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Highly Diastereo- and Enantioselective Aldol Reactions in Common Organic Solvents Using *N*-Arylprolinamides as Organocatalysts with Enhanced Acidity

Jarugu Narasimha Moorthy*[a] and Satyajit Saha[a]

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A broad set of *N*-arylprolinamides **1**–**8** with increasing NH acidity and steric crowding has been synthesized and its catalytic activity explored for enantioselective aldol reactions. In DMF containing 10 mol-% of TFA, all arylamides are found to catalyze the reaction between cyclohexanone and a variety of electrophilic aldehydes leading to aldols in excess of 90 % yield and >95 % enantioselectivity. The perfluorophenyl catalyst **8** is found to perform best with a broad substrate scope as compared to all other *N*-arylamides **1**–**7**. It is shown that **8** can indeed be employed in highly nonpolar as well as polar solvents including brine to afford high yields of aldols with excellent diastereo- as well as enantioselectivity. The results observed for **8** are amongst the best reported so far for prolinamides that do not contain additional stereogenic center(s) and hydrogen-bonding site(s). The molecular structures of **7** and **8**, determined by X-ray crystallography and presumed to reflect the most stable conformations, reveal a notable difference in the conformations of the *N*-aryl rings; the aryl ring exhibits tendency to lie coplanar with the amide functionality in the case of **7**, while the perfluorophenyl ring twists almost orthogonally with respect to the plane of the amide of functionality in **8**. The superior performance of the latter is attributed to, in addition to the enhanced NH acidity, the tendency of the perfluorophenyl ring to lie orthogonally to the amide group, which may facilitate a stronger binding of the electrophilic aldehyde via hydrogen bonding in the transition state.

Introduction

There is a growing interest at the current time in organocatalytic reactions to accomplish enantioselective C–C bond forming reactions,[1] as the environmentally-benign organocatalysts obviate the use of copious amounts of organometallic hazardous and scarce counterparts. A wide variety of catalysts are constantly being developed to provide a facile and atom economic access to optically pure compounds.[2] Insofar as the C–C bond forming enantioselective reactions are concerned, asymmetric aldol reaction holds a special significance from the following points of view: i) the reaction may be catalyzed by a base as well as an acid, ii) it affords 1,3-dioxygenated products, which may be further structurally elaborated, and iii) the reaction offers a challenge, with appropriate reaction partners, to control diastereochemistry as well as enantioselectivity at the same time.[3] Not surprisingly, this reaction constitutes one of the immensely investigated amongst C–C bond forming reactions in the realm of organocatalysis. Since the pioneering work of List et al.,[4] who demonstrated the use of L-proline in catalyzing the direct aldol reaction of *p*-nitrobenzaldehyde with acetone, a number of organocatalysts that function based on the principle of the so-called "enamine catalysis" have been reported.[5] Although the acidic proton of the carboxylic group of proline is responsible for enantioselectivity in aldol reactions, it is sufficiently clear that the carboxylic acid group is not indispensable for catalysis. A variety of pyrrolidine-based organocatalysts that are devoid of carboxyl groups have been designed and shown to be efficient.[6] The underpinning requirement in these catalysts is that they must possess functional groups or molecular moieties,[1] which may involve in hydrogen bonding interactions.[7] Of course, highly acidic hydrogen atoms,[8] additional hydrogen bonding sites[9] and additional stereogenic centres[10] contribute to high differentiation in the diastereomeric transition states.

In the course of our studies on hydrogen bond-mediated molecular self-assembly and hydrogen bond-controlled photochemical Norrish Type II processes,[11] our interest was drawn toward exploiting hydrogen bonding in organocatalysis. With organocatalytic enantioselective photochemical reactions as our primary goal, we designed a broad set of *N*-aryl-L-prolinamides with graded NH acidity and varying magnitudes of steric crowding around the amide functionality. The initial studies by Gong et al.[12] on enantioselective aldol reactions using *N*-arylprolinamides as organocatalysts prompted us to examine the extent to which the various catalysts in Figure 1 catalyze the aldol reaction enantioselectively. Motivations for these investigations were:

[a] Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India
E-mail: moorthy@iitk.ac.in

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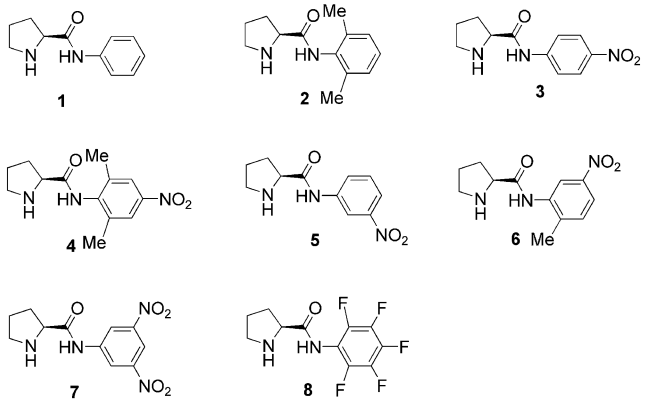


Figure 1. Structures of various prolinamides **1**–**8** examined for enantioselective aldol reactions.

(i) The enantioselectivities observed by Gong et al.[12] are not significantly high with simple prolinamides, e.g., *ee* ca. 50% for the aldol product of *p*-nitrobenzaldehyde and acetone, which leaves ample scope for further improvement.

(ii) Very simple proline derivatives are rarely reported to yield aldol products with high (>90%) enantioselectivity as well as diastereoselectivity.[13] It is the bifunctional proline derivatives or those that contain additional stereogenic centre(s) that are often found to catalyze aldol reactions leading to products with enantioselectivity in excess of 95%.[14] Thus, the catalytic activity of simple proline derivatives was deemed still underexplored.

(iii) The aryl rings of *N*-aryl-L-prolinamides could be anticipated in some way to interfere with the diastereomeric transition states of the aldol reaction such that it manifests in enantio- as well as diastereocontrol.

Herein, we report facile synthesis of *N*-aryl-L-prolinamides **1**–**8** and results of enantioselective aldol reactions catalyzed by them. It is shown that all arylamides **1**–**8** enantioselectively catalyze the aldol reactions. In particular, the reactions proceed with catalyst **8** in a variety of common organic solvents to afford aldol products in a high diastereo- and enantioselectivity (>96%) and in significantly reduced reaction times (20–36 h); the enhancement of amide NH acidity and careful screening of reaction conditions are the basis for observed stereoselectivities.

Results and Discussion

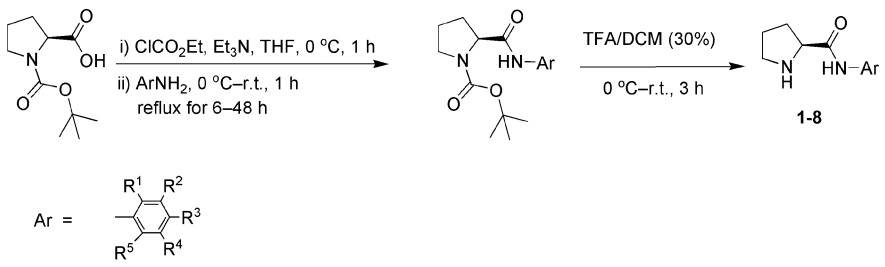
Synthesis of *N*-Aryl-L-prolinamides 1–8

All arylprolinamides **1**–**8** were synthesized starting from Boc-protected L-proline, which was treated with ethyl chloroformate in THF in the presence of Et_3N at 0 °C to afford the mixed anhydride (Scheme 1). The latter was treated with substituted amines to afford Boc-protected *N*-aryl-L-prolinamides, the deprotection of which under standard conditions involving 30% TFA in DCM at 0 °C led to *N*-aryl-L-prolinamides **1**–**8** in respectable overall yields.

Screening of the Catalytic Activity of *N*-Arylamides in Various Solvents

To establish the solvent and temperature conditions that promote the reactivity as well high enantioselection, the arylamide **6** with a moderate steric influence as well as acidity was considered as a representative case. The catalytic reactivity of **6** was examined for the aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone in a variety of solvents with or without an additive as shown in Table 1. In a typical experiment, 0.3–0.4 mmol of *p*-nitrobenzaldehyde was treated with cyclohexanone in the presence of 20 mol-% of the catalyst. After monitoring the reaction at various temperatures, 3 ± 1 °C was uniformly maintained for the reaction in various solvents and/or additives as shown in Table 1. The progress of reaction in each case was monitored by TLC as well as HPLC analyses.

A perusal of the results in Table 1 shows that the reaction occurs in a variety of solvents, but faster in DMF containing 10 mol-% of TFA; in the latter, the reaction also leads to a high enantioselectivity. The aldol product was isolated, after 36 h, in >90% yield with the *anti* product being

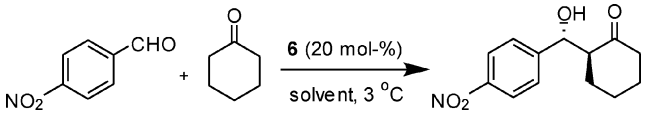


1: $R^1 = R^2 = R^3 = R^4 = R^5 = H$
2: $R^2 = R^3 = R^4 = H$; $R^1 = R^5 = CH_3$
3: $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = NO_2$
4: $R^2 = R^4 = H$; $R^1 = R^5 = CH_3$; $R^3 = NO_2$
5: $R^1 = R^2 = R^3 = R^5 = H$; $R^4 = NO_2$
6: $R^2 = R^3 = R^5 = H$; $R^1 = CH_3$; $R^4 = NO_2$
7: $R^1 = R^3 = R^5 = H$; $R^2 = R^4 = NO_2$
8: $R^1 = R^2 = R^3 = R^4 = R^5 = F$

Scheme 1.

formed in ca. 96% *ee* (entry 9); although similar enantioselectivity was observed in THF and dioxane, the reaction times were found to be much longer. Surprisingly, the reaction was found to be slower with 20 mol-% TFA in DMF in addition to the fact that the enantioselectivity was comparably lower (entry 8). This critical dependence of reaction as well as enantioselectivity on the mol-% of TFA employed is quite inexplicable. What is otherwise noteworthy is that the catalyst works in a variety of solvents and solvent combinations, with the exception of DMF/H_2O (entry 14), leading to the aldol product with ≥ 80% *ee* for the *anti* diastereomer. Although high diastereo- and enantioselectivities were observed in dioxane and THF solvents, the reaction times were much longer (entries 5 and 10, Table 1). Thus, the solvent-additive combination involving DMF-TFA (10 mol-%) was considered singularly exceptional for examining the organocatalytic activity of all other *N*-arylprolinamides in Figure 1 for performing aldol reactions.

Table 1. Results of *N*-arylprolinamide **6**-catalyzed aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in various solvents with/without an additive.[a]



Entry	Solvent	Additive	Time [h]	Yield [%]	*dr*[b] [*anti*/*syn*]	*ee* [%][c]
1	none	–	74	94	82:18	87
2	H_2O	–	76	85	80:20	87
3	DCM	–	76	70	90:10	92
4	DMSO	–	76	70	84:16	85
5	dioxane	–	76	62	97:3	93
6	toluene	–	76	68	90:10	83
7	DMF	–	74	62	82:18	87
8	DMF	TFA(20 mol-%)[d]	74	71	87:13	90
9	**DMF**	**TFA(10 mol-%)**[d]	**36**	**92**	**97:3**	**96**
10	THF	–	76	75	96:4	93
11	DCM	PhCOOH (10%) [d]	76	90	85:15	83
12	DME	–	76	87	68:32	79
13	2-propanol	–	76	84	84:16	80
14	DMF	H_2O[e]	76	90	84:16	67

[a] The reactions in all solvents were run under identical conditions by employing 20 mol-% of the catalyst **6** (relative to the aldehyde). The reactions were run on 0.3–0.4 mmol of *p*-nitrobenzaldehyde, and the reaction temperature was maintained at 3 ± 1 °C. [b] From 400-MHz ^{1}H NMR spectroscopy. [c] Based on chiral HPLC analyses for the major diastereomer. [d] Based on *p*-nitrobenzaldehyde. [e] DMF/H_2O = 1:1.

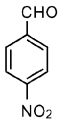
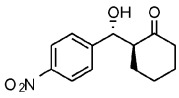
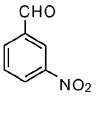
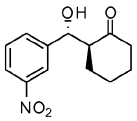
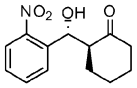
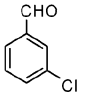
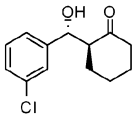
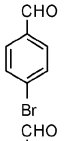
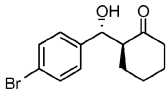
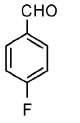
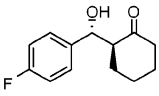
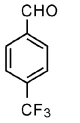
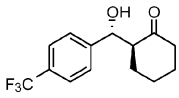
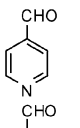
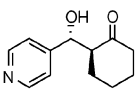
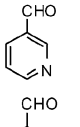
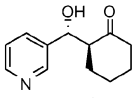
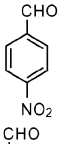
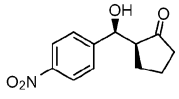
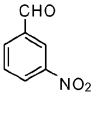
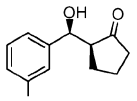
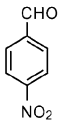
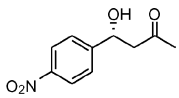
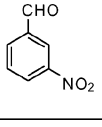
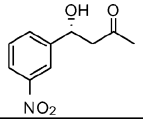
Results of Enantioselective Aldol Reactions Catalyzed by *N*-Arylamides 1–8

To begin with, the reaction between cyclohexanone and *p*-nitrobenzaldehyde with *N*-arylprolinamides **1**–**8** was examined with 20 mol-% of the catalyst in DMF/TFA (10 mol-%) at 3 ± 1 °C. Typically, the reactions were conducted for 36 h by employing ca. 0.5 mmol of *p*-nitrobenzaldehyde and 20 equiv. of cyclohexanone in DMF. Subsequent to a routine work-up, the crude product was analyzed by ^{1}H NMR analysis. For analysis of the enantiomeric excess, the crude product was rapidly filtered through a short pad of silica gel and the product mixture was submitted to HPLC. Thus, the diastereomeric ratio (*anti*/*syn*) and *ee* (for the major diastereomer) in each case were determined by ^{1}H NMR (see Supporting Information) and HPLC analyses, respectively. The values given in Table 2 are based on two or more independent determinations. As can be seen from Table 2, the aldol product was obtained in 75% yield with an *ee* of 77% for *N*-phenylprolinamide **1** (entry 1, Table 2). The reaction progressed sluggishly with the sterically hindered 2,6-dimethylphenylprolinamide **2** leading to a mere 20% yield of the product (entry 2). Otherwise, all other catalysts, i.e., *p*-(nitrophenyl)prolinamide **3**, *m*-(nitrophenyl)prolinamide **5**, 3,5-dinitrophenylprolinamide **7**, *N*-(perfluorophenyl)prolinamide **8** and sterically hindered 2,6-dimethyl-4-nitrophenylprolinamide **4** were found to catalyze the reaction and afford the aldols in 95–97% *ee* (entries 3–8). A comparison of the results with catalyst **1**, **2** and **4** clearly shows that steric hindrance retards the reaction, while enhancement of the acidity through substitution of nitro group(s) overrides the steric factor. A similar scenario was uniformly observed for the reaction of cyclohexanone in the presence of catalysts **3**–**8** with a variety of aldehydes that include *m*- and *o*-nitrobenzaldehydes, *m*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *p*-fluorobenzaldehyde and *p*-(trifluoromethyl)benzaldehyde (entries 9–20 and SI); in view of better results with **7** and **8** only the results for these catalysts are shown in Table 2. With the exception of *p*-bromo and *p*-fluorobenzaldehydes, the yields of aldols in all cases were in excess of ca. 72%; for bromo- and fluorobenzaldehydes, the isolated yields were in the range of 40–64% (entries 15–18). Remarkably, the enantioselectivity for most cases was found to be >95%. In particular, with (3,5-dinitrophenyl)- (**7**) and (perfluorophenyl)prolinamide (**8**) catalysts, both diastereo- and enantioselectivities (>95%) were found to be higher for all aldols of cyclohexanones with diverse aldehydes. Indeed, **7** and **8** were found to catalyze the reactions of cyclohexanone with heteroaromatic aldehydes, viz., pyridine-3-carboxaldehyde and pyridine-4-carboxaldehyde, quite rapidly leading to the formation of aldols in 70–90% isolated yields within 3–4 h; of course, the enantioselectivity in each case was found to be in excess of >85% (entries 21–24).

The reaction of cyclopentanone with *p*-nitrobenzaldehyde in the presence of catalysts **1**–**8** over a period of 36 h, under similar conditions as described above, led to comparatively lower yields of aldols. As for cyclohexanone, a high enantioselectivity was observed with the perfluorophenylprolinamide **8** (entry 26). A similar trend was observed for the reaction of cyclopentanone with *m*-nitrobenzaldehyde as well (entries 27 and 28).

The encouraging results described above for the aldol reaction of cyclopentanone and cyclohexanone spurred us to test the catalytic activity of **3**–**8** in mediating the aldol reaction between acyclic acetone and *p*- and *m*-nitrobenzalde-

Table 2. Results of enantio- and diastereoselective aldol reactions catalyzed by *N*-arylprolinamides **1**–**8** in DMF containing 10 mol-% of TFA.[a]

Entry	Ketone	Aldehyde	Catalyst	Time [h]	Product	Yield [%]	*dr*[b]	*ee* [%][c]
1			**1**	36		75	96:4	77
2			**2**	36		20	93:7	68
3			**3**	36		88	97:3	96
4			**4**	36		84	98:2	96
5			**5**	36		90	99:1	97
6			**6**	36		92	98:2	96
7			**7**	36		88	98:2	95
8			**8**	**36**		**88**	**98:2**	**98**
9			**7**	36		86	97:3	95
10			**8**	**36**		**88**	**98:2**	**98**
11			**7**	36		80	99:1	97
12			**8**	**36**		**86**	**99:1**	**98**
13			**7**	70		88	94:6	94
14			**8**	**70**		**90**	**98:2**	**96**
15			**7**	86		64	99:1	96
16			**8**	**86**		**62**	**99:1**	**98**
17			**7**	62		44	99:1	96
18			**8**	**62**		**42**	**99:1**	**96**
19			**7**	50		79	98:2	96
20			**8**	**50**		**76**	**96:4**	**96**
21			**7**	3		87	97:3	96
22			**8**	**3**		**86**	**98:2**	**97**
23			**7**	4		72	98:2	85
24			**8**	**4**		**70**	**98:2**	**90**
25			**7**	36		77	32:68	89
26			**8**	**36**		**76**	**34:66**	**95**
27			**7**	36		90	36:64	86
28			**8**	**36**		**84**	**36:64**	**95**
29			**1**	36		68		71
30			**3**	36		76		72
31			**4**	36		72		72
32			**5**	36		74		72
33			**6**	36		74		71
34			**7**	36		78		72
35			**8**	**36**		**80**		**90**
36			**8**	**22**		**69**		**90**

[a] All reactions were run on a 0.5–0.7 mmol scale with 20 mol-% of the catalyst in 0.8–1.5 mL of DMF containing 10 mol-% of TFA. The temperature was uniformly maintained at 3 ± 1 °C. [b] The diastereomeric ratios were calculated based on integrations of the diagnostic signals of the *syn* and *anti* diastereomers in the ^{1}H NMR spectra of the crude reaction mixture. [c] The *ee* values were calculated from HPLC profiles of the reaction mixtures, see text; the *ee* values reported are for the major enantiomer.

hydes. Under similar reaction conditions, i.e., DMF-TFA (10 mol-%) at 3 ± 1 °C and 20 mol-% of catalyst loading, the aldols were obtained in 68–80% isolated yields (entries 29–35). With the exception of catalyst **8**, the *ee* values for all other catalysts, i.e., **3**–**7**, were found to be 71–73%. The fact that the enantioselectivity does not vary significantly in spite of varying magnitudes of steric factors associated with **3**–**6** indicates that NH acidity plays a pivotal role. For catalyst **8**, a remarkably high enantioselectivity was observed (entry 35). While further enhancement of acidity is definitely one reason for the increase in enantioselectivity, the conformational factors associated with the perfluorophenyl ring in **8** vis-à-vis nitro-substituted phenyl rings in **3**–**7** may also contribute to the observed difference in the enantioselectivities, vide infra. Similar to the reaction of acetone with *p*-nitrobenzaldehdye, a high enantioselectivity was observed in the presence of **8**, for the reaction with *m*-nitrobenzaldehyde as well (entry 36).[15]

N-(Perfluorophenyl)prolinamide Reactions in Nonpolar as well as Polar Solvents

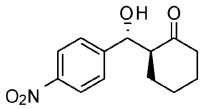
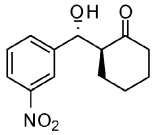
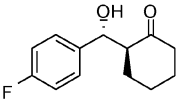
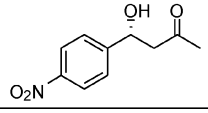
We were encouraged by the high diastereo- and enantiodifferentiation observed with perfluorophenylprolinamide **8** to explore its potential in common organic solvents. Thus, the catalytic behavior of **8** was examined for the reaction of cyclohexanone and *p*-nitrobenzaldehyde in diverse solvents that include nonpolar hexane/toluene, polar aprotic acetonitrile and polar protic solvents such as methanol, water, etc. at two different temperatures, i.e., 3 ± 1 and 22 ± 1 °C, for 36 and 20 h, respectively, Table 3; it should be noted that TFA as an additive was mandatory, lest the reactions were found to occur slowly. The results collected in Table 3 show that the catalyst works in all solvents, but in varying isolated yields of the products and enantio- and diastereoselectivities. In particular, the aldols were isolated in >95%

Table 3. Results of *N*-(perfluorophenyl)prolinamide-catalyzed aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in various solvents.[a]

Entry	Solvent	Temp. [°C]	Time [h]	Yield [%][d]	*dr*[b]	*ee* [%][c]
1	cyclohexane	3	36	88	98:2	95
2		**22**	**22**	**95**	**95:5**	**94**
3	dichloromethane	3	36	86	98:2	95
4		**22**	**22**	**92**	**93:7**	**93**
5	acetonitrile	**22**	**22**	**88**	**95:5**	**93**
6	toluene	3	20	76	98:2	93
7	water	3	20	79	98:2	96
8	brine	3	20	75	99:1	97
9		**22**	**22**	**97**	**99:1**	**96**
10		**33**	**24**	**96**	**96:4**	**94**
11	methanol	3	40	72	99:1	95
12		**22**	**22**	**82**	**95:5**	**96**
13	ethyl formate	3	40	80	98:2	94
14		**22**	**22**	**95**	**95:5**	**93**

[a] The reactions in all solvents were run under identical conditions by employing 20 mol-% of the catalyst **8** (relative to the aldehyde) with 10 mol-% TFA as an additive. The reactions were run on 0.4 mmol of *p*-nitrobenzaldehyde at the temperature shown. [b] *anti*/*syn* was determined by 400-MHz ^{1}H NMR spectroscopy. [c] Based on HPLC analyses using chiral column; the *ee* values are for the major enantiomer. [d] Isolated yields of both diastereomers.

Table 4. Results of aldol reactions catalyzed by *N*-(perfluorophenyl)prolinamide **8** at room temp. (22 ± 1 °C) in cyclohexane and brine.[a]

Entry	Product	Solvent	Time [h]	Yield [%][b]	*dr* [*anti*:*syn*][c]	*ee* [%][d]
1		cyclohexane	20	95	94:6	92
2		**brine**	**20**	**97**	**96:4**	**97**
3		cyclohexane	20	96	95:5	92
4		**brine**	**20**	**95**	**96:4**	**97**
5		cyclohexane	72	74	94:6	94
6		**brine**	**72**	**76**	**97:3**	**96**
7		cyclohexane	36	40(64)[e]	–	76(80)[e]
8		**brine**	**36**	**45(36)**[e]	–	**79(83)**[e]

[a] The reactions were run under identical conditions on 0.4 mmol of the aldehyde by employing 20 mol-% of the catalyst **8** (relative to the aldehyde) and10 mol-% TFA as an additive. [b] Isolated yields of both diastereomers. [c] *anti*/*syn* was determined by 400 MHz ^{1}H NMR spectroscopy. [d] Based on HPLC analyses using chiral AD-H column; the *ee* values are for the major enantiomer. [e] At 3 ± 1 °C. For reactions at 22 ± 1 °C, poor yield was due to the formation of elimination product at the employed conditions of the reaction.

within 20 h in cyclohexane and brine at 22 °C (entries 2, 9 and 10); it should be noted that the reaction in brine was biphasic.[16] The loss of enantio- and diastereoselectivity was found to be only marginal for a considerable reduction in the duration of the reaction. Hence, the aldol reactions of a select few ketones and aldehydes were conducted at room temp. (22 ± 1 °C) with 20 mol-% of **8** and 10 mol-% of TFA in cyclohexane and brine, cf. Table 4.

The aldol products of the reaction of cyclohexanone with *m*- and *p*-nitrobenzaldehydes were obtained in >95% isolated yields in 20 h with impressive optical purities (entries 1–4, Table 4). Even for a poor substrate such as *p*-fluorobenzaldehyde, the aldol product was obtained in 74% isolated yield with >94% *ee* in both cyclohexane and brine (entries 5 and 6, Table 4). Under the employed conditions of the reaction, the reaction of acetone with *p*-nitrobenzaldehyde was found to lead to significant amounts of elimination product (entries 7 and 8). The aldol was obtained in ca. 40–45% yield in both cyclohexane and brine with ca. 76–79% *ee*; indeed, no respectable improvement was observed when the reactions were run for the two solvents at 3 °C (entries 7 and 8). Clearly, the novelty of catalyst **8** is evident from its enhanced reactivity as well as solubility in a range of solvents; while the former facilitates occurrence of reactions rapidly at room temp., the latter renders, in appropriate solvents, the work-up quite simple.

X-ray Crystal Structure Determinations of *N*-Arylprolinamides 7 and 8

We determined the crystal structures of *N*-arylamides **7** and **8** to gauge variations in the structures of the two catalysts; the crystals were readily grown by slow evaporation of their solutions in MeOH and diethyl ether, and the X-ray intensity data were collected, cf. SI. In Figure 2 are shown the X-ray determined molecular structures of **7** and **8**. A striking difference between the two structures is that the 3,5-dinitrophenyl ring is virtually coplanar with the amide moiety (–CONH–) moiety in the case of **7** (6.58°), while the perfluorophenyl ring is twisted by ca. 76.15° in **8**. Except for this feature, all other geometrical parameters are unexceptional. Given that fluorine is isosteric with hydrogen,[17] it is intriguing that the conformation of perfluorophenyl ring in **8** differs so drastically as compared to the conformation of 3,5-dinitrophenyl ring in **7**.

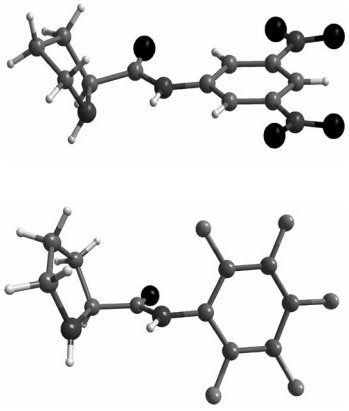


Figure 2. Perspective views of the structures of *N*-prolinamides **7** (top) and **8** (bottom). Notice that the 3,5-dinitrophenyl ring in **7** is coplanar with the amide functionality, while the perfluorophenyl ring is nearly orthogonal in **8**.

Mechanistic Rationalization of Enantioselectivity

As mentioned at the outset, Gong et al. first showed that the stereoselectivity in aldol reactions increases as the electron-withdrawing nature of the substituent in *N*-arylprolinamide increases.[12] They also showed that prolinamide derivatives that contain additional stereogenic centre(s) and hydrogen bonding site(s) lead to a very high stereocontrol in aldol reactions.[12] Subsequent to these findings, simple *N*-arylprolinamides have been further modified and their catalytic activity has been explored in aldol reactions.[8] While our investigations with *N*-arylamides were in progress, Shirai et al. reported *N*-arylamides as organocatalysts with enhanced acidity for enantioselective aldol reactions.[18] Indeed, Shirai et al. also examined the catalytic behavior of catalysts **3** and **8** in addition to 2,4,6-trinitro derivative of **1**.[18] However, we note that the results reported by them suffer from several drawbacks. First of all, the solvent employed for demonstrating high stereocontrol is hazardous HMPA. Second, the reaction durations are considerably longer, >90 h. Third, their investigations are limited to branched acyclic ketones, and broad substrate scope was not illustrated. Finally, the potential of *N*-(perfluorophenyl)prolinamide was explored only little, if any. In contrast, the results described herein, which hinge on a careful screening of solvent and reactions conditions, highlight several following advantages of *N*-arylamides as organocatalysts for aldol reactions:

(i) The ease of synthesis starting from Boc-L-proline and arylamines makes *N*-arylamides particularly attractive organocatalysts.

(ii) All *N*-arylamides **1**–**8** function as catalysts, and those with high NH acidity, i.e., **7** and **8** effect high diastereo- and enantiodiscrimination (>95%). Indeed, the results observed for **8** surpass those reported so far for *simple* prolinamide derivatives and are comparable to those of the organocatalysts of much more structural complexity.[8,9,14]

(iii) The catalyst **8**, in particular, can be employed in both nonpolar as well as polar common organic solvents. The reactions in solvents such as cyclohexane/brine obviate the tedious work-up leading to facile isolation of the aldol products.

(iv) For heteroaromatic aldehydes as electrophilic counterparts, the reactions go to completion in such short durations as 3–4 h.

(v) The catalyst **8** works efficiently at room temp. (22 ± 1 °C) with only a marginal sacrifice of the enantio- and diasteroselectivity. Only very few catalysts are known that work at room temp. to afford aldol products with >90% enantiopurity.[10a,10e,16a]

Why is it that (perfluorophenyl)prolinamide performs best of all *N*-arylprolinamides investigated in the present study? Aside from the enhanced acidity, we believe, as mentioned earlier, that the differences in the conformations of the aryl rings in **3**–**7** and **8** may also contribute to the observed outcome. The structural attributes available from X-ray single crystal structure determinations may shed some light on the enamine catalysis. More often than not, the conformationally-flexible molecules are found to exist in the solid state in or near lowest-energy conformations.[19] Based on this premise, one observes a perceptible difference in the conformations of **7**, a representative case for sterically unhindered **1**, **3**, **5**–**7** and **8**, for which the X-ray structures were determined. As can be seen in Figure 2, the 3,5-dinitrophenyl ring is almost coplanar with the amide functionality in **7**, while the perfluorophenyl ring is twisted almost orthogonally with respect to the amide group in the case of **8**. We have analyzed the crystal structures of compounds that contain acyclic *N*-phenylcarboxamide moiety deposited in the Cambridge Structural Database (CSD). In several *N*-arylamides that are closely related to **7** and **8** and do not contain any alkyl groups at ortho positions, the aryl ring is found to be near coplanar with the amide moiety; of course, for *N*-arylamides that contain 2,6-dimethyl substituents, the aryl ring is found to be nearly orthogonal. The angles between the plane comprised of the amide moiety (CON atoms) and the aryl ring are found to vary within 0–40°, see Supporting Information. Clearly, the aryl rings in secondary *N*-arylamides tend to exploit conjugative stabilization via overlap with the *p*-orbitals of the amide functionality. In contrast, the near orthogonality (ca. 76.15°) observed in **8** suggests that the loss of stability through extended conjugation of the perfluorophenyl ring with the amide group is not significant in this case. Presumably, the highly electron-withdrawing nature of fluorine renders loss of conjugation with the nitrogen *p*-orbital, which is already involved in a primary electronic effect with the carbonyl of the amide group, less meaningful.[20] This difference in the geometries of the aryl rings around the amide functionalities in **1**, **3**, **5**–**7** vis-à-vis **8** presumably translates into the corresponding transition state geometries for the aldol reactions. The fact that the reactions of all substrates proceed with comparatively higher stereoselectivities with **8**, when compared to **7**, suggests that the perfluorophenyl ring may exhibit conformational flexibility to facilitate better binding of the electrophilic aldehyde via hydrogen bonding with the amide NH group; of course, the enhanced acidity is definitely a chief factor. Presumably, the twisting of the perfluorophenyl ring allows the aromatic aldehyde to be castled in the transition state via N–H···O hydrogen bond more comfortably around *N*-arylamide functionality (Figure 3); notice the *anti* geometry for the enamine in the presumed transition state structures.[4c] For all other arylamides, i.e., **1**–**7**, the varying amounts of steric crowding between the aldehyde and the coplanar aryl ring of the catalyst may not permit such strong binding as in **8** leading to manifest in considerable reduction in the stereocontrol for some substrates, cf. Figure 3. Further, it is also likely that weak interactions due to the perfluorophenyl ring (C–H···F, π···π, etc.)[21] in **8** also abet the transition state structure in some way.

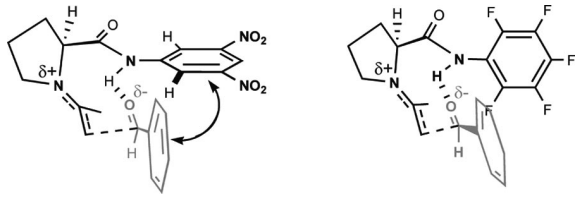


Figure 3. The proposed transition state geometries for the aldol reactions with catalysts **7** (left) and **8** (right).

Conclusions

A broad set of secondary *N*-arylprolinamides **1**–**8** with increasing NH acidity and steric crowding has been synthesized in a facile manner and its catalytic activity explored for enantioselective aldol reactions. It is shown from that in DMF containing 10 mol-% of TFA, all catalysts with moderate to high NH acidity catalyze the reaction between cyclohexanone and a variety of electrophilic aldehydes leading to aldols in excess of 90% yield and >95% enantioselectivity. However, catalyst **8** performs best with a broad substrate scope as compared to all other *N*-arylamides **1**–**7**. Indeed, the simple and readily accessible catalyst **8** can be employed in highly nonpolar as well as polar solvents including brine to afford high yields of aldols with excellent diastereo- as well as enantioselectivity, and the results uncovered for **8** are among the best reported so far for prolinamides.[13,16] The X-ray determined molecular structures of **7** and **8**, which are presumed to reflect the most stable conformations, reveal a notable difference in the conformations of the *N*-aryl rings in that the aryl ring exhibits tendency to lie coplanar with the amide functionality in the case of **7**, while the perfluorophenyl ring twists almost orthogonally with respect to the plane of the amide of functionality in **8**. The superior performance of the latter is attributed to, in addition to the enhanced NH acidity, the tendency of the perfluorophenyl ring to lie orthogonal to the amide group, which may facilitate a stronger binding of the electrophilic aldehyde via hydrogen bonding in the transition state.

Experimental Section

General: 2,6-Dimethylaniline, 2,6-dimethyl-4-nitroaniline, and 3,5-dinitroaniline were prepared by following the literature-reported procedures. Other arylamines like aniline, 4-nitroaniline, perfluoroaniline, 2-methyl-5-nitroaniline, and 3-nitroaniline are commercially available and were used as such.

General Procedure for the Preparation of Catalysts 1–8: To a two-necked round-bottomed flask containing Boc-L-proline (2.54 g, 11.8 mmol) in 30 mL dry THF was added TEA (1.19 g, 11.8 mmol) under N_2 atmosphere. The resultant solution was cooled to 0 °C. Subsequently, ethyl chloroformate (1.27 g, 11.8 mmol) was introduced dropwise over a period of 30 min. After the solution was stirred at this temperature for 1 h, aniline (1.0 g, 10.7 mmol) was

added, under N_2 atmosphere, in small portions. The reaction mixture was stirred at 0 °C for 1 h, at room temp. for 2 h, and heated at reflux for 6–48 h (6 h for aniline and 48 h for perfluoroaniline); the reaction was continually monitored by TLC analyses. At the end of the reaction as judged by TLC analysis, the reaction mixture was cooled to room temp. and filtered. The filtrate was concentrated to get hold of the crude product, which was further purified by silica-gel cloumn chromatography.

The above product was dissolved in dry 25 mL of DCM and cooled to 0 °C. TFA (7.5 mL) was slowly added to this solution at 0 °C and stirred for 3 h at room temp. The reaction mixture was evaporated in vacuo and washed thoroughly with petroleum ether. The oil was dissolved in a minimum amount of water and basified with NH_4OH, extracted with chloroform, washed thoroughly with water, dried with anhydrous Na_2SO_4 and concentrated to get hold of the pure carboxamide (1.67 g, 82% overall yield for catalyst **1**).

(*S*)-*N*-Phenyl-pyrrolidine-2-carboxamide (1):[12] Yield 82%; m.p. 72 °C. $[\alpha]_D^{27}$ = –43.95 (*c* = 0.5, EtOH). IR (KBr): $\tilde{\nu}$ = 1668, 2873, 2967, 3225, 3351 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.70–1.79 (m, 2 H), 2.00–2.06 (m, 1 H), 2.15–2.24 (m, 1 H), 2.95–3.00 (m, 1 H), 3.05–3.10 (m, 1 H), 3.87 (dd, 1 H, J_1 = 9.1 Hz, J_2 = 5.1 Hz), 7.07 (t, 1 H, *J* = 7.3 Hz), 7.30 (t, 2 H, *J* = 7.3 Hz), 7.58–7.60 (m, 2 H) 9.74 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.2, 30.7, 47.2, 61.0, 119.2, 123.8, 128.8, 137.8, 173.2 ppm.

(*S*)-*N*-(2,6-Dimethylphenyl)pyrrolidine-2-carboxamide (2):[12] Yield 74%; m.p. 78 °C. $[\alpha]_D^{27}$ = –27.89 (*c* = 0.5, $CHCl_3$). IR (KBr) 1637, 3044, 3215. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.92–1.98 (m, 2 H), 2.04–2.22 (m, 1 H), 2.08 (s, 6 H), 2.41–2.46 (m, 1 H), 2.8 (br. s, 1 H), 3.25–3.34 (m, 2 H), 4.96 (br. s, 1 H), 6.94–7.06 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.9, 24.3, 30.1, 46.1, 59.9, 127.6, 128.1, 132.8, 135.1, 167.5 ppm.

(*S*)-*N*-(4-Nitrophenyl)pyrrolidine-2-carboxamide (3):[12] Yield 66%; m.p. 88–90 °C. $[\alpha]_D^{27}$ = –49.41 (*c* = 0.5, EtOH). IR (KBr): $\tilde{\nu}$ = 1345, 1690, 2875, 3214, 3373 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.73–1.78 (m, 2 H), 2.00–2.06 (m, 1 H), 2.19–2.25 (m, 1 H), 2.95–2.99 (m, 1 H), 3.07–3.12 (m, 1 H), 3.88 (dd, J_1 = 9.4, J_2 = 5.4 Hz, 1 H), 7.76 (d, *J* = 9.7 Hz, 2 H), 8.18 (d, *J* = 9.2 Hz, 2 H), 10.17 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.5, 30.8, 47.5, 61.1, 118.8, 125.1, 143.3, 143.7, 174.3 ppm.

(*S*)-*N*-(2,6-Dimethyl-4-nitrophenyl)pyrrolidine-2-carboxamide (4): Yield 60%; m.p. 110–112 °C. $[\alpha]_D^{27}$ = –31.67 (*c* = 0.5, EtOH). IR (KBr): $\tilde{\nu}$ = 1346, 1676, 2850, 2924, 3234, 3365, 3434 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.82–1.87 (m, 2 H), 2.06–2.12 (m, 1 H), 2.25–2.34 (m, 4 H), 3.05–3.09 (m, 1 H), 3.13–3.21 (m, 1 H), 4.07 (br. s, 1 H), 7.94 (s, 2 H), 9.55 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.8, 26.3, 30.9, 47.5, 60.8, 123.0, 136.1, 140.4, 145.7, 173.1 ppm. ESI-MS^+ *m*/*z* calcd. for $C_{13}H_{17}N_3O_3$ 264.1348 [M + H]; found 264.1348.

(*S*)-*N*-(3-Nitrophenyl)pyrrolidine-2-carboxamide (5): Yield 64%; gummy liquid. $[\alpha]_D^{27}$ = –40.71 (*c* = 0.57, EtOH). IR (KBr) 1352, 1681, 2874, 2971, 3092, 3258. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.72–1.80 (m, 2 H), 1.95–2.03 (m, 1 H), 2.16–2.26 (m, 1 H), 2.97–3.03 (m, 1 H), 3.06–3.12 (m, 1 H), 3.38 (br. s, 1 H), 3.96 (dd, J_1 = 11.6, J_2 = 6.7 Hz), 7.38 (t, *J* = 10.4 Hz, 1 H), 7.83 (dd, J_1 = 9.9, J_2 = 2.4 Hz), 8.35 (t, *J* = 2.4 Hz), 10.14 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.3, 30.7, 47.3, 60.9, 113.9, 118.4, 124.9, 129.7, 138.9, 148.5, 174.0 ppm. ESI-MS^+ *m*/*z* calcd. for $C_{11}H_{13}N_3O_3$ 236.1035 [M + H]; found 236.1035.

(*S*)-*N*-(2-Methyl-5-nitrophenyl)pyrrolidine-2-carboxamide (6): Yield 63%; m.p. 92–94 °C. $[\alpha]_D^{27}$ = –57.79 (*c* = 0.5, EtOH). IR (KBr): $\tilde{\nu}$ = 1686, 2847, 2980, 3129, 3370 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.73–1.80 (m, 2 H), 2.02–2.10 (m, 1 H), 2.18–2.27 (m, 1 H), 2.33 (s, 3 H), 2.95–3.01 (m, 1 H), 3.08–3.14 (m, 1 H), 3.92 (dd, J_1 = 9.2, J_2 = 4.8 Hz, 1 H), 7.23–7.28 (m, 1 H), 7.80 (dd, J_1 = 8.4, J_2 = 2.2 Hz, 1 H), 9.02 (d, *J* = 2.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.8, 26.3, 30.7, 47.4, 61.2, 115.2, 118.5, 130.5, 134.4, 136.8, 146.9, 173.5 ppm. ESI-MS^+ *m*/*z* calcd. for $C_{12}H_{15}N_3O_3$ 250.1190 [M + H]; found 250.1151.

(*S*)-*N*-(3,5-Dinitrophenyl)pyrrolidine-2-carboxamide (7): Yield 60%; m.p. 174–176 °C. $[\alpha]_D^{27}$ = –39.06 (*c* = 0.5, EtOH). IR (KBr): $\tilde{\nu}$ = 1347, 1674, 2960, 3105, 3202 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.80–1.85 (m, 2 H), 2.02–2.09 (m, 1 H), 2.25–2.33 (m, 1 H), 3.03–3.07 (m, 1 H), 3.14–3.18 (m, 1 H), 4.02 (dd, J_1 = 9.1, J_2 = 5.3 Hz, 1 H), 8.71 (d, *J* = 2.3 Hz, 1 H), 8.82 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR($CDCl_3$, 100 MHz) δ = 26.3, 30.7, 47.4, 60.9, 113.1, 118.7, 140.2, 148.8, 174.3 ppm. ESI-MS^+ *m*/*z* calcd. for $C_{11}H_{12}N_4O_5$ 281.0885 [M + H]; found 281.0885.

(*S*)-*N*-(Perfluorophenyl)pyrrolidine-2-carboxamide (8):[18] Yield 67%; m.p. 82–84 °C. $[\alpha]_D^{27}$ = –36.46 (*c* = 0.5, EtOH). IR (KBr): $\tilde{\nu}$ = 1668, 2873, 2967, 3225, 3351 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.76–1.85 (m, 2 H), 2.04–2.07 (m, 1 H), 2.19–2.26 (m, 1 H), 2.99–3.04 (m, 1 H), 3.08–3.13 (m, 1 H), 3.96–3.97 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.2, 30.9, 47.4, 60.7, 112.0, 112.1, 112.2, 136.8, 138.7, 141.8, 143.8, 174.0 ppm. ESI-MS^+ *m*/*z* calcd. for $C_{11}H_9N_2OF_5$ 281.0713 [M + H]; found 281.0712.

General Procedure for Aldol Reaction: A mixture of catalyst **3** (0.031 g, 0.13 mmol), ketone (1.21 g, 13.2 mmol) and TFA (0.0075 g, 0.066 mmol) contained in 1.0 mL of DMF (1.0 mL) was stirred at room temp. for 45 min. Subsequently, the temperature was brought down to 3 °C and the aldehyde (0.1 g, 0.66 mmol) was introduced. The reaction mixture was stirred at 3 °C until the reaction was judged to be complete based on TLC analysis. The reaction was quenched by adding saturated NH_4Cl solution, and the organic material was extracted with ethyl acetate (2 × 20 mL). The combined organic extract was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography to give the pure aldol adduct.

The crude product before SiO_2 chromatography was submitted to ^1H NMR analysis to determine diastereomeric ratio. The product after SiO_2 chromatography was analyzed by HPLC to determine the enantiomeric as well as the diastereomeric ratios; the latter matched, within allowable limits, the values determined by ^1H NMR analysis. The *syn* and *anti* diastereomers of the aldols were readily distinguished in ^1H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton, cf. SI for the chemical shift data.

CCDC-697386 (for **7**) and -697387 (for **8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Details of synthesis, ^1H and ^{13}C NMR spectral reproductions of all the catalysts **1**–**8**, ^1H NMR diagnostic chemical shift data for *syn* and *anti* aldols, HPLC profiles for all results in Tables 2 and 4, crystal data for **7** and **8**, and the results of CSD search for *N*-arylamides.

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[15] The catalytic activity of *N*-arylprolinamide **8**, in particular, was tested for the reaction of cyclohexanone with less electrophilic aldehydes such as benzaldehyde, *p*-methoxybenzaldehyde, etc. The aldol reactions with these aldehydes were found to be too sluggish leading to <20% of the products even after 48 h.

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[20] The observed near-orthogonality of the perfluorphenyl ring with respect to the amide functionality is unlikely to be a result of crystal packing. We are currently carrying out structural studies of a number of perfluorophenylamides and other related systems to establish the conformational preference observed for **8**.

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