and acetone requires substantial energy and would inhibit further progress of the reaction. This was also reported by Maruoka et al. as one of the reasons for the increased reactivity of their bifunctional-binaphthyl based secondary amine catalyst.[11a] In this case, the absence of a substituent α- to the secondary amine group decreases steric repulsion in the enamine intermediate. It has been reported that the rate determining step of the proline catalyzed aldol reaction is the C–C bond formation and not the enamine formation.[15e] Our results indicate that with sterically hindered catalysts, the enamine formation is sufficiently slowed down and thus it becomes the rate determining step.

The majority of enamine organocatalysts containing an amide group are derived from proline carboxylate due to their ease of synthesis for example **6a**, **6b,** and **7**.[18a] For this reason, prolinamide organocatalysts are of contemporary interest. We were interested to know the behavior of amides derived from chiral pyrrolidine methylamine and achiral acids. One such sulfonamide has been used for Michael reactions.[17e] Herein we prepared carboxamides **5a** and **5b** from a chiral amine (*S*)-benzyl 2-(aminomethyl)pyrrolidine-1-carboxylate[17e] (Scheme 2).

Table 2
Pyrrolidine derivatives with different positions of the amide carbonyl[a]

No	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**5a**	60	65	10
2	**5b**	60	68	5
3[d]	**6a**	24	88	37
4[d]	**6b**	24	55	15
5[d]	**7**	24	82	21

[a] All reactions run under neat conditions at a concentration of 1.0 M solution.
[b] Isolated yield of aldol product (**A**).
[c] The ee of the (*R*)-enantiomer determined by chiral HPLC analysis.
[d] Reported[18a] using 20 mol % of catalyst.

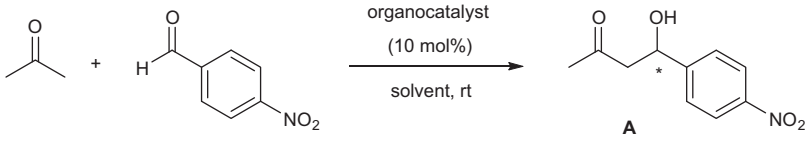
The behavior of these catalysts was then examined in direct aldol reactions under neat conditions and the results compared with those reported for analogous catalysts **6a**, **6b.** and **7**[17a] (Table 2).

It was observed that both the rate as well as the enantioselectivity decreased considerably (Table 2, entry 3 vs 1 and entry 4 vs 2) as the carbonyl group moves away from the pyrrolidine ring. It can thus be concluded that for pyrrolidine derived amide organocatalysts, the carbonyl part should derive from proline.

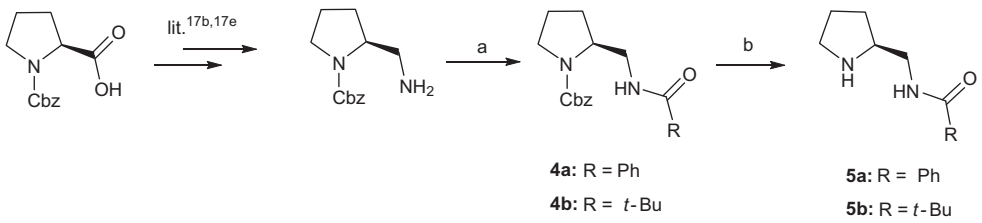
It is generally accepted that the strength of hydrogen bonding interactions increases with increasing acidity of the heteroatom–hydrogen bond involved. Unlike other pyrrolidine derivatives, the carboxamide N–H of prolinamides are weak hydrogen bond donors and in the majority of cases provide extra hydrogen bonding,[12] the addition of water or external acids[19] is used to obtain better selectivities. However, the effect of the acidity of these different hydrogen bond donors on the catalytic activity and stereoselectivity in this reaction has not been investigated in detail.[20] Therefore to study the effect of increased acidity of the carboxamide NH, imides **8a** and **8b**[17f] were chosen as catalysts. To evaluate the effect of additional hydrogen bonding, urea derivatives **9a** and **9b** were selected. Amide derivatives **10** and **11** would provide information about the more acidic functionality. All the required organocatalysts were prepared from *N*-Cbz proline as shown in Scheme 3.

These catalysts were then used in the direct aldol reaction and the results were compared with those of analogous catalysts **6a**, **6b,**[18a] and **10**[18b] (Table 3).

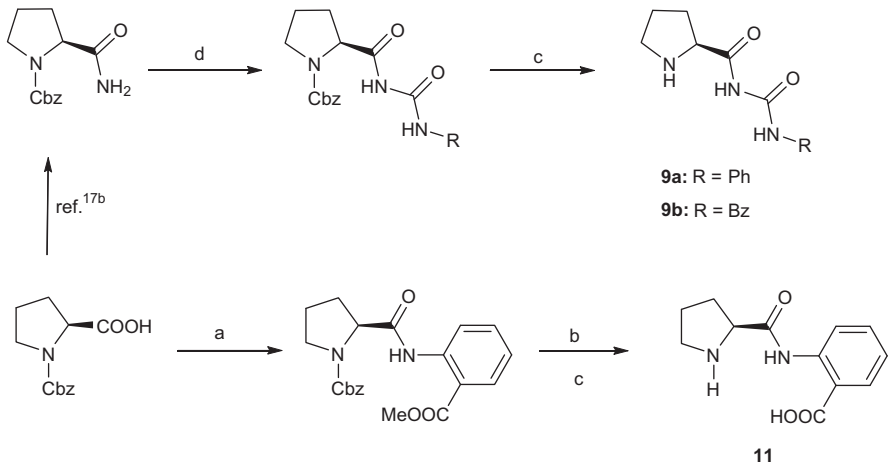
It was observed that imide **8a**, even with a higher acidity, does not catalyze the reaction while the corresponding amide **6a** gave good yields (Table 3, entry 3 vs 1). The reaction rate as well as enantioselectivity decreased considerably from **6b** to **8b** (Table 3,



Scheme 1. Representative example of a direct aldol reaction used herein.



Scheme 2. Preparation of the amides. Reagents and conditions: (a) (i) RCOCl, pyridine, $CHCl_3$, 0 °C; (b) H_2-Pd/C, MeOH.



Scheme 3. Preparation of organocatalysts. Reagents and conditions: (a) (i) EtOCOCl, Et_3N, $CHCl_3$, 0 °C; (ii) methyl 2-aminobenzoate; (b) LiOH, MeOH, 25 °C; (c) H_2-Pd/C, MeOH; (d) RNCO, toluene, reflux.

Table 3
Comparison of catalysts with varying acidities of the hydrogen bonding sites

No	Catalyst	Solvent	Time (h)	Yield[a] (%)	ee[b] (%) (conf.)
1[c]	**6a**	Neat	24	88	37 (*R*)
2[c]	**6b**	Neat	24	55	15 (*R*)
3	**8a**	Neat	120	No reaction	—
4	**8b**	Neat	36	59	<5 (*R*)
5	**9a**	Neat	24	89	31 (*R*)
6	**9a**	aq DMF[d]	72	79	39 (*R*)
7	**9b**	Neat	48	No reaction	—
8	**9b**	aq DMF[d]	48	No reaction	—
9[d]	**10**	Neat	48	21	62 (*R*)
10	**11**	Neat	48	48	52 (*S*)
11	**11**	aq DMF[e]	28	53	32 (*S*)

[a] Isolated yield of aldol product **A**.
[b] Determined by chiral HPLC analysis.
[c] Reported[18a] using 20 mol % of catalyst.
[d] Reported[18b] using 20 mol % of catalyst.
[e] 3 vol % water in DMF.

entry 2 vs 4). This finding is contradictory to the common understanding that the more acidic N–H bond in the imides should provide better catalytic efficiency than in the corresponding amides. This may be due to the complete delocalization of the imide proton forming a stable six membered intramolecular hydrogen bond with the carbonyl groups. Such an arrangement would lead to a loss in the catalytic activity. However, the good yield of the aldol product obtained in the reaction catalyzed by monoacyl urea **9a** (Table 3, entry 5 and 6) rules out this possibility. The corresponding diacyl derivative **9b** did not catalyze the reaction (Table 3, entry 7 and 8). These results support the conclusion that the effect of the hydrogen bond donors in the organocatalytic reactions is dependent on the substrates and the reaction conditions, as observed by Yan et al.[20] A few of these organoctalysts were also used employing aqueous DMF as the solvent, which leads to only a marginal improvement in the enantioselectivity (e.g. Table 3, entry 6).

With catalysts **10** and **11**, which possess a more acidic proton for hydrogen bonding, the results did not provide any convincing information. It is noteworthy that as the ring size of the hydrogen bonding interactions in the transition state increases from 7 to 8, the absolute configuration of the product changes from (*R*) to (*S*).

3. Conclusion

The design and synthesis of a nearly ideal organocatalyst involved modifications based on the original design. After screening various simple proline derivatives, we have observed that sterics at the α-position had an adverse effect on the outcome of the direct aldol reaction, which is in accordance with the results of Maruoka et al.[11a] and theoretical calculations by Boyd et al.[15a] Herein we have reported that with sterically hindered catalysts, the rate determining step shifts from C–C bond formation to enamine formation. The position of the carbonyl group in the pyrrolidine derived amides is also important and easily accessible prolinamides were found to be better than the amides of (*S*)-pyrrolidin-2-yl-methanamine. In contrast to the sulfonamide[17f] and *N*-sulfinyl prolinamides;[17g] increased acidity of the N–H of carboxamides and urea derivatives had an adverse effect on either the yield or selectivity. Our findings support the report[20] that the effect of hydrogen bond donors in the organocatalytic reactions is possibly dependent on the substrates and the reaction conditions. These results provide useful information for the development of the next generation of organocatalysts.

4. Experimental

4.1. General

All reagents and solvents were purified and dried according to the literature.[21] Organocatalysts **1c**,[17a] **2a**,[17b] **2b**,[17c] **3a**,[17d] **8a**, **8b**,[17f] *N*-Cbz-prolinamide,[17b] and (*S*)-benzyl 2-(aminomethyl)pyrrolidine-1-carboxylate[17e] were prepared according to the reported procedures. The reactions were monitored by TLC using silica gel 60 F254 pre-coated plates and were visualized with UV, in an iodine chamber or with a phosphomolybdic acid spray. The products were purified by column chromatography on silica gel (100–200 or 230–400 mesh) and characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis or HRMS. The data of the aldol products were found to be in good agreement with the reported values.[18a,c] All melting points were recorded on a Büchi B-540 electro thermal melting point apparatus and are uncorrected. Optical rotations were measured on Bellimheam + Standley ADP220 digital polarimeter and IR spectra were recorded on a Shimadzu FTIR-8400 spectrophotometer. ^{1}H spectra were recorded at 200 MHz with TMS as the internal standard and ^{13}C NMR spectra were recorded at 50 MHz with $CDCl_3$ (δ 77) or MeOH (δ 49) as the reference. Microanalysis was performed using a Carlo-Erba CHNS-0 EA 1108 elemental analyzer. HRMS were recorded on Thermoscientific *Q EXACTIVE* mass spectrometer. The enantiomeric excess was determined using a chiral column on HPLC. The absolute configuration of the aldol products was assigned from $[\alpha]_D$ values and HPLC retention times as reported in the literature.[18a]

4.2. Preparation of organocatalysts

4.2.1. Preparation of (*R*)-(2-benzylpyrrolidin-2-yl)methanol 3b

In an oven dried 25 mL side armed flask equipped with a reflux condenser, $LiAlH_4$ (230 mg, 5 mmol) was taken. It was then cooled to 0 °C and freshly distilled anhydrous tetrahydrofuran (10 mL) was added under an argon atmosphere. To the resulting suspension, (*R*)-2-benzylpyrrolidine-2-carboxylic acid[17a] (615 mg, 3 mmol) was added portionwise through a solid addition funnel. The mixture was then heated at reflux. After completion of the reaction (5 h) as indicated by TLC, it was cooled to 0 °C, diluted with tetrahydrofuran (10 mL) and quenched by the dropwise addition of 1 M NaOH (2 mL). The white solid was then removed by filtration. The filtrate and THF washings were combined together, dried over anhydrous Na_2SO_4, and concentrated to give a crude product. The residue was purified by column chromatography using methanol/dichloromethane (1:9) as the eluent to obtain **3b** (530 mg, 92%) as a white hygroscopic solid. Mp 110–112 °C; R_f (10% methanol/dichloromethane): 0.3; $[\alpha]_D^{25} = +20.5$ (*c* 1.27, $CHCl_3$); IR (Nujol) $\upsilon(cm^{-1})$: 3325, 2956, 2871, 1604, 1056; ^1H NMR ($CDCl_3$) δ: 1.40–1.86 (m, 4H), 2.46 (br s, 1H), 2.54 (br s, 1H), 2.67–3.05 (m, 4H), 3.20–3.34 (m, 2H), 7.14–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 25.6, 32.2, 42.3, 45.7, 65.5, 65.9, 126.4, 128.2, 130.2, 137.6; HRMS (ESI^+) for $C_{12}H_{17}NO$; Calculated: 192.1383 $[M+H]^+$. Found: 192.1384.

4.2.2. Preparation of (*S*)-*N*-(pyrrolidin-2-ylmethyl)benzamide 5a

4.2.2.1. (S)-Benzyl 2-(benzamidomethyl)pyrrolidine-1-carboxylate 4a. A solution of (*S*)-benzyl 2-(aminomethyl)pyrrolidine-1-carboxylate (470 mg, 2 mmol) and pyridine (1.62 mL, 20 mmol) in anhydrous $CHCl_3$ (4 mL) was cooled to 0 °C. Freshly distilled benzoyl chloride (0.27 mL, 2.2 mmol) was added dropwise and stirring continued. After completion of the reaction (30 min) as indicated by TLC, 1 M HCl (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layer was successively washed with aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL) and dried over anhydrous Na_2SO_4. It was then concentrated and the residue was purified by column chromatography using ethyl acetate: petroleum ether (1:3) as the eluent to obtain **4a** (580 mg, 86%) as a sticky mass. R_f (30% EtOAc/hexane): 0.4; $[\alpha]_D^{25} = +27.9$ (*c* 1.22, $CHCl_3$); IR (Neat) $\upsilon(cm^{-1})$: 3334, 3065, 2953, 2883, 1697, 1659, 1538, 1414, 1104; ^1H NMR ($CDCl_3$) δ: 1.70–2.22 (m, 4H), 3.31–3.72 (m, 4H), 4.09–4.34 (m, 1H), 5.05–5.32 (m, 2H), 7.22–7.55 (m, 8H), 7.84 (d, *J* = 6.32 Hz, 2H), 8.25 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.9, 29.6, 46.6, 47.0, 56.9, 67.2, 127.0, 127.7, 128.0, 128.3, 128.4, 131.1, 134.0, 136.3, 157.2, 167.4; LCMS for: $C_{20}H_{22}N_2O_3$; Calculated: 338.16 $[M+H]^+$. Found: 339.19.

4.2.2.2. (*S*)-*N*-(Pyrrolidin-2-ylmethyl)benzamide 5a. To a solution of **4a** (545 mg, 1.6 mmol) in methanol (10 mL), 10% Pd/C (80 mg) was added and stirred vigorously under the balloon-pressure of hydrogen. After completion of the reaction (8 h) as indicated by TLC, argon was bubbled through the reaction mixture and filtered through a small pad of Celite. The filtrate and the washings were concentrated and the resulting crude product was purified by filtration column chromatography using methanol/dichloromethane (1:4) as the eluent to obtain **5a** (300 mg, 92%) as a sticky mass. R_f (MeOH): 0.3; $[\alpha]_D^{25} = +29.0$ (*c* 1.0, $CHCl_3$); IR (Neat) $\upsilon(cm^{-1})$: 3303, 3060, 2958, 2871, 1639, 1603, 1538, 1303; ^1H NMR ($CDCl_3$) δ: 1.35–2.05 (m, 4H), 2.94 (t, *J* = 6.69 Hz, 2H), 3.19–3.52 (m, 3H), 3.55–3.70 (m, 1H), 7.24 (br s, 1H), 7.35–7.55 (m, 3H), 7.83 (dd, *J* = 6.66, 1.64 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 25.6, 28.9, 43.5, 46.1, 57.9, 127.0, 128.3, 131.3, 134.3, 167.6; HRMS (ESI^+) for $C_{12}H_{16}N_2O$; Calculated: 205.1335 $[M+H]^+$. Found: 205.1334.

4.2.3. Preparation of (*S*)-*N*-(pyrrolidin-2-ylmethyl)pivalamide 5b

4.2.3.1. (*S*)-Benzyl-2-(pivalamidomethyl)pyrrolidine-1-carboxylate 4b. The procedure described above for the preparation of **4a** was followed using (*S*)-benzyl 2-(aminomethyl) pyrrolidine-1-carboxylate (470 mg, 2 mmol) and pivaloyl chloride (0.28 mL, 2.2 mmol). The usual work-up gave a crude product, which was purified by column chromatography using ethyl acetate: petroleum ether (1:3) as eluent to give **4b** (550 mg, 86%) as a sticky mass. R_f (40% EtOAc/hexane): 0.4; $[\alpha]_D^{25} = -53.7$ (*c* 1.34, $CHCl_3$); IR (Neat) $\upsilon(cm^{-1})$: 3359, 2963, 1697, 1659, 1528, 1412, 1106; ^1H NMR ($CDCl_3$) δ: 1.15 (s, 9H), 1.60–2.15 (m, 4H), 3.07–3.60 (m, 4H), 4.00–4.20 (m, 1H), 5.14 (ABq, *J* = 12.38, 6.19 Hz, 2H), 7.27–7.50 (m, 6H); ^{13}C NMR ($CDCl_3$) δ: 23.9, 27.5, 29.5, 38.5, 46.0, 46.9, 56.9, 67.1, 127.8, 128.0, 128.5, 136.5, 156.9, 179.2; HRMS (ESI^+) for $C_{18}H_{26}N_2O_3$; Calculated: 319.2016 $[M+H]^+$. Found: 319.2010.

4.2.3.2. (*S*)-*N*-(Pyrrolidin-2-ylmethyl)pivalamide 5b. The procedure described above for Cbz-deprotection of **4a** was followed for **4b** (510 mg, 1.6 mmol). After stirring for 10 h, the usual work-up and purification by column chromatography using methanol/dichloromethane (1:3) as eluent gave **5b** (250 mg, 85%) as a sticky mass. R_f (methanol): 0.2; $[\alpha]_D^{25} = +8.85$ (*c* 1.21, $CHCl_3$); IR (Neat) $\upsilon(cm^{-1})$: 3338, 2956, 2873, 1640, 1535, 1402, 1212; ^1H NMR ($CDCl_3$) δ: 1.20 (s, 9H), 1.29–1.53 (m, 1H), 1.59–1.98 (m, 3H), 2.76 (br s, 1H), 2.92 (t, *J* = 6.44 Hz, 2H), 3.00–3.16 (m, 1H), 3.22–3.47 (m, 2H), 6.35 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 25.6, 27.5, 28.7, 38.6, 42.9, 43.0, 46.1, 57.9, 179.0; Analysis for: $C_{10}H_{20}N_2O$; Calculated: C, 65.18; H, 10.94; N, 15.20. Found: C, 65.40, H, 10.63, N, 15.42.

4.2.4. Preparation of (*S*)-*N*-(phenylcarbamoyl)pyrrolidine-2-carboxamide 9a

4.2.4.1. (*S*)-Benzyl 2-((phenylcarbamoyl)pyrrolidine-1-carboxylate. In an oven dried 10 mL side armed flask equipped with a reflux condenser, *N*-Cbz prolinamide (496 mg, 2 mmol) was suspended in anhydrous toluene (4 mL). Phenyl isocyanate (0.22 mL, 2 mmol) was then added under an argon atmosphere and the solution was refluxed. After completion of the reaction (40 h) as indicated by TLC, the solvent was evaporated to give a white residue, which was purified by column chromatography using ethyl acetate: petroleum ether (1:4) as eluent to give the desired product (600 mg, 82%) as a white solid. Mp 173–174 °C; R_f (25% EtOAc/PE): 0.2; $[\alpha]_D^{25} = -105.3$ (*c* 1.11, $CHCl_3$); IR (KBr) $\upsilon(cm^{-1})$: 3242, 3188, 1728, 1702, 1667, 1603, 1553, 1218, 1183; ^1H NMR ($CDCl_3$) δ: 1.86–2.42 (m, 4H), 3.40–3.71 (m, 2H), 4.30–4.58 (m, 1H), 5.17 (ABq, *J* = 12.26, 10.73 Hz, 2H), 7.05–7.55 (m, 10H), 8.71 and 9.21 (br s, 1H, rotamers), 10.36 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.7, 24.4, 29.3, 31.2, 47.0, 47.4, 61.1, 67.5, 120.3, 124.3, 128.0, 128.1, 128.4, 128.9, 136.0, 137.0, 151.1, 154.4, 155.8, 174.1, 174.8; Analysis for: $C_{20}H_{21}N_3O_4$; Calculated: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.67; H, 5.48; N, 11.60.

4.2.4.2. (*S*)-*N*-(Phenylcarbamoyl)pyrrolidine-2-carboxamide 9a. The procedure described above for the Cbz-deprotection of **4a** was followed for (*S*)-benzyl 2-((phenylcarbamoyl) carbamoyl) pyrrolidine-1-carboxylate (368 mg, 1 mmol). After stirring for 8 h and the usual work-up, **9a** (210 mg, 90%) was obtained as a white solid. Mp 78–79 °C; R_f (40% ethyl acetate/hexane): 0.2; $[\alpha]_D^{25} = -72.5$ (*c* 1.09, $CHCl_3$); IR (Nujol) $\upsilon(cm^{-1})$: 3344, 3234, 2954, 2926, 2859, 1702, 1690, 1600, 1222; ^1H NMR ($CDCl_3$) δ: 1.65–2.35 (m, 5H), 2.91–3.15 (m, 2H), 3.87 (dd, *J* = 9.35, 5.95 Hz, 1H), 7.10 (tt, *J* = 7.32, 1.33 Hz, 1H), 7.25–7.37 (m, 2H), 7.47–7.57 (m, 2H), 9.86 (br s, 1H), 10.44 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 26.0, 30.7, 47.1, 60.5, 120.1, 124.0, 128.8, 137.2, 150.2, 177.4; Analysis for $C_{12}H_{15}N_3O_2$: Calculated: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.73; H, 6.49; N, 18.04.

4.2.5. (*S*)-*N*-(Benzoylcarbamoyl)pyrrolidine-2-carboxamide 9b

4.2.5.1. (*S*)-Benzyl2-((benzoylcarbamoyl)carbamoyl)pyrrolidine-1-carboxylate. The procedure described above was followed using *N*-Cbz prolinamide (496 mg, 2 mmol) and benzoyl isocyanate[22a] (0.25 mL, 2 mmol). After refluxing for 2 h and the usual work-up followed by column chromatography using ethyl acetate: petroleum ether (1:2) as the eluent, gave the desired product (700 mg, 89%) as a white solid. Mp 63–66 °C; R_f (35% EtOAc/hexane): 0.2; $[\alpha]_D^{25} = -81.7$ (*c* 1.05, $CHCl_3$); IR (Nujol) $\upsilon(cm^{-1})$: 3189, 2947, 2922, 2852, 1774, 1703, 1675, 1599, 1181; ^1H NMR ($CDCl_3$) δ: 1.87–2.45 (m, 4H), 3.42–3.80 (m, 2H), 4.44–4.69 (m, 1H), 4.98–5.28 (m, 2H), 7.09–7.70 (m, 8H), 7.77–8.00 (m, 2H), 10.40 (br s, 1H), 10.79 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 24.4, 29.4, 29.6, 31.1, 47.0, 47.40, 61.6, 67.5, 127.3, 127.9, 128.1, 128.4, 128.9, 132.0, 133.5, 136.1, 149.4, 155.8, 166.1, 173.7; Analysis for: $C_{21}H_{21}N_3O_5$; Calculated: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.94; H, 5.48; N, 10.25.

4.2.5.2. (*S*)-*N*-(Benzoylcarbamoyl)pyrrolidine-2-carboxamide 9b. The procedure described for the Cbz-deprotection of **4a** was followed for (*S*)-benzyl 2-((benzoylcarbamoyl) carbamoyl) pyrrolidine-1-carboxylate (617 mg, 1.7 mmol). After completion of the reaction (6 h) and the usual work-up followed by column chromatographic purification using ethyl acetate/petroleum ether (1:2) as eluent, **9b** (380 mg, 86%) was obtained as a white solid. Mp 94–96 °C; R_f (40% EtOAc/PE):0.2; $[\alpha]_D^{25} = -76.4$ (*c* 1.27, $CHCl_3$); IR (Neat) $\upsilon(cm^{-1})$: 3373, 3175, 3061, 2951, 2922, 2857, 1758, 1728, 1710, 1658, 1624, 1230, 1112, 1080; ^1H NMR ($CDCl_3$) δ: 1.65–2.34 (m, 4H), 3.15–3.30 (m, 1H), 3.62–3.77 (m, 1H), 4.14 (dd, *J* = 9.10, 7.45 Hz, 1H), 6.29 (br s, 2H), 7.40–7.60 (m, 3H), 7.78–7.88 (m, 2H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.0, 27.2, 45.1, 64.6, 127.3, 128.4, 131.8, 133.2, 161.0, 170.1, 175.1; Analysis for: $C_{13}H_{15}N_3O_3$; Calculated: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.88; H, 6.09; N, 16.04.

4.2.6. Preparation of (*S*)-2-(pyrrolidine-2-carboxamido)benzoic acid 11

4.2.6.1. (*S*)-Benzyl 2-((2-(methoxycarbonyl)phenyl)carbamoyl) pyrrolidine-1-carboxylate. A solution of *N*-benzyloxycarbonyl-L-proline (1.25 g, 5 mmol) and triethylamine (0.7 mL, 5 mmol) in anhydrous $CHCl_3$ (5 mL) was cooled to 0 °C. Ethyl chloroformate (0.48 mL, 5 mmol) was then added dropwise and the resulting white suspension was stirred at 0 °C for 0.5 h. Methyl anthranilate (0.65 mL, 5 mmol) was then added and stirring was continued for 0.5 h at the same temperature. The reaction mixture was gradually warmed to room temperature and monitored by TLC. After completion of the reaction (1 h), it was diluted with dichloromethane (20 mL). The organic layer was washed successively with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using ethyl acetate: petroleum ether (1:5) as the eluent to obtain the desired product (1.5 g, 78%) as a sticky mass. R_f (20% EtOAc/PE): 0.2; $[\alpha]_D^{25} = -133.3$ (*c* 1.23, $CHCl_3$); IR (Neat) $\upsilon(cm^{-1})$: 3268, 2953, 2882, 1699, 1603, 1586, 1525, 1267, 1156, 1090; ^1H NMR ($CDCl_3$) δ: 1.85–2.40 (m, 4H), 3.50–3.90 (m, 5H), 4.37–4.59 (m, 1H), 4.95–5.31 (m, 2H), 6.99–7.60 (m, 7H), 8.01 (d, *J* = 7.83 Hz, 1H), 8.74 (t, *J* = 8.46 Hz, 1H), 11.48 and 11.61 (s,1H, rotamers); ^{13}C NMR ($CDCl_3$) δ: 23.6, 24.2, 30.3, 31.4, 46.9, 47.3, 52.2, 62.3, 67.0, 67.1, 115.3, 120.0, 120.1, 122.6, 127.7, 128.0, 128.3, 130.7, 134.4, 136.2, 136.6, 140.7, 140.9, 154.6, 155.4, 168.0, 168.4, 171.3, 171.7; HRMS (ESI^+) for $C_{21}H_{22}N_2O_5$; Calculated: 383.1601 $[M+H]^+$. Found: 383.1606.

4.2.6.2. (*S*)-2-(1-((Benzyloxy)carbonyl)pyrrolidine-2-carboxamido)benzoic acid. To a solution of (S)-benzyl 2-((2-(methoxycarbonyl)phenyl)carbanoyl)pyrrolidene-1-carboxylate (1.45 g, 3.8 mmol) in methanol (8 mL), lithium hydroxide monohydrate (319 mg, 7.6 mmol) was added and the solution was stirred at room temperature. After completion of the reaction (15 h) as indicated by TLC, the solvent was removed on a rotavapour and the residue was acidified to pH 4 using 2 M HCl. It was then extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to obtain a crude product. Purification of the product was carried out via column chromatography using ethyl acetate as the eluent to afford the desired product (1.3 g, 93%) as a white solid. Mp 62–64 °C; R_f (EtOAc): 0.3; $[\alpha]_D^{25} = -126.4$ (*c* 1.25, $CHCl_3$); IR (Nujol) $\upsilon(cm^{-1})$: 3186, 2928, 2857, 1689, 1603; ^1H NMR ($CDCl_3$) δ: 1.85–2.40 (m, 4H), 3.50–3.87 (m, 2H), 4.40–4.80 (m, 2H), 4.97–5.39 (m, 2H), 6.90–7.33 (m, 6H), 7.34–7.67 (m, 1H), 7.87 and 8.06 (d, *J* = 7.71, 1H, rotamers), 8.75 (dd, *J* = 8.34, 4.17 Hz, 1H), 11.58 (d, *J* = 7.57 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.5, 24.2, 29.6, 30.6, 31.4, 47.0, 47.4, 62.3, 67.4, 67.6, 114.5, 115.0, 120.0, 122.8, 122.9, 127.8, 128.0, 128.2, 128.4, 131.6, 131.7, 135.0, 135.9, 136.2, 141.0, 141.3, 155.1, 155.9, 170.9, 171.1, 171.2, 171.4, 171.7; HRMS (ESI^+) for $C_{20}H_{20}N_2O_5$; Calculated: 369.1445 $[M+H]^+$. Found: 369.1442.

4.2.6.3. (*S*)-2-(Pyrrolidine-2-carboxamido)benzoic acid 11. The procedure described above for the Cbz-deprotection of **4a** was followed for (*S*)-2-(1-((benzyloxy)carbonyl pyrrolidine-2-carboxamido)benzoic acid (1.29 g, 3.5 mmol). After stirring vigorously under a balloon pressure of hydrogen for 6 h, the usual work-up afforded the crude product, which was purified by a filtration column using methanol/dichloromethane (1:4) as the eluent to yield **11** (750 mg, 92%) as a white solid. Mp 240–242 °C (Lit.[22b] 225–227 °C); R_f (20% methanol/dichloromethane): 0.3; $[\alpha]_D^{25} = -84.5$ (*c* 1.04, H_2O); IR (Nujol) $\upsilon(cm^{-1})$: 3359, 2948, 2923, 2857, 1690, 1626, 1041, 1020; ^1H NMR (D_2O) δ: 2.01–2.30 (m, 3H), 2.42–2.65 (m, 1H), 3.35–3.51 (m, 2H), 4.55 (t, *J* = 7.20 Hz, 1H), 7.23 (dt, *J* = 7.58, 0.88 Hz, 1H), 7.48 (dt, *J* = 7.58, 1.52 Hz, 1H), 7.86 (dd, *J* = 7.84, 1.39 Hz, 1H), 8.02 (d, *J* = 7.83 Hz, 1H); ^{13}C NMR (D_2O) δ: 24.0, 29.3, 46.5, 60.9, 122.0, 125.2, 131.2, 133.5, 137.2, 167.5, 171.7; Analysis for: $C_{12}H_{14}N_2O_3$; Calculated: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.47; H, 6.16; N, 11.86.

4.3. Representative procedure for direct aldol reactions

A 10 mL round bottomed flask was charged with the catalyst (0.2 mmol), appropriate solvent, and acetone (0.4 mL) followed by 4-nitrobenzaldehyde (302 mg, 2 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, the solvent was evaporated on a rotavapor and the residue was redissolved in 10 mL of ethyl acetate. The organic layer was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, concentrated, and the resulting product was purified by column chromatography using ethyl acetate/pet ether (1:3) as the eluent. Characterization of the purified product was carried out by IR and ^1H NMR. The spectroscopic data were found to be in good agreement with the reported values.[18a,c] The enantiomeric excess was determined by HPLC using a Chiralcel OJ-H column and *iso*-propanol/hexane (30:70) as the mobile phase.

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