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Functionalized proline with double hydrogen bonding potential: highly enantioselective Michael addition of carbonyl compounds to β-nitrostyrenes in brine

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ABSTRACT

Simple synthetic manipulation of *S*-proline allows access to prolinamides **5–7** as organocatalysts capable of double hydrogen bonding for enantioselective Michael addition reactions of carbonyl compounds to β-nitrostyrenes. It is shown that prolinamide catalyst **7** leads to addition products with a high diastereo- as well as enantioselectivity. The transition state structure involving the binding of electrophilic nitrostyrene via two H-bonds is believed to be further stabilized by π,π stacking interactions mediated by the tosyl ring.

The growing interest in environmental-friendly and metal-free reactions has led to great progress in organocatalysis.[1] In particular, Michael reaction represents one of the most important reactions for C–C bond formation in organic synthesis, and offers atom-efficient access to 1,4-bifunctional products.[2] Since the pioneering work by Barbas and List, independently on the asymmetric Michael reaction,[3] significant strides have been made in the design and development of organocatalysts that lead to high catalytic efficiency.[4,5] Some of the organocatalysts that promote Michael reactions with a high enantioselectivity are shown in Figure 1.[6] Despite a wide variety of catalysts, the quest for new and simpler catalytic systems that surpass the existing ones in terms of catalytic behavior continues unabated.

We have recently shown that the organocatalysts **1**–**4** (Fig. 2) with enhanced acidity and double hydrogen bonding potential efficiently catalyze direct Aldol reaction with excellent enantio- and diastereoselectivity.[7a] As a logical extension of our studies on organocatalysts with enhanced acidity and hydrogen bonding,[7] the catalyst **4** was particularly screened for catalyzing the Michael addition reaction of cyclohexanone to β-nitrostyrenes. The frustratingly poor enantioselectivities observed with **4** led us to modified catalysts **5**–**7** (Fig. 2), which were designed based on the following rationale: first, a quick perusal of the reported organocatalysts for Michael reaction in Figure 1 reveals that the catalysts ought to enjoy conformational flexibility, which is introduced in **5**–**7** via reduction of the carbonyl group; second, the bis-amide functionality created from *o*-aminobenzoic acid permits enhanced acidity and double hydrogen bonding for binding the electrophilic nitrostyrene reactant. Herein, we report that the readily accessible catalyst **7**, which is devoid of additional chiral center other than that of proline, catalyzes the Michael reactions of diverse carbonyl compounds with nitrolefins in high enantioselectivity; the reactions are found to occur in brine at rt in the presence of benzoic acid as an additive.

The synthetic routes for the preparation of catalysts **5**–**7** are shown in Scheme 1. The catalysts were readily prepared by coupling *o*-nitrobenzoic acid with Boc-protected prolinamine followed by the reduction of the nitro functionality to amine; the latter was subsequently derivatized with tosyl, mesyl, and pentafluorosulphonyl groups. The Boc group was deprotected at the end to get hold of catalysts **5**–**7**.

In our initial experiments, the catalyst **7** containing tosyl group was employed to establish experimental conditions at which the Michael addition between β-nitrostyrene and cyclohexanone, representative reactants, leads to high enantioselectivity. A variety of solvents were screened in the presence of 10 mol % of **7** with/without an additive by conducting the reactions on a 0.3–0.4 mmol scale at room temperature. The results of screening shown in Table 1 reveal that the reaction in solvents such as DCM, water, and brine works better as compared to that in other solvents such as DMSO, MeOH, dioxane, and THF Further, the reaction in brine (saturated NaCl solution, ca. 5.0 M) gave relatively better yields and enantiodiscrimination as compared to that in water (entries 7 and 8). Thus, the influence of additive was examined carefully in an organic solvent such as DCM and brine carefully. Clearly, best results are observed with benzoic acid as an additive in brine as the reaction medium and with only 5 equiv of cyclohexanone (entry 19). The change of additive from benzoic acid to 2,4-dinitrobenzoic acid/tartaric acid/pentafluorobenzoic acid/*p*-toluenesulphonic acid/*o*-nitrobenzoic acid/TFA led to either longer reaction times or no reaction at all and poor enantiodiscrimination.

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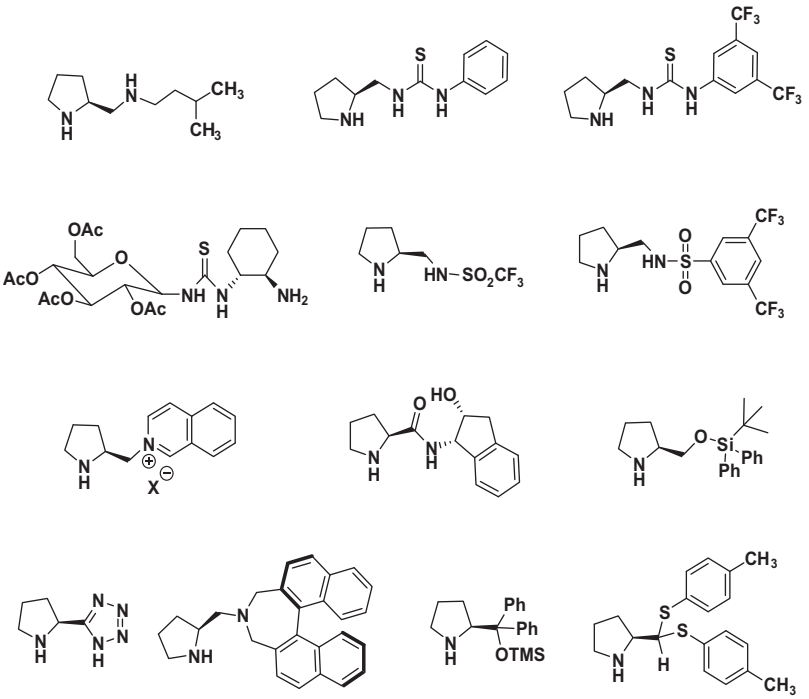


Figure 1. Structures of organocatalysts typically employed for enanatioselective Michael addition reactions.

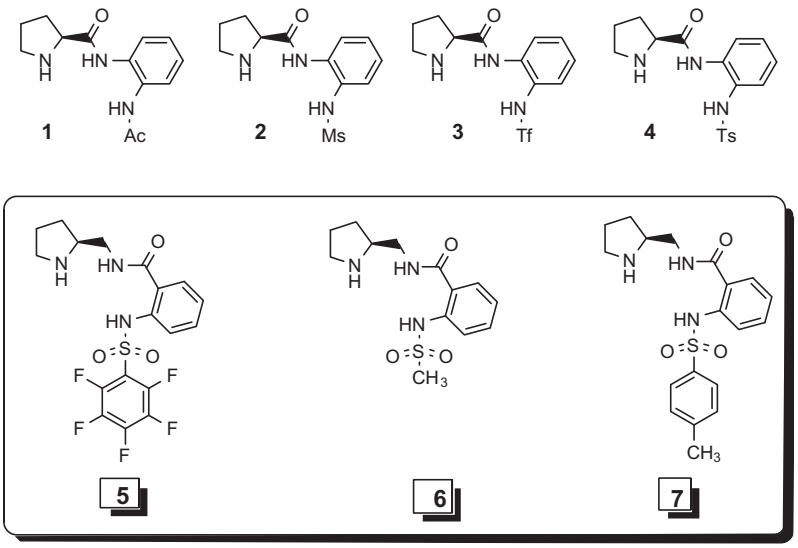
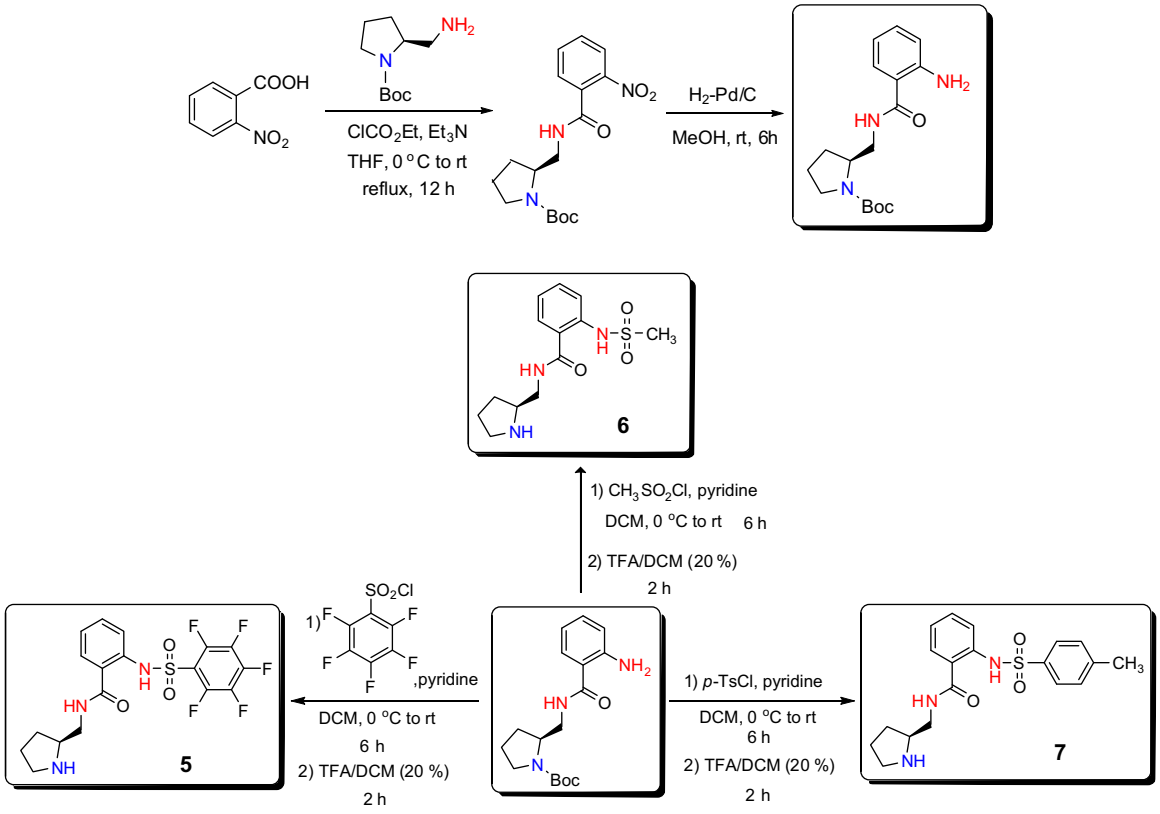


Figure 2. The structures of catalysts explored for enantioselective Michael reaction.

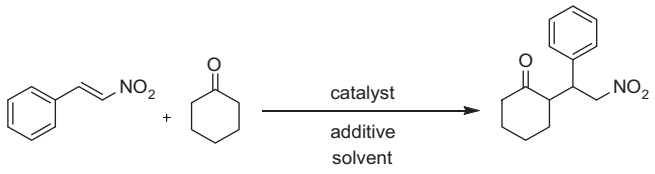
Under the optimized conditions, the other two catalysts, that is, **5** and **6**, were found to be inferior to **7** in terms of reactivity as well as enantioselectivity. Thus, with catalyst **7** in 10 mol %, enantioselective Michael addition reactions of a variety of aldehydes and ketones with differently substituted nitrostyrene derivatives were conducted on 0.3–0.4 mmol of nitrostyrene with 10 mol % of benzoic acid additive in brine at 25 °C. The results of enantioselective Michael additions are compiled in the Table 2. It is noteworthy that a critical dependence of the reactions was observed on the temperatures; while the reactions were found to be too sluggish at lower temperatures (3–5 °C), only moderate reactivity was observed even at 15 °C. At 25 °C, all the reactions were found to proceed smoothly to completion in 10–18 h.

As can be seen, the reactions work well with cyclohexanone leading to excellent enantio- as well as diastereoselectivity. However, the catalyst **7** leads to rather lower selectivity with cyclopentanone and acyclic ketones as substrates. For cyclohexanone as the reactant, the diastereoselectivity for *syn* product is found to vary from 94–97% with no discernible effect of the nature of nitrostyrene (entries 1–13). The ee values are found to range from 92–95%. For cyclopentanones, the diastereo- as well as enantioselectivities are markedly low (entries 14–16). This, indeed, is generally the case with a variety of organocatalysts. With propanaldehyde, the diastereoselectivity in favor of the *syn* product is 92%, while the enantioselectivity is only 83% (entry 19). For simple acetone and anthrone, the enantioselectivity for the conjugate addition product is 80–84% (entries 17, 18 and 20).[8]



Scheme 1. Synthetic routes for the preparation of catalysts **5**–**7**.

Table 1
Results of screening of the direct catalytic enantioselective Michael addition reaction of cyclohexanone to β-nitrostyrene in various solvents using catalyst **7** with/without an additive[a]



Entry	Solvent	Additive	Time (h)	Yield[b] (%)	*dr*[c] (*syn*:*anti*)	ee[d] (%)
1	DCM	—	28	95	97:3	80
2	DMSO	—	48	—[e]	—	—
3	MeOH	—	48	—[e]	—	—
4	THF	—	48	15	nd[i]	nd[i]
5	Dioxane	—	48	18	nd[i]	nd[i]
6	DMF	—	48	—[e]	—	—
7	Water	—	48	54	94:6	80
8	Brine	—	48	60	95:5	86
9	DCM	TFA	24	—[e]	—	—
10	DCM	DNBA	48	20	nd[i]	nd[i]
11	DCM	(+)-CSA	48	—[e]	—	—
12	DCM	PhCOOH	50	85	98:2	83
13	$CHCl_3$	PhCOOH	32	94	98:2	88
14	DMSO	PhCOOH	48	—[e]	—	—
15	MeOH	PhCOOH	48	30	95:5	78
16	Water	PhCOOH	16	88	98:2	90
17	Brine	PhCOOH	12	90	98:2	90
18	Brine	PhCOOH	18	92[f]	98:2	90
19	Brine	PhCOOH	14	94[g]	98:2	94
20	Brine	PhCOOH	30	—[e,h]	—	—
21	Brine	*o*-Nitrobenzoic acid	48	24	nd[i]	nd[i]

(*continued on next page*)

Table 1 (*continued*)

Entry	Solvent	Additive	Time (h)	Yield[b] (%)	*dr*[c] (*syn*:*anti*)	ee[d] (%)
22	Brine	TFA	48	—[e]	—	—
23	Brine	C_6F_5COOH	30	—[e]	—	—
24	Brine	Tartaric acid	30	—[e]	—	—

[a] The reactions were run on 0.3–0.4 mmol of β-nitrostyrene, 10 equiv of cyclohexanone and 10 mol % additive at 25 °C under identical conditions by employing 10 mol % of **7**.
[b] Based on β-nitrostyrene.
[c] From 400 MHz ^{1}H NMR spectroscopy.
[d] Based on chiral HPLC analysis of the major *syn* diastereomer.
[e] Sluggish reaction.
[f] With 20 mol % of PhCOOH as an additive.
[g] 5 equiv cyclohexanone was used.
[h] Reaction performed at 3 °C.
[i] Not determined.

Table 2
Results of enantioselective Michael reactions with catalyst **7**[a]

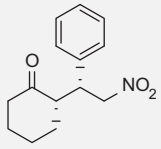
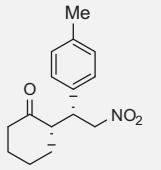
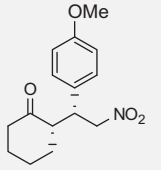
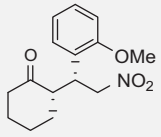
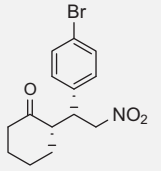
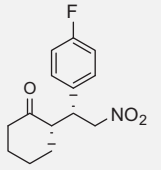
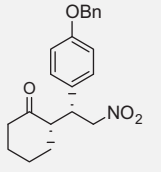
Entry	Product	Time (h)	Yield[b] (%)	*dr*[c] (*syn*:*anti*)	ee[d] (%)
1		14	94	94:6	94
2		12	92	94:6	94
3		14	95	97:3	95
4		12	96	95:5	93
5		12	96	96:4	93
6		14	97	96:4	92
7		12	90	94:6	94

Table 2 (*continued*)

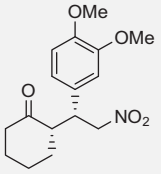
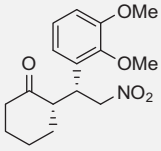
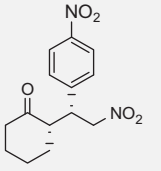
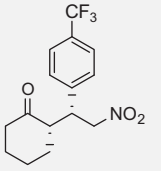
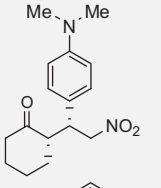
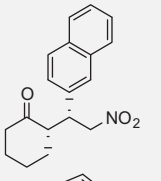
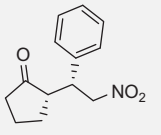
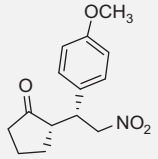
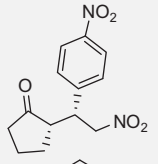
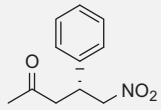
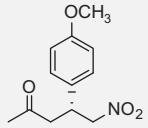
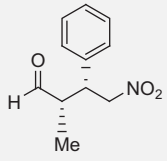
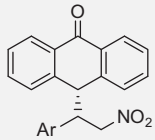
Entry	Product	Time (h)	Yield[b] (%)	*dr*[c] (*syn*:*anti*)	ee[d] (%)
8		14	97	94:6	95
9		14	96	96:4	94
10		12	94	97:3	92
11		12	96	94:6	93
12		18	84	95:5	94
13		16	90	97:3	92
14		13	85	75:25	84

Table 2 (*continued*)

Entry	Product	Time (h)	Yield[b] (%)	*dr* [c] (*syn*:*anti*)	ee[d] (%)
15		16	74	77:23	81
16		14	72	75:25	83
17		12	94	—	81
18		12	86	—	80
19		12	95	92:8	83
20		10	94	—	84

[a] The reactions were run on 0.3–0.4 mmol of β-nitrostyrene derivatives at 20 °C under identical conditions by employing 10 mol % of **7** and 10 mol % PhCOOH as an additive.

[b] Based on nitroolefins.

[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 *syn* diastereomers. The values reported are for

Why is it that the reactions work best in brine in which the reactants as well as the catalyst are not soluble? Indeed, the reaction mixture appeared truly biphasic. The fact that added NaCl in water brings about perceptible reduction in the reaction times together with enhancement of enantiodiscrimination as compared to the result in plain water (entries 7 and 8, Table 1) clearly emphasizes the role of the medium, and excludes the possibility of the reaction occurring in neat conditions without any role of the medium. There are two possible ways that the reactions in brine are supposedly promoted: (i) hydrophobic aggregation[9] and (ii) reactions under biphasic conditions.[4f,10] While we are not sure which of the two considerations is applicable to our reaction conditions, we believe that brine and the additive, namely benzoic acid, should somehow stabilize the polar transition state via local medium effects to account for the observed differences in results going from organic media to highly polar medium.[11] Further, why the reactions work better with benzoic acid only as an additive is intriguing. Presumably, TFA, dinitrobenzoic acid, camphor sulfonic acid, etc. with lower pK_a values lead to catalyst poisoning; the reactions did not progress at all with these acids. We, therefore, believe that there appears to be an optimum pK_a for the acid to be effective, which in the present case is benzoic acid.

The plausible transition state geometry that accounts for high enantioselectivity observed with catalyst **7** is shown in Figure 3.

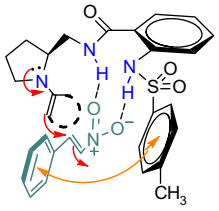


Figure 3. The proposed transition state structure for the Michael reaction between ketone and β-nitrostyrene.

Accordingly, the electrophilic β-nitrostyrene is proposed to be bound by two hydrogen bonds formed with the amide part of the catalyst. The fact that the catalyst **5** with enhanced acidity of the NH hydrogen due to pentafluorophenyl ring does not function as good is intriguing. We believe that charge transfer interaction or π,π stacking between the bound electrophilic β-nitrostyrene and the tosyl group possibly contributes to the stabilization of the transition state to some degree.

In conclusion, we have designed organocatalysts based on proline that are capable of double hydrogen bonding for asymmetric Michael reactions between carbonyl compounds and nitroolefins. It is shown that the catalyst **7**, which can be readily accessed by a simple synthetic protocol, works remarkably well in *brine* to afford addition products in a high diastereo- as well as enantioselectivty. Thus, superior performance of **7** as compared to analogous catalysts **5** and **6** presumably arises from the possible π,π stacking interactions between the tosyl ring of the catalyst **7** and aromatic ring of the nitroolefin. Given that the incorporation of additional stereogenic center for reinforced chirality is precluded and that the Michael reactions occur with a very high enantioselectivity with catalyst **7**, the advantage of double hydrogen bonding to bind the electrophilic reactant and regulate the stereochemical outcome of the reactions is compellingly evident from the results described herein.

Acknowledgments

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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.2010.07.164.

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