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Highly enantioselective aldol reactions using *N*-arylprolinamides with enhanced acidity and double H-bonding potential

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ABSTRACT

We have designed and synthesized *N*-arylprolinamides **7–10** with a potential to involve in the binding of electrophilic aldehydes via two N–H···O hydrogen bonds for application in organocatalytic aldol reactions. The catalyst **10** is shown to afford aldol products in excellent isolated yields with very high diastereo- and enantioselectivites. In addition to enhanced acidity and double hydrogen bonding, the stacking interactions of the *p*-toluenesulfonyl ring in **10** with the electrophilic aldehyde are proposed to stabilize the transition state.

There is a surge of interest in developing organocatalysts for enantioselective organic reactions at the present time due to the advantage associated with obviating the use of scarce and hazardous transition metals.[1] Aldol reaction constitutes one of the tremendously explored reactions in the realm of organocatalysis in general; continued interest in this reaction owes its origin to (i) the importance of 1,3-dioxygenated aldol products that can be structurally further elaborated, (ii) significance associated with C–C bond formation, and (iii) creation of two contiguous chiral centers with the possibility of regulation of both diastereo- and enantioselectivity.[2] List et al. showed during the initial years of the ascendency of organocatalysis that very abundant and naturally occurring L-proline regulates enantioselectivity in aldol reactions, albeit moderately.[3] A variety of catalysts with diverse functional features have since been designed[4] and explored for stereoregulation in aldol reactions; these include catalysts with reinforced chirality,[5] enhanced amide acidity,[6] and double hydrogen-bonding potential[7] as shown for some catalysts in Chart 1. A fact that appears to emerge compellingly as applied to aldol reactions is that the enhanced acidity of the amide hydrogen contributes to better enantiodiscrimination.[6] We recently showed that L-*N*-perfluorophenylprolinamide **6** catalyzes the reaction between cyclohexanone and a variety of electrophilic aldehydes leading to aldols in excess of 90% yield and with >95% enantioselectivity.[8] The fantastic performance of **6** was attributed, in addition to the enhanced NH acidity, to the tendency of the perfluorophenyl ring to lie orthogonally with respect to the amide group, which facilitates stronger binding of the electrophilic aldehyde via hydrogen bonding in the transition state. In continuation of these studies, we were inspired to design simple and improved catalysts that feature two sites for hydrogen bonding of the electrophilic aldehydes. Herein, we report that *N*-(*o*-aminophenyl)prolinamide can be functionalized conveniently to afford a novel set of organocatalysts with graded *H*-bonding potential and with/without aryl rings that may further augment stabilization of the transition state. Of the four catalysts, that is, **7–10**, the tosyl-functionalized prolinamide **10** is shown to afford aldols with remarkable diastereo- as well as enantioselectivity.

The synthetic routes for all catalysts **7–10** are shown in Scheme 1.[9] The catalysts **7**, **9,** and **10**[10] were synthesized by DCC-mediated coupling of ***N***-Boc-protected proline with *N*-acetyl-, *N*-mesyl-, and *N*-tosyl-protected 1,2-diaminobenzene, followed by deprotection using TFA. For catalyst **8**, Boc-protected *N*-(2-aminophenyl)-prolinamide was reacted with triflic anhydride in the presence of triethylamine to yield Boc-protected derivative, which was subsequently deprotected by treatment with TFA.

To identify the experimental conditions at which the prolinamides **7–10** yield best results, catalyst **10** with tosyl moiety (20 mol %) was typically employed, and the stereocontrol in the aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde as a representative reaction was examined under varied solvent conditions with and without an additive. All the experiments were uniformly conducted at 3 ± 1 °C on 0.3–0.4 mmol of *p*-nitrobenzaldehyde. As shown in Table 1, best results were observed with DMF as the solvent and with TFA (10 mol %) as an additive; it is noteworthy that under identical conditions, change of the additive from TFA to camphor sulfonic acid (CSA)/*p*-toluene sulfonic acid (PTSA)/3,5-dinitrobenzoic acid (DNBA) led to longer reaction time and/or relatively poor enantiodiscrimination, cf. Table 1; for example, the reaction went to completion in 20 h with TFA as an additive, and the reac-

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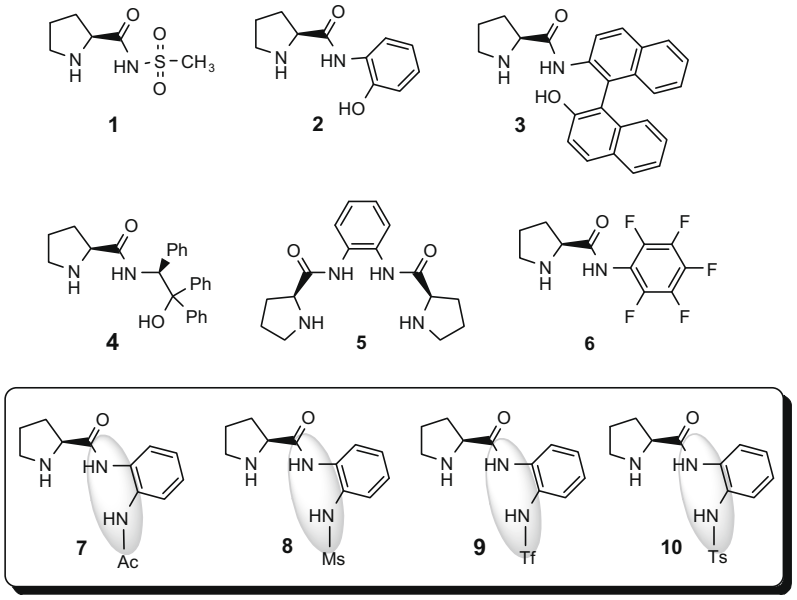
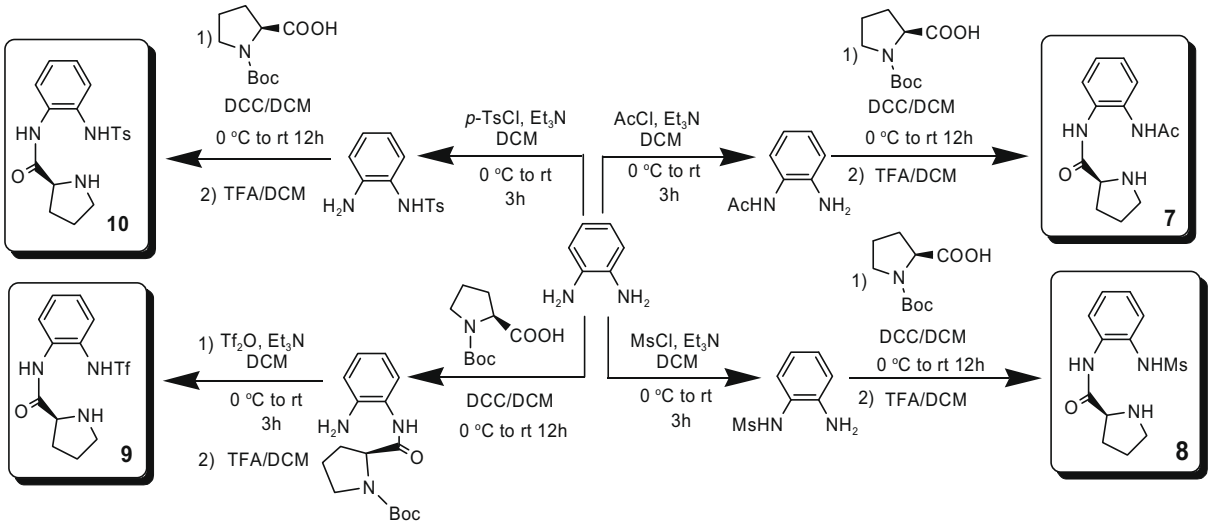


Chart 1.

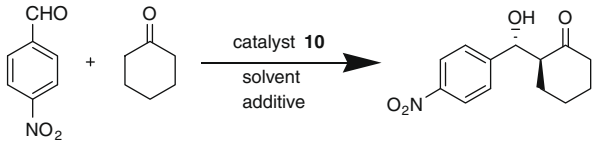


Scheme 1. Synthetic routes for the preparation of the catalysts **7–10.**

tion durations were as long as ca. 60 h with CSA and PTSA. Thus, the experimental conditions involving the use of DMF, 20 mol % catalyst, and 10 mol % TFA as an additive were deemed ideal for enantioselective aldol reactions of ketones with a variety of electrophilic aldehydes. Similar conditions were employed to gauge the effectiveness of the catalysts **7–9**. As shown in Table 2, the tosyl-prolinamide catalyst **10** was found to be best in terms of reaction durations as well as diastereo- and enantiodiscrimination.

Based on the screening results described above, we employed the catalyst **10** for enantioselective aldol reactions of a variety of cyclic as well as acyclic ketones with differently substituted electrophilic benzaldehydes, cf. Table 3. All the aldol reactions were conducted on 10–15 mmol of the aldehyde at 3 ± 1 °C by employing 20 mol % tosyl-prolinamide **10** in DMF containing 10 mol % TFA as an additive.[10] The results of the enantioselective aldol reactions are shown in Table 3. As can be seen, cyclohexanone undergoes aldol reaction with diverse aromatic aldehydes to afford aldols with a very high *anti* diastereoselectivity (95–98%). Further, one obtains the *anti* aldols with enantiomeric excess higher than 97% (entries 1–10, Table 3). The reaction of cyclopentanone with *p*-nitrobenzaldehyde and *m*-nitrobenzaldehyde leads to aldols with rather attenuated diastereo- and enantioselectivities (entries 11 and 12). Further, there is a stereochemical reversion in the sense that the major aldol product corresponds to the one with *syn* stereochemistry as revealed by the chemical shifts for the diagnostic methine protons of *syn* and *anti* diastereomers in the ^{1}H NMR spectra.[5d,8] A similar trend is observed for the reaction of acyclic ketone, viz., acetone, with *m*- and *p*-nitrobenzaldehydes (entries 13 and 14). The aldols were obtained in 90% optical purity; the stereochemistry shown in Table 1 was established by comparing their optical rotations and HPLC profiles with those reported in the literature.[5d,8]

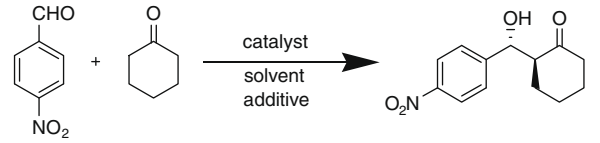
Table 1
The screening of catalysts **10** for enantioselective aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone in various solvents with different additives[a]



Entry	Solvent	Additive	Time (h)	Yield[b] (%)	(*anti*:*syn*)[c]	ee[d] (%)
1	DCM	—	48	65	90:10	90
2	Brine	—	48	60	88:12	91
3	DCM	TFA	28	72	92:8	92
4	Brine	TFA	28	89	92:8	91
5	IPA	TFA	28	88	90:10	94
6	Hexane	TFA	28	82	93:7	93
7	DMF	—	62	66	90:10	91
8	**DMF**	**TFA**	**20**	**94**	**97:3**	**>98**
9	DMF	PTSA	62	90	90:10	92
10	DMF	(+)-CSA	62	92	96:4	95
11	DMF	DNBA	26	92	95:5	97

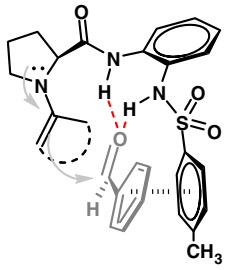
[a] The reactions in all solvents were run on 0.3–0.4 mmol of p-nitrobenzaldehyde at 3±1 °C under identical conditions by employing 20 mol% of the catalyst **10**.
[b] Based on *p*-nitrobenzaldehyde.
[c] From 400 MHz ^{1}H NMR spectroscopy.
[d] Based on chiral HPLC analyses for the major *anti* diastereomer.

Table 2
Screening of catalysts **7**–**10** in direct enantioselective aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone[a]



Catalyst	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
7	32	78	>95:5	95
8	30	82	>95:5	96
9	36	56	94:6	96
10	**29**	**94**	**97:3**	**>98**

[a] The reactions were run on 0.4 mmol of *p*-nitrobenzaldehyde at 3 ± 1 °C under identical conditions by employing 20 mol % of the catalyst.
[b] Based on *p*-nitrobenzaldehyde.
[c] From 400 MHz ^{1}H NMR spectroscopy.
[d] Based on chiral HPLC analyses for the major *anti* diastereomer.



Scheme 2. Proposed transition state structure for enantioselective aldol reaction catalyzed by the catalyst **10**.

Overall, the observed results are comparable to or even better than those reported for a variety of organocatalysts.[11] What is more remarkable is the fact that the reactions go to completion in relatively short durations (ca. 6–12 h) for activated electrophilic aldehydes. Given that the structural features render the catalyst **10** rather easily accessible synthetically, the observed high diastereo- and enantioselectivities are indeed remarkable for such simple catalysts.[12] Further, the derivatization of proline improves the solubility to permit application of such catalysts in common organic solvents as well. Incidentally, the catalyst **10** was earlier synthesized by Fu et al.,[13] but was found to mediate the aldol reaction between *o*-nitrobenzaldehyde and acetone, in the absence of any additive, to afford the corresponding aldol in negligible enantiomeric excess. The better performance of catalyst **10** over analogous acetyl/mesyl/triflyl derivatives (**7–9**) should be attributed to some role of the toluenesulfonyl ring. If acidity were the sole factor, one should expect the triflic amide catalyst **9** to be equally effective. We believe that the toluenesulfonyl ring in catalyst **10** may involve in the transition state stabilization to account for its subtle yet superior functioning in the stereocontrol of aldol reactions. Scheme 2 shows our proposed transition state structure, in which the stacking interaction involving the toluenesulfonyl ring is presumed to stabilize the transition state.

In conclusion, we have shown that *N*-arylprolinamides can be readily modified to include features that permit double hydrogen bonding with tunable acidity. It is shown that the catalysts based on *N*-(2-aminophenyl)prolinamide perform remarkably well in the stereoregulation of aldol reactions of cyclic ketones with arylaldehydes. The aldols are shown to be formed with high diastereo as well as enantioselectivities (>96%). The superior performance of the tosyl-derived catalyst **10** is attributed, in addition to enhanced acidity,

Table 3
Results of enantioselective Aldol reactions with catalyst **10**[a]

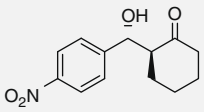
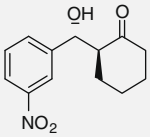
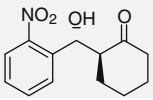
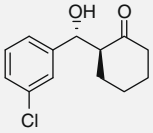
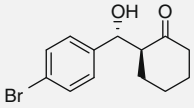
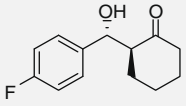
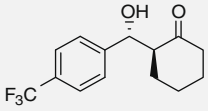
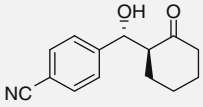
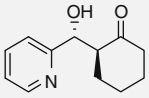
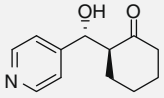
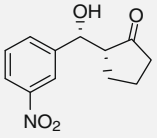
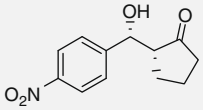
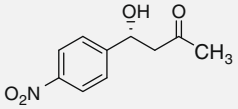
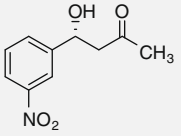
Entry	Product	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1		20	94	97:3	>98
2		20	92	98:2	>98
3		20	86	98:2	>99

Table 3 (*continued*)

Entry	Product	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
4		84	74	95:5	98
5		50	50	96:4	>98
6		84	47	95:5	97
7		50	84	97:3	>99
8		22	78	95:5	97
9		6	88	98:2	>97
10		6	82	97:3	98
11		36	82	30:70	84
12		36	80	30:70	85
13		12	80	—	90
14		12	78	—	90

[a] All reactions were run on a 0.5–0.7 mmol scale at 3 ± 1 °C with 20 mol % of the catalyst and 10 mol % of TFA in DMF (0.8–1.5 mL) containing TFA (10 mol %).
[b] Based on aldehyde.
[c] Ratios of diastereomers were calculated based on integrations in the ^{1}H NMR spectrum of the crude reaction mixture in each case.
[d] The ee values were calculated from HPLC profiles of the silica gel column-purified enantiomeric mixture of the *anti* diastereomer. The values reported are for the major *anti* diastereomer.

to the participation of the toluenesulfonyl ring in the stabilization of the transition state via stacking interactions. We are currently exploring how double hydrogen bonding based on the design demonstrated herein may augment enantioselective organocatalytic processes accomplished by bifunctional proline-derived catalysts.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.014.

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9. See 'Supplementary data' for the preparation and characterization of organocatalysts **7**-**10**.
10. *Representative procedure for the enantioselective aldol reaction with catalyst* **10**: A mixture of catalyst **10** (31 mg, 0.13 mmol), cyclohexanone (646 mg, 6.6 mmol), and TFA (7.5 mg, 0.066 mmol) contained in 1.0 mL of DMF (1.0 mL) was stirred at room temperature for 45 min. Subsequently, the temperature was brought down to 3 °C and the aldehyde (100 mg, 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 mixture was directly passed through a short silica gel column to isolate the pure aldol product.
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