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Prolinamides derived from aminophenols as organocatalysts for asymmetric direct aldol reactions

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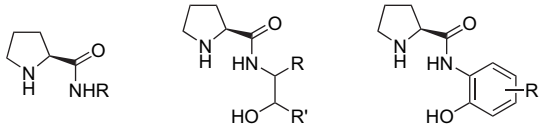
Abstract—*N*-(2-Hydroxyphenyl)-prolinamides were synthesized with the aim to introduce an additional hydrogen bonding site to the prolinamide structure. These compounds were evaluated as organocatalysts for asymmetric aldol reactions between aromatic aldehydes and cyclohexanone. Very good yields, diastereoselectivities, and enantioselectivities were achieved in both organic solvents and water. The importance of the additional hydrogen bonding site was confirmed by comparative experiments with prolinamide derivatives without the hydroxyl group.

1. Introduction



1 **2** **3**

The development of metal-free organocatalysts has emerged as a new frontier in asymmetric catalysis.[1] Since the pioneering disclosure by List and Barbas III[2] that L-proline is an effective catalyst in the intermolecular direct aldol reactions, the use of small organic molecules as catalysts has received great attentions. In recent years, L-proline and derivatives have been continuously developed for aldol and many other reactions.[3] The presence of both pyrrolidine ring and a substituent carrying at least one hydrogen bonding site are considered essential for the catalytic activities. Despite their conformity to the above rules, simple prolinamides **1** were generally observed to be inefficient catalysts for asymmetric direct aldol reactions.[4] Recently, Tang and co-workers have demonstrated that introduction of additional hydrogen bonding sites to prolinamides as in **2** can dramatically improve their performance as catalysts in asymmetric aldol reactions.[5] Other related designs based on the concept of cooperative hydrogen bonding have recently appeared in the literature.[6,7]

This research aims to develop conceptually similar, but less structurally complicated prolinamide derivatives as catalysts for asymmetric aldol reactions. We consider the aminophenol-based prolinamide **3** as a potential target. The adjacent hydroxyl and NH groups can act as hydrogen bond donors, which should help fixing the aldehyde substrate in place in the same manner as the catalyst **2**. These organocatalysts should be easily prepared from proline and aminophenols. The use of aminophenol framework allows convenient adjustment of steric and electronic properties of the hydrogen bonding sites by introduction of substituents onto the aromatic ring, which might help improving the catalytic efficiency. Very recently, Fu and co-workers have reported a similar catalyst design based on the same concept.[8] They synthesized prolinamides **3**, with and without *tert*-butyl substituents on the aminophenol moiety, and demonstrated that these compounds are good catalysts for asymmetric direct aldol reactions. Here we wish to report the results from our independent investigation.

2. Results and discussion

The prolinamide derivatives **3** bearing substituents with different steric and electronic properties were synthesized by conventional peptide coupling between Boc-L-proline and aminophenols using EDC·HCl as a coupling reagent. Deprotection of the Boc group by TFA afforded **3** in the form of TFA salt (Scheme 1). For the coupling reaction of the poorly nucleophilic 2-amino-4-chloro-5-nitrophenol,

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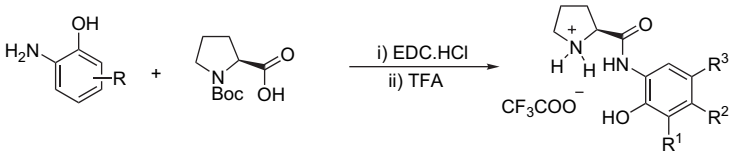
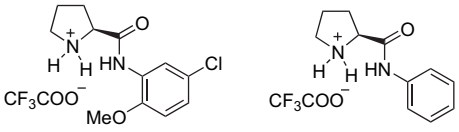


3a-3m

Scheme 1.

Boc-L-proline was pre-activated by methyl chloroformate/Et_3N rather than EDC·HCl. Aminophenols that were not commercially available were prepared by nitration of the corresponding phenols to afford *o*-nitrophenols followed by catalytic hydrogenation or tin reduction (for nitrophenol derivatives bearing halogen substituents). The yield of the prolinamide catalysts **3** is summarized in Table 1.



4a **4b**

In addition, prolinamide derivatives **4a** and **4b** lacking the *ortho*-hydroxyl group have also been prepared as controls in order to confirm the beneficial effect of the additional hydrogen bonding site.

The well-documented aldol reaction between cyclohexanone and 4-nitrobenzaldehyde was chosen as a model to test the efficacy of these catalysts. The reaction conditions were first optimized using the representative catalysts **3a** and **3b** at 10 mol % catalyst loading (Table 2). In all cases, the desired aldol product **5a** was obtained as a mixture of diastereomers, with *anti*-(1′*R*,2*S*) isomer being predominant. The enantioselectivities of the *anti* diastereomeric pairs were considerably better than that of the *syn* diastereomers. Since the *syn* diastereomers were always the minor products, the ee values of the *anti* diastereomers were primarily considered. The reaction proceeded with moderate to good enantioselectivities at room temperature (30 °C). Decreasing the reaction temperature did not result in improvement of the enantioselectivities (data not shown). A notable improvement of the enantioselectivity was observed when the TFA salt of the catalyst was used in place of the free base, although the yields were quite similar (entries 4,5 and 8,9).[9] Chloroform was found to be superior over more polar solvents. A high enantioselectivity was still obtained at very low catalyst loading (1 mol %) (entry 7). However, the yield was poor and the reaction rate was impractically slow, therefore 10 mol % was the preferred catalyst loading. The catalysts **4a** and **4b**, without the additional hydrogen bonding sites, gave much poorer yields and enantioselectivities under otherwise identical conditions. This strongly confirms the important role of the additional hydrogen bonding site in the prolinamide catalysts.

The difference in the reactivities and enantioselectivities provided by the catalysts **3a** and **3b** suggested that it might be possible to improve the catalyst further. Encouraged by these preliminary results, a series of prolinamide catalysts **3** with different (mostly electron-withdrawing) substituents were prepared and evaluated in the same model aldol reaction. The results are shown in Table 3.

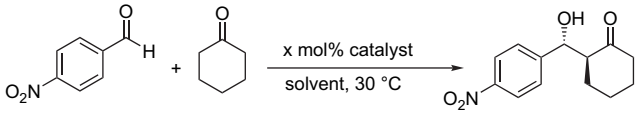
Pleasingly, most catalysts bearing one or more electron-withdrawing groups gave very high enantioselectivities (>90% ee) as well as diastereoselectivities (>90:10). The 3′-chloro-5′-fluoro catalyst **3k** was chosen for further studies on the basis of good enantioselectivity and ease of preparation in large scale. The catalyst was tested in aldol reactions

Table 1. Structure and yield of prolinamide catalysts **3** synthesized

Entry	Catalyst	R^1	R^2	R^3	Yield (%)	
					Coupling	Deprotection[a]
1	**3a**	H	H	Cl	89	80
2	**3b**	H	H	H	95	98
3	**3c**		—[b]		73	Quant.
4	**3d**	^{t}Bu	H	^{t}Bu	80	Quant.
5	**3e**	H	H	^{t}Bu	90	90
6	**3f**	H	H	NO_2	79	84
7	**3g**	H	H	CO_2Et	87	92
8	**3h**	H	CF_3	H	85	96
9	**3i**	Cl	H	H	75	96
10	**3j**	Cl	H	Cl	82	95
11	**3k**	Cl	H	F	75	92
12	**3l**	F	H	F	76	88
13	**3m**	H	NO_2	Cl	78	94

[a] As trifluoroacetate salt.
[b] The aminophenol used was 1-amino-2-naphthol.

Table 2. Optimization conditions for the direct aldol reaction catalyzed by **3**

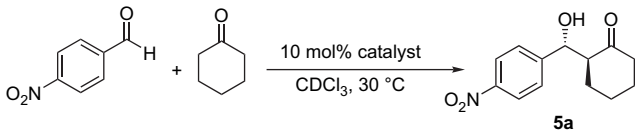


5a

Entry	Catalyst	Loading (mol %)	Time (h)	Solvent	Yield[a] (%)	dr[b] (*anti*:*syn*)	% ee[b] *anti*(*syn*)
1	**3a**[c]	10	44	THF	92	80:20	75 (50)
2	**3a**[c]	10	48	DMF	63	73:27	70 (50)
3	**3a**[c]	10	48	EtOH	78	79:21	74 (34)
4	**3a**[c]	10	29	$CHCl_3$	93	85:15	84 (61)
5	**3a**[d]	10	29	$CHCl_3$	95	90:10	91 (7)
6	**3a**[d]	5	48	$CHCl_3$	89	93:7	94 (24)
7	**3a**[d]	1	48	$CHCl_3$	41	88:12	93 (5)
8	**3b**[c]	10	72	$CHCl_3$	92	76:24	68 (47)
9	**3b**[d]	10	72	$CHCl_3$	93	86:14	89 (36)
10	**4a**[d]	10	29	$CHCl_3$	47	96:14	65 (13)
11	**4b**[d]	10	72	$CHCl_3$	41	77:23	66 (6)

[a] Isolated yield of mixture of all four diastereomers.
[b] Determined by chiral HPLC (Chiralpak AD-H column, 90:10 hexanes/isopropanol, 0.5 mL/min, detected at 245 nm).
[c] Free base form.
[d] TFA salt.

Table 3. Evaluation of prolinamide derivatives **3** as catalysts for the model asymmetric aldol reaction

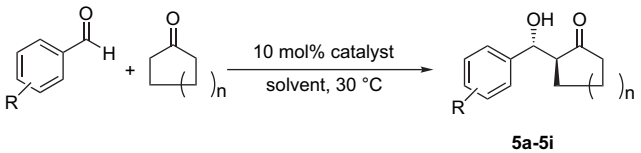


5a

Entry	Catalyst[a]	Time (h)	Yield[b] (%)	dr[c] (*anti*:*syn*)	% ee[c] *anti*(*syn*)
1	**3a**	29	95	90:10	91 (7)
2	**3b**	72	87	86:14	89 (34)
3	**3c**	72	75	80:20	78 (27)
4	**3d**	72	68	78:22	79 (17)
5	**3e**	72	87	86:14	89 (34)
6	**3f**[d]	144	90	87:13	92 (23)
7	**3g**	42	86	90:10	90 (12)
8	**3h**	40	92	93:7	92 (10)
9	**3i**	29	91	93:7	95 (7)
10	**3j**	29	90	91:9	92 (13)
11	**3k**	29	93	91:9	96 (30)
12	**3l**	29	93	93:7	94 (7)
13	**3m**	29	89	91:9	90 (1)

[a] All catalysts were in the form of TFA salts.
[b] Isolated yield of mixture of all four diastereomers.
[c] Determined by chiral HPLC (Chiralpak AD-H column, 90:10 hexanes/isopropanol, 0.5 mL/min, detected at 245 nm).
[d] The reaction was inhomogeneous due to the poor solubility of the catalyst in the reaction media. All other reactions were homogeneous.

Table 4. Evaluation of the prolinamide derivative **3k** as catalyst for asymmetric aldol reactions



5a-5i

Entry	Product	R	*n*	Solvent	Time (h)	Yield[a] (%)	dr[b] (*anti*:*syn*)	% ee[b] *anti*(*syn*)
1	**5a**	4-O_2N	2	$CHCl_3$	29	93	93:7	94 (7)
2	**5b**	2-O_2N	2	$CHCl_3$	48	82	95:5	95 (75)
3	**5c**	4-NC	2	$CHCl_3$	48	96	86:14	91 (16)
4	**5d**	4-Cl	2	$CHCl_3$	72	75	89:11	88 (10)
5	**5e**	4-Br	2	$CHCl_3$	72	83	88:12	89 (3)
6	**5f**	4-H	2	$CHCl_3$	72	71	81:19	81 (7)
7	**5a**	4-O_2N	2	H_2O	24	91	94:6	97 (35)
8	**5b**	2-O_2N	2	H_2O	48	65	97:3	97 (67)
9	**5c**	4-NC	2	H_2O	48	91	91:9	96 (59)
10	**5d**	4-Cl	2	H_2O	72	70	88:12	94 (24)
11	**5e**	4-Br	2	H_2O	72	71	90:10	93 (55)
12	**5f**	4-H	2	H_2O	72	68	88:12	90 (29)
13	**5g**	4-O_2N	1	$CHCl_3$	29	96	33:67	79 (67)
14	**5g**	4-O_2N	1	H_2O	48	78	49:51	79 (33)
15	**5h**	4-O_2N	3	$CHCl_3$	72	30	61:39	37 (22)
16	**5i**	4-O_2N	—[c]	$CHCl_3$	48	65	—	69

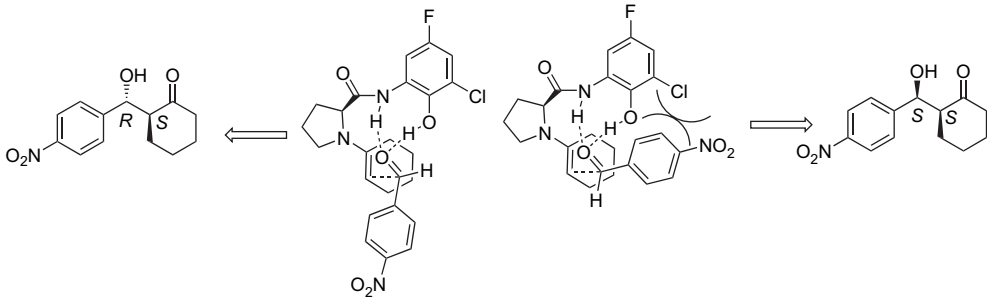
[a] Isolated yield of mixture of all four diastereomers.
[b] Determined by chiral HPLC. Absolute and relative configurations were assigned by analogy.
[c] Acetone was used as the ketone component.

between different aromatic aldehyde acceptors and ketone donors. Due to a widespread successful use of water as a reaction medium for similar reactions,[10] it was decided to conduct reactions in water for comparison purposes. The results are shown in Table 4.

In general, in addition to 4-nitrobenzaldehyde, other aromatic aldehydes were also good substrates for aldol reactions with cyclohexanone catalyzed by the prolinamide catalyst **3k**. The best enantioselectivities were obtained with aldehyde substrates carrying strong electron-withdrawing groups. The reactions performed in water gave consistently better ee values (90–97%) compared to that in chloroform (81–95%). However, the yields of the reactions in water tended to be lower than in chloroform. Other ketones including cyclopentanone, cycloheptanone, and acetone were poor substrates for the aldol reaction catalyzed by **3k**. This is possibly a consequence of the rather more flexibility of the enamine intermediates.

A transition state model analogous to that described earlier[8,11] was proposed in order to explain the sense of asymmetric induction. The transition state A leading to the 1′*R*,2*S* product should be more favored than the transition state B (1′*S*,2*S*). The other two transition states involving the alternative *syn*-enamine intermediate leading to the 1′*S*,2*R* and 1′*R*,2*R* products were expected to be of substantially higher energy and therefore less favored (Scheme 2).[11]

The results are in good agreement with earlier findings[7,8] that the presence of additional hydrogen bond donors can have beneficial effect to the prolinamide-catalyzed aldol reactions. The main advantages of these aminophenol-based prolinamide systems include the ease of synthesis and the ability to provide high diastereo- and enantioselectivities even at ambient temperature. The performance of the catalysts can be further fine tuned by appropriate substituents on the aromatic ring. The enantioselectivity and diastereoselectivities obtained are better than proline or simple prolinamides and, in many cases, are competitive with other catalysts with more complex design.



Scheme 2.

3. Conclusions

A series of prolinamides derived from 2-aminophenols were synthesized and evaluated as organocatalysts for asymmetric aldol reactions. Very good yields, diastereoselectivities (up to 95:5 *anti*:*syn*), and enantioselectivities (up to 95% ee in favor of the *anti*-(1′*R*,2*S*) isomer) were achieved for asymmetric aldol reactions between aromatic aldehydes and cyclohexanone catalyzed by these proline derivatives. Improved enantioselectivities (up to 97% ee), with the expense of yield, were observed when the reaction medium was changed from chloroform to water.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 melting point apparatus and were uncorrected. Optical rotations were measured on a Jasco P-1010 Polarimeter. Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-400 plus operating at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. Elemental analysis was performed on a CHNS/O Analyzer (Perkin–Elmer PE2400 Series II) at Scientific and Technological Research Equipment Center, Chulalongkorn University.

Chemicals were purchased from standard suppliers and were used as received. Commercial grade solvents for column chromatography were distilled before use. Solvents for the reactions were of AR grade and used without further purification. Unless otherwise stated, all reactions were performed in oven-dried glasswares under ambient conditions.

4.2. General protocol for the synthesis of prolinamide catalysts 3

The 2-aminophenol derivative (1.5 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (1.5 mmol) was added. After the solution was stirred for 5 min, *N*-Boc-L-proline (1.5 mmol) and EDC·HCl (1.6 mmol) were added and the reaction mixture was stirred overnight. The resulting solution was washed with water and the solvent removed under reduced pressure. The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent. The *N*-Boc-L-prolinamide derivative (0.7 mmol) was then dissolved in 1:1 trifluoroacetic acid/dichloromethane (2 mL) and left for 2 h at 30 °C. The organic solvent was removed by rotary evaporation to afford the product as trifluoroacetate salt.

The compounds **3b**–**3d** and **4b** have been previously prepared and their characterization data reported elsewhere.[4,7b,8]

4.2.1. Pyrrolidine-2-carboxylic acid (5′-chloro-2′-hydroxy-phenyl)-amide trifluoroacetate (3a). Brown solid (0.319 g, 71% two steps); mp 155.7–158.9 °C, $[\alpha]_D^{25}$ −28.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 [m, 3H, CH_aH$_b$(3) and CH_2(4)], 2.35 [m, 1H, CH$_a$$H_b$(3)], 3.25 (m, 2H, C$H_2$N), 4.51 (m, 1H, C*H*N), 6.91 [d, *J*=8.8 Hz, 1H, Ar-*H*(3)], 7.01 [dd, *J*=8.8, 2.0 Hz, 1H, Ar-*H*(4)], 7.93 [d, *J*=2.0 Hz, 1H, Ar-*H*(6)], 8.70 and 9.30 (br, pyrrolidine NH), 9.97 (amide NH), 10.57 (OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 [*C*H$_2$(4)], 30.4 [*C*H$_2$(3)], 46.4 (*C*H$_2$N), 60.0 (*C*HN), 117.6 (q, $^1J_{CF}$=298.4 Hz, *C*F$_3$ TFA), 116.9 (aromatic *C*H), 122.1 (aromatic *C*H), 122.4 (aromatic *C*H), 125.0 (aromatic *C*H), 126.9 (aromatic *C*H), 147.5 (aromatic *C*H), 158.8 (q, $^2J_{CF}$=30.9 Hz, *C*O TFA), 168.0 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3443 (br), 1667 (s), 1550 (m), 1427 (w), 1197 (m), 1137 (w); Anal. Calcd for $C_{13}H_{14}ClF_3N_2O_4$: C, 44.02; H, 3.98; N, 7.90. Found: C, 44.05; H, 3.92; N, 7.93%.

4.2.2. Pyrrolidine-2-carboxylic acid (5′-*tert*-butyl-2′-hydroxy-phenyl)-amide trifluoroacetate (3e). White solid (0.169 g, 81% two steps); mp 120.2–123.8 °C, $[\alpha]_D^{25}$ −23.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 9H, 3×CH_3), 1.92 [m, 3H, CH_aH$_b$(3) and CH_2(4)], 2.36 [m, 1H, CH$_a$$H_b$(3)], 3.24 (m, 2H, C$H_2$N), 4.49 (m, 1H, C*H*N), 6.81 [d, *J*=8.4 Hz, 1H, Ar-*H*(3)], 6.99 [dd, *J*=8.4, 2.4 Hz, 1H, Ar-*H*(4)], 7.87 [d, *J*=2.4 Hz, 1H, Ar-*H*(6)], 8.70 and 9.40 (br, pyrrolidine NH), 9.77 and 9.79 (amide NH and OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2 [*C*H$_2$CH$_2$(4)], 30.4 [*C*H$_2$(3)], 31.8 (3×*C*H$_3$), 34.3 [*C*(CH$_3$)$_3$], 46.4 (*C*H$_2$N), 60.1 (*C*HN), 117.7 (q, $^1J_{CF}$=298.8 Hz, *C*F$_3$ TFA), 115.3 (aromatic *C*H), 120.1 (aromatic *C*H), 122.5 (aromatic *C*H), 124.9 (aromatic *C*H), 141.5 (aromatic *C*H), 146.4 (aromatic *C*H), 158.5 (q, $^2J_{CF}$=30.9 Hz, *C*O TFA), 167.6 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3279 (br), 2963 (m), 1669 (s), 1562 (m), 1523 (w), 1429 (w), 1386 (w), 1199 (s), 1135 (m); Anal. Calcd for $C_{17}H_{23}F_3N_2O_4$: C, 54.25; H, 6.16; N, 7.44. Found: C, 54.08; H, 6.18; N, 7.45%.

4.2.3. Pyrrolidine-2-carboxylic acid (2′-hydroxy-5′-nitro-phenyl)-amide trifluoroacetate (3f). Yellow solid (0.215 g, 66% two steps); mp 205.8–208.2 °C, $[\alpha]_D^{25}$ −25.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95 [m, 3H, CH_aH$_b$(3) and CH_2(4)], 2.35 [m, 1H, CH$_a$$H_b$(3)], 3.26 (m, 2H, C$H_2$N), 4.57 (m, 1H, C*H*N), 7.07 [d, *J*=8.8 Hz, 1H, Ar-*H*(3)], 7.95 [dd, *J*=8.8, 2.4 Hz, 1H, Ar-*H*(4)], 8.91 [d, *J*=2.4 Hz, 1H, Ar-*H*(6)], 9.20 (br, pyrrolidine NH), 10.20 (br, amide NH), 12.20 (br, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 [*C*H$_2$(4)], 30.4 [*C*H$_2$(3)], 46.4 (*C*H$_2$N), 60.0 (*C*HN), 115.4 (aromatic *C*H), 117.5 (q, $^1J_{CF}$=297.3 Hz, *C*F$_3$ TFA), 117.7 (aromatic *C*H), 122.0 (aromatic *C*H), 126.1 (aromatic *C*H), 139.3 (aromatic *C*H), 155.1 (aromatic *C*H), 158.9 (q, $^2J_{CF}$=31.4 Hz, *C*O TFA), 168.4 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3439 (br), 3153 (br), 1670 (s), 1599 (m), 1551 (m), 1340 (m), 1292 (m), 1199 (m), 1135 (w); Anal. Calcd for $C_{13}H_{14}F_3N_3O_6$: C, 42.75; H, 3.86; N, 11.50. Found: C, 42.77; H, 3.89; N, 11.55%.

4.2.4. Pyrrolidine-2-carboxylic acid (2′-hydroxy-5′-ethoxycarbonyl-phenyl)-amide trifluoroacetate (3g). White solid (0.253 g, 80% two steps); mp 179.8–181.6 °C (dec), $[\alpha]_D^{25}$ −22.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (t, *J*=6.8 Hz, 3H, OCH$_2$CH_3), 1.90 [m, 3H, CH_aH$_b$(3) and CH_2(4)], 2.36 [m, 1H, CH$_a$$H_b$(3)], 3.28 (m, 2H, C$H_2$N), 4.23 (q, *J*=6.8 Hz, 2H, OCH_2CH$_3$), 4.55 (m, 1H, C*H*N), 7.02 [d, *J*=8.4 Hz, 1H, Ar-*H*(3)], 7.62 [d, *J*=8.4 Hz, 1H, Ar-*H*(4)], 8.52 [s, 1H, Ar-*H*(6)], 9.30 (br, pyrrolidine NH), 10.00 (amide NH), 11.30 (OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.7 (OCH$_2$*C*H$_3$), 24.0 [*C*H$_2$(4)],

30.4 [CH_2(3)], 46.3 (CH_2N), 60.0 (*C*HN), 60.7 (OCH_2CH_3), 115.5 (aromatic *C*H), 117.5 (q, $^1J_{CF}$=296.6 Hz, *C*F_3 TFA), 120.7 (aromatic *C*H), 124.1 (aromatic *C*H), 125.6 (aromatic *C*H), 127.5 (aromatic *C*H), 153.4 (aromatic *C*H), 159.3 (q, $^2J_{CF}$=31.1 Hz, *C*O TFA), 165.9 (*C*O ester), 168.0 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3440 (br), 3129 (br), 1667 (s), 1607 (m), 1561 (m), 1449 (w), 1386 (w), 1276 (m), 1189 (m), 1135 (m); Anal. Calcd for $C_{16}H_{19}ClF_3N_2O_6$: C, 48.98; H, 4.88; N, 7.14. Found: C, 48.99; H, 4.88; N, 7.12%.

4.2.5. Pyrrolidine-2-carboxylic acid (2′-hydroxy-4′-trifluoromethyl-phenyl)-amide trifluoroacetate (3h). White solid (0.186 g, 82% two steps); mp 205.5–207.7 °C (dec), $[\alpha]_D^{25}$ −35.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 [m, 3H, CH_aH_b(3) and CH_2(4)], 2.38 [m, 1H, CH$_a$$H_b$(3)], 3.27 (m, 2H, C$H_2$N), 4.55 (m, 1H, C*H*N), 7.16 [d, *J*=8.0 Hz, 1H, Ar-*H*(5)], 7.18 [s,1H, Ar-*H*(3)], 8.11 [d, *J*=8.0 Hz, 1H, Ar-*H*(6)], 9.00 (br, pyrrolidine NH), 10.10 (amide NH), 11.08 (OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.1 [CH_2(4)], 30.4 [CH_2(3)], 46.4 (CH_2N), 60.1 (*C*HN), 111.8 (aromatic *C*H), 116.2 (aromatic *C*H), 117.3 (q, $^1J_{CF}$=129.1 Hz, *C*F_3 TFA), 122.5 (aromatic *C*H), 124.5 (q, $^1J_{CF}$=270.0 Hz, *C*F_3), 125.4 (q, $^2J_{CF}$=31.7 Hz, aromatic *C*H), 129.6 (aromatic *C*H), 148.6 (aromatic *C*H), 158.8 (q, $^2J_{CF}$=31.1 Hz, *C*O TFA), 168.3 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3435 (br), 3160 (br), 1670 (s), 1618 (m), 1556 (m), 1428 (m), 1343 (m), 1191 (m), 1122 (m); Anal. Calcd for $C_{14}H_{14}F_6N_2O_4$: C, 43.31; H, 3.63; N, 7.22. Found: C, 43.52; H, 3.68; N, 7.14%.

4.2.6. Pyrrolidine-2-carboxylic acid (3′-chloro-2′-hydroxy-phenyl)-amide trifluoroacetate (3i). White solid (0.238 g, 96% two steps); mp 110.3–113.2 °C (dec), $[\alpha]_D^{25}$ −39.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 [m, 3H, CH_aH_b(3) and CH_2(4)], 2.36 [m, 1H, CH$_a$$H_b$(3)], 3.24 (m, 2H, C$H_2$N), 4.49 (m, 1H, C*H*N), 6.85 [t, *J*=8.0 Hz, 1H, Ar-*H*(5)], 7.19 [d, *J*=8.0 Hz, 1H, Ar-*H*(4)], 7.60 [d, *J*=8.0 Hz, 1H, Ar-*H*(6)], 8.90 and 9.40 (br, pyrrolidine NH), 9.80 (amide NH), 10.08 (OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.1 [CH_2(4)], 35.2 [CH_2(3)], 51.4 (CH_2N), 65.0 (*C*HN), 117.9 (q, $^1J_{CF}$=298.2 Hz, *C*F_3 TFA), 125.5 (aromatic *C*H), 126.7 (aromatic *C*H), 128.1 (aromatic *C*H), 131.7 (aromatic *C*H), 132.7 (aromatic *C*H), 160.7 (aromatic *C*H), 163.5 (q, $^2J_{CF}$=30.7 Hz, *C*O TFA), 173.2 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3442 (br), 1680 (s), 1602 (w), 1546 (w), 1459 (w), 1201 (m), 1139 (m); Anal. Calcd for $C_{13}H_{14}ClF_3N_2O_4$: C, 44.02; H, 3.98; N, 7.90. Found: C, 44.03; H, 4.00; N, 7.94%.

4.2.7. Pyrrolidine-2-carboxylic acid (3′,5′-dichloro-2′-hydroxy-phenyl)-amide trifluoroacetate (3j). White solid (0.259 g, 78% two steps); mp 150.2–152.3 °C (dec), $[\alpha]_D^{25}$ −34.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89 [m, 2H, CH_2(4)], 1.97 [m, 1H, CH_aH_b(3)], 2.32 [m, 1H, CH$_a$$H_b$(3)], 3.23 (m, 2H, C$H_2$N), 4.49 (m, 1H, C*H*N), 7.34 [s, 1H, Ar-*H*(4)], 7.82 [s, 1H, Ar-*H*(6)], 9.30 (br, pyrrolidine NH and amide NH), 10.20 (OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 [CH_2(4)], 30.2 [CH_2(3)], 46.4 (CH_2N), 60.0 (*C*HN), 117.6 (q, $^1J_{CF}$=298.1 Hz, *C*F_3 TFA), 122.1 (aromatic *C*H), 122.5 (aromatic *C*H), 123.3 (aromatic *C*H), 125.5 (aromatic *C*H), 128.9 (aromatic *C*H), 144.5 (aromatic *C*H), 158.8 (q, $^2J_{CF}$=31.1 Hz, *C*O TFA), 168.5 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3434 (br), 3172 (br), 1669 (s), 1591 (m), 1547 (m), 1420 (w), 1318 (w), 1184 (m), 1137 (m); Anal. Calcd for $C_{13}H_{13}Cl_2F_3N_2O_4$: C, 40.12; H, 3.37; N, 7.20. Found: C, 40.18; H, 3.37; N, 7.30%.

4.2.8. Pyrrolidine-2-carboxylic acid (3′-chloro-5′-fluoro-2′-hydroxy-phenyl)-amide trifluoroacetate (3k). Brown solid (0.240 g, 69% two steps); mp 151.9–154.1 °C (dec), $[\alpha]_D^{25}$ −44.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 [m, 3H, CH_aH_b(3) and CH_2(4)], 2.35 [m, 1H, CH$_a$$H_b$(3)], 3.25 (m, 2H, C$H_2$N), 4.54 (m, 1H, C*H*N), 7.16 [d, $^3J_{HF}$=8.0 Hz, 1H, Ar-*H*(4)], 7.67 (d, $^3J_{HF}$=10.0 Hz, 1H, Ar-*H*(6)], 8.70 (br, pyrrolidine NH), 9.88 (amide NH), 10.23 (OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 [CH_2(4)], 30.3 [CH_2(3)], 46.3 (CH_2N), 60.0 (*C*HN), 109.0 (d, $^2J_{CF}$=27.2 Hz, aromatic *C*H), 112.6 (d, $^2J_{CF}$=26.1 Hz, aromatic *C*H), 117.5 (q, $^1J_{CF}$=297.0 Hz, *C*F_3 TFA), 122.2 (d, $^3J_{CF}$=12.9 Hz, aromatic *C*H), 128.9 (d, $^3J_{CF}$=12.3 Hz, aromatic *C*H), 141.7 (aromatic *C*H), 154.8 (d, $^1J_{CF}$=235.6 Hz, aromatic *C*H), 159.0 (q, $^2J_{CF}$=33.7 Hz, *C*O TFA), 168.5 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3446 (br), 3262 (br), 1672 (s), 1609 (m), 1552 (m), 1480 (m), 1446 (m), 1322 (w), 1198 (s), 1134 (m); Anal. Calcd for $C_{13}H_{13}ClF_4N_2O_4$: C, 41.89; H, 3.52; N, 7.52. Found: C, 41.90; H, 3.57; N, 7.52%.

4.2.9. Pyrrolidine-2-carboxylic acid (3′,5′-difluoro-2′-hydroxy-phenyl)-amide trifluoroacetate (3l). White solid (0.2195 g, 67% two steps); mp 166.7–168.8 °C (dec), $[\alpha]_D^{25}$ −40.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 [m, 3H, CH_aH_b(3) and CH_2(4)], 2.36 [m, 1H, CH$_a$$H_b$(3)], 3.25 (m, 2H, C$H_2$N), 4.55 (m, 1H, C*H*N), 7.04 [m, 1H, Ar-*H*(4)], 7.54 (m, 1H, Ar-*H*(6)], 8.80 and 9.30 (br, pyrrolidine NH), 10.21 (2H, amide NH and OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 [CH_2(4)], 30.4 [CH_2(3)], 46.4 (CH_2N), 60.0 (*C*HN), 100.4 (dd, $^2J_{CF}$=27.0, 23.5 Hz, aromatic *C*H), 104.9 (d, $^2J_{CF}$=27.3 Hz, aromatic *C*H), 117.7 (q, $^1J_{CF}$=298.0 Hz, *C*F_3 TFA), 128.8 (aromatic *C*H), 132.8 (d, $^3J_{CF}$=16.5 Hz, aromatic *C*H), 151.5 (dd, $^2J_{CF}$=237.9, $^3J_{CF}$=14.9 Hz, aromatic *C*H), 154.2 (dd, $^1J_{CF}$=233.4, $^3J_{CF}$=12.3 Hz, aromatic *C*H), 158.6 (q, $^2J_{CF}$=30.8 Hz, *C*O TFA), 168.3 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3154 (br), 1671 (s), 1625 (m), 1562 (m), 1500 (w), 1463 (m), 1379 (w), 1237 (m), 1184 (s), 1135 (m); Anal. Calcd for $C_{13}H_{13}ClF_5N_2O_4$: C, 43.83; H, 3.68; N, 7.86. Found: C, 44.03; H, 3.99; N, 7.94%.

4.2.10. Pyrrolidine-2-carboxylic acid (5′-chloro-2′-methoxy-phenyl)-amide trifluoroacetate (4a). White solid (0.243 g, 82% two steps); mp 185.5–186.9 °C, $[\alpha]_D^{25}$ −28.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 [m, 3H, CH_aH_b(3) and CH_2(4)], 2.34 [m, 1H, CH$_a$$H_b$(3)], 3.26 (m, 2H, C$H_2$N), 3.83 (s, 3H, OC$H_3$), 4.55 (m, 1H, C*H*N), 7.08 [d, *J*=8.8 Hz, 1H, Ar-*H*(3)], 7.17 [dd, *J*=8.8, 2.4 Hz, 1H, Ar-*H*(4)], 7.99 [d, *J*=2.4 Hz, 1H, Ar-*H*(6)], 9.10 (br, pyrrolidine NH), 10.09 (amide N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0 [CH_2(4)], 30.4 [CH_2(3)], 46.3 (CH_2N), 56.6 (OCH_3), 60.0 (*C*HN), 113.3 (aromatic *C*H), 117.6 (q, $^1J_{CF}$=296.6 Hz, *C*F_3 TFA), 122.0 (aromatic *C*H), 124.2 (aromatic *C*H), 125.1 (aromatic *C*H), 127.9 (aromatic *C*H), 149.2 (aromatic *C*H), 158.9 (q, $^2J_{CF}$=27.3 Hz, *C*O TFA), 168.2 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3275 (m), 2991 (w), 1673 (s), 1601 (m), 1545 (s), 1485 (m), 1425 (w), 1318 (w), 1201 (s), 1131(s); Anal. Calcd for

$C_{14}H_{16}ClF_3N_2O_4$: C, 45.60; H, 4.37; N, 7.60. Found: C, 45.67; H, 4.35; N, 7.61%.

4.2.11. Pyrrolidine-2-carboxylic acid (5′-chloro-2′-hydroxy-4′-nitro-phenyl)-amide trifluoroacetate (3m).

N-Boc-L-proline (0.323 g, 1.5 mmol) and triethylamine (210 μL, 1.5 mmol) were dissolved in THF. To the solution was added dropwise methylchloroformate (116 μL, 1.5 mmol) at 0 °C over a period of 15 min. After the solution was stirred for 30 min at 0 °C, 2-amino-4-chloro-5-nitrophenol (0.283 g, 1.5 mmol) was added dropwise over a period of 15 min. The resulting solution was stirred at 0 °C for 1 h and at room temperature overnight. The solution was diluted with ethyl acetate and washed with water, any solids were filtered off, and the residue was dried in vacuo. The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent. The Boc-protected intermediate was obtained as a yellow oil (0.451 g, 78%). This material (0.270 g, 0.7 mmol) was treated with TFA (1 mL) to obtain the final product as a yellow solid (0.263 g, 94%); mp 206.1–208.9 °C (dec), $[\alpha]_D^{25}$ −33.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 [m, 3H, CH_aH$_b$(3) and CH_2(4)], 2.35 [m, 1H, CH$_a$$H_b$(3)], 3.27 (m, 2H, C$H_2$N), 4.62 (m, 1H, C*H*N), 7.61 [s, 1H, Ar-*H*(3)], 8.33 [s, 1H, Ar-*H*(6)], 9.20 (br, pyrrolidine NH), 10.38 (amide N*H*), 11.80 (br, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2 [*C*H$_2$(4)], 30.6 [*C*H$_2$(3)], 46.7 (*C*H$_2$N), 60.4 (*C*HN), 117.8 (q, *J*=297.3 Hz, *C*F$_3$ TFA), 112.6 (aromatic *C*H), 116.1 (aromatic *C*H), 123.1 (aromatic *C*H), 131.9 (aromatic *C*H), 142.7 (aromatic *C*H), 147.6 (aromatic *C*H), 159.2 (q, *J*=31.7 Hz, *C*O TFA), 169.2 (*C*O amide); IR (KBr, ν_{max}, cm^{-1}): 3143 (br), 1673 (s), 1589 (m), 1549 (s), 1390 (m), 1345 (m), 1264 (w), 1192 (s), 1138 (m); Anal. Calcd for $C_{13}H_{14}ClF_3N_3O_6$: C, 39.06; H, 3.28; N, 10.51. Found: C, 39.18; H, 3.23; N, 10.52%.

4.3. General procedure for the direct aldol reaction in $CHCl_3$

The L-prolinamide derivatives (0.05 mmol) and corresponding aldehyde (0.5 mmol) were stirred in 2 mL of chloroform/cyclohexanone (1:1) at 30 °C. The reaction mixture was stirred for 29–72 h. The mixture was treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with hexanes/ethyl acetate.

4.4. General procedure for the direct aldol reaction in water

The L-prolinamide derivative (0.05 mmol) and the aldehyde (0.5 mmol) were stirred in 1 mL of water at 30 °C, and then cyclohexanone (1.0 mmol) was added. The reaction mixture was stirred for 24–72 h. The mixture was extracted with ethyl acetate (2×5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with hexanes/ethyl acetate.

The aldol products **5a–5i** are known compounds. Spectroscopic data of all the aldol products synthesized in this work were consistent with those reported in the literature: **5a**,[7c,8,5b,10f,g] **5b**,[7c,8,10f,g] **5c**,[7c,10f,g] **5d**,[7c,8,10f,g] **5e**,[7c,10f,g] **5f**,[7c,10f,g] **5g**,[5b,10f,g] **5h**,[10f,g] **5i**.[5b,10f,g]

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Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **3a**, **3e–3m**, **4a** and chiral HPLC chromatograms of aldol products **5a–5i** are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.086.

References and notes

1. Reviews: (a) Schreiner, P. *Chem. Soc. Rev.* **2003**, *32*, 289–296; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, 3726–3748; (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, 5138–5175; (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.
2. (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
3. Reviews: (a) List, B. *Synlett* **2001**, 1675–1686; (b) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (c) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591.
4. Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755–5760.
5. (a) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289; (b) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263.
6. Reviews: (a) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579; (b) Pihco, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064.
7. (a) Shi, L.-X.; Sun, Q.; Ge, Z.-M.; Zhu, Y.-Q.; Cheng, T.-M.; Li, R.-T. *Synlett* **2004**, 2215–2217; (b) Tanimori, S.; Naka, T.; Kirihata, M. *Synth. Commun.* **2004**, *34*, 4043–4048; (c) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543–4545; (d) Raj, M.; Vishnumaya; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097–4099; (e) Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263–1266; (f) He, L.; Jiang, J.; Tang, Z.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2007**, *18*, 237–242; (g) Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2754–2760; (h) Zheng, J.-F.; Li, Y.-X.; Zhang, S.-Q.; Yang, S.-T.; Wang, X.-M.; Wang, Y.-Z.; Bai, J.; Liu, F.-A. *Tetrahedron Lett.* **2006**, *47*, 7793–7796; (i) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198–8202.
8. Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351–3357.

9. Beneficial effects of protic additive in prolinamide-catalyzed reactions have been previously observed: (a) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197–208; (b) Gryko, D.; Zimnicka, M.; Lipinski, R. *J. Org. Chem.* **2007**, *72*, 964–970.
10. (a) Giacalonea, F.; Gruttadauria, M.; Marculescua, A. M.; Noto, R. *Tetrahedron Lett.* **2007**, *48*, 255–259; (b) Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108–2119; (c) Majewski, M.; Niewczas, I.; Palyam, N. *Synlett* **2006**, 2387–2390; (d) Cheng, C.-L.; Wei, S.-Y.; Sun, J. *Synlett* **2006**, 2419–2422; (e) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653–4655; (f) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734–735; (g) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420.
11. (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283; (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.