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Proline-Mediated Enantioselective Construction of Tetrahydropyridines *via* a Cascade Mannich-Type/Intramolecular Cyclization Reaction

Rong-Gang Han,[a] Yao Wang,[a] Yu-Ye Li,[a] and Peng-Fei Xu[a,*]

[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, People's Republic of China
Fax: (+86)-931-891-5557; e-mail: xupf@lzu.edu.cn

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Abstract: A highly diastereo- and enantioselective synthesis of 2,3-disubstituted tetrahydropyridines was accomplished *via* a proline-mediated cascade Mannich-type/intramolecular cyclization reaction from preformed *N*-PMP (*p*-methoxyphenyl) aldimines and inexpensive aqueous tetrahydro-2*H*-pyran-2,6-diol.

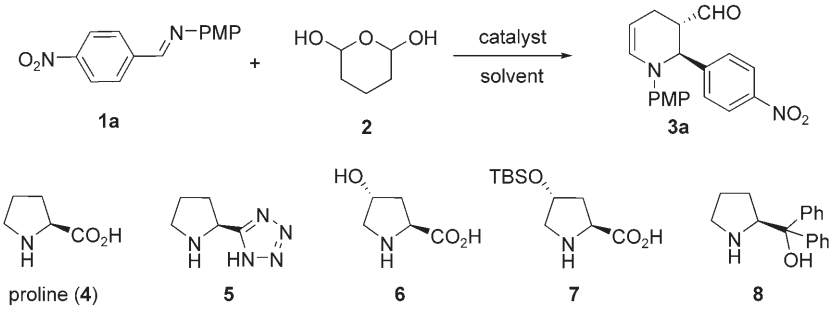
Keywords: cascade reactions; imines; Mannich-type reaction; organocatalysis; tetrahydropyridines

The functionalized tetrahydropyridine and piperidine ring systems are not only important starting materials for numerous biologically active compounds, but are also important structural building blocks of many natural products and pharmaceuticals.[1] Therefore, a continuous interest exists in the development of new methodologies for the asymmetric synthesis of this classes of six-membered nitrogen-containing heterocycles.[2,3] The development of cascade or tandem reactions[4] is a recent new direction in organocatalysis, which allows the rapid construction of structurally complex molecules from simple and readily available starting materials in only one operation, thereby decreasing the formation of waste products and increasing the economy of the process. For example, Hayashi et al. successfully used aqueous tetrahydro-2*H*-pyran-2,6-diol in a highly enantioselective synthesis of optically active cyclohexane derivatives[5a] and substituted tetrahydropyrans[5b] in domino processes.

We anticipated that pentane-1,5-dial, a synthetically useful five-carbon unit generated from aqueous tetrahydro-2*H*-pyran-2,6-diol under equilibrium conditions, might be utilized for the formation of optically active tetrahydropyridines by a cascade Mannich-type[6]/intramolecular cyclization reaction catalyzed by organic molecules in the presence of water. Actually, Barbas et al.[7] assessed the impact of the presence of water on the Mannich-type reaction profile and found that this reaction could tolerate a significant amount of water in the reaction mixture without compromising the enantiomeric excess obtained for the Mannich product. Other groups[8] also reported that some Mannich-type reactions could proceed enantioselectively in the presence of water or under aqueous conditions. Thus, it is expected that commercially available, aqueous tetrahydro-2*H*-pyran-2,6-diol could be employed directly in this cascade reaction. Herein, we report the highly diastereo- and enantioselective synthesis of 2,3-disubstituted tetrahydropyridines in the presence of water from *N*-PMP aldimines and tetrahydro-2*H*-pyran-2,6-diol.

First, we studied the reaction of *N*-PMP aldimine **1a** preformed from *p*-nitrobenzaldehyde and aqueous tetrahydro-2*H*-pyran-2,6-diol **2**, using L-proline **4** as an organocatalyst (Table 1, entry 1). To our delight, the reaction afforded the desired tetrahydropyridine **3a** in 74% yield with high diastereoselectivity ($dr > 25:1$) and enantioselectivity (98% *ee*). Encouraged by this result, we performed a catalyst screen with various chiral amines **5–8** and found that all the catalysts except **8** could catalyze the reaction efficiently to furnish the desired product **3a** in good yields. Among them, 4-hydroxyproline **6** was as effective as proline (entry **6**) and siloxyproline **7**, even producing slightly higher enantioselectivity (entry **7**). Because proline is inexpensive and both enantiomers are readily available, we examined several solvents with L-proline as the catalyst and found that DMSO was optimal for this cascade process. We also tried to decrease the catalyst loading(entry 11), but this led to a longer reaction time and a slight reduction in chemical yield due to the lability of the imine in the presence of water. Thus, we preferred to perform this cascade reaction with 20 mol% L-proline as the catalyst.

Table 1. Effect of catalyst and solvent in the reaction of *N*-PMP aldimine and aqueous tetrahydro-2*H*-pyran-2,6-diol.[a]

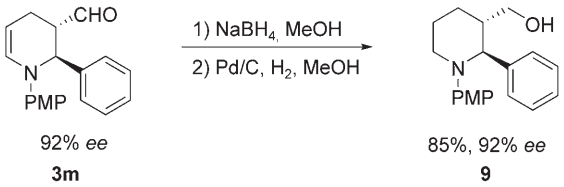


Entry	Catalyst	Solvent	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**4**	DMSO	3.5	74	>25:1	98
2	**5**	DMSO	5	59	>25:1	73
3	**6**	DMSO	4	72	>25:1	98
4	**7**	DMSO	4	73	>25:1	99
5	**8**	DMSO	12	n.r.	–	–
6	**4**	DMF	4	72	>25:1	96
7[e]	**4**	DMF	7	64	>25:1	98
8	**4**	NMP	6	62	>25:1	96
9	**4**	dioxane	12	40	>25:1	96
10	**4**	toluene	12	n.r.	–	–
11[f]	**4**	DMSO	8	71	>25:1	98

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.5 mmol), **2** (50% in water,1.5 mmol), and organocatalyst (20 mol%) in the indicated solvent (5.0 mL) at room temperature.
[b] Isolated yield after flash chromatography.
[c] Determined by ^{1}H NMR analysis of crude products.
[d] Determined by chiral-phase HPLC analysis (OD column).
[e] Reaction was performed at 0 °C.
[f] With 10 mol% of catalyst loading.

Using these optimized reaction conditions, the generality of the reaction was investigated by employing several preformed *N*-PMP aldimines. The results are summarized in Table 2. The reaction proceeded very fast with both electron-deficient and electron-rich arylimines, while the yield was a little lower with electron-rich aryl and alkyl derivatives (entries 12, 14 and 15), presumably due to partial hydrolysis of the imines. In the cases of imines preformed from 2-substituted benzaldehydes, the reactions were rather slow and the yields were comparatively poor, perhaps because of the steric hindrance (entries 4, 7 and 16). The diastereoselectivity of the reaction was essentially not affected and good to excellent enantioselectivity was obtained regardless of the substituents on the imine moiety.

To determine the absolute configuration of the corresponding product of this cascade Mannich-type/intramolecular cyclization reaction, the compound **3m** was converted into piperidine **9** by reduction with $NaBH_4$ and subsequent hydrogenation under the catalysis of palladium/carbon without compromising the enantioselectivity [Eq. (1)]. The absolute configuration of the compound **9** was determined to be (2*S*,3*S*) by comparing its $[\alpha]_D$ value and NMR data with those

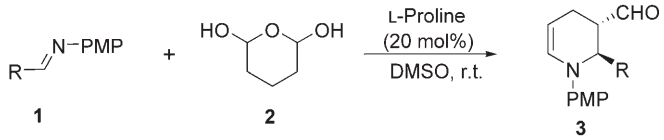


(1)

described in the literature[9] (see Supporting Information). This absolute configuration is in accordance with that expected from an L-proline-mediated Mannich-type reaction.

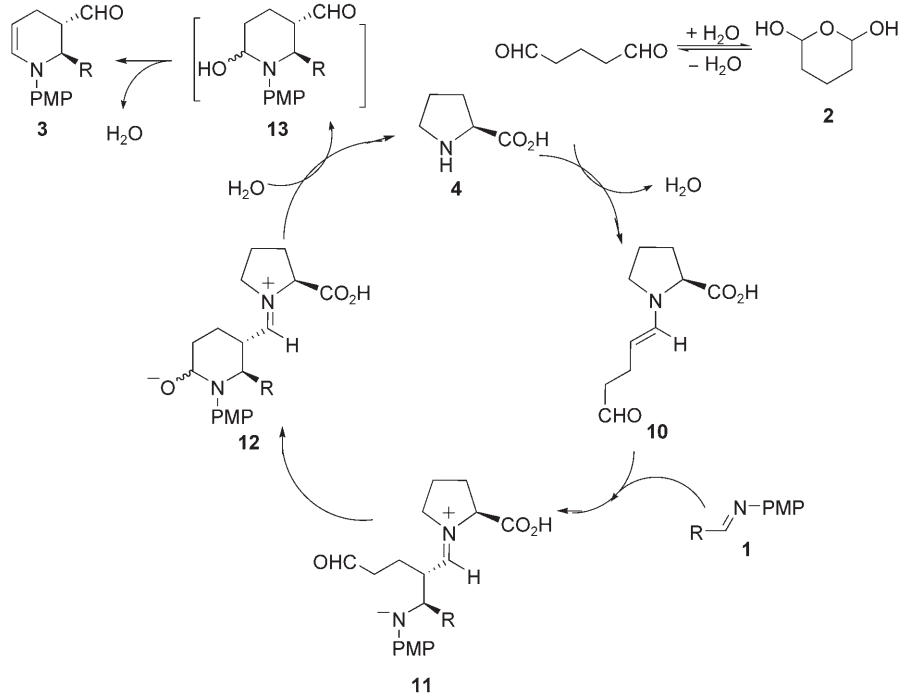
Based on the absolute stereochemistry of **9** and previous experience with Mannich reactions involving the catalyst L-proline, the following stepwise cascade Mannich-type/intramolecular cyclization mechanism was proposed to account for the stereochemical outcome of the reaction. As shown in Scheme 1, pentane-1,5-dial, generated from tetrahydro-2*H*-pyran-2,6-diol under equilibrium conditions, would react with L-proline **4** to form enamine **10**. Enamine **10** would react with preformed *N*-PMP aldimine to give **11** *via* a Mannich-type reaction, followed by hemiaminal formation to provide intermediate piperidine **13** with regeneration of proline **4**. Under acidic condi-

Table 2. Organocatalytic reaction of aqueous tetrahydro-2*H*-pyran-2,6-diol with preformed *N*-PMP aldimines for the formation of optically active tetrahydropyridines.[a]



Entry	R	Product	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	4-$NO_2C_6H_4$	**3a**	3.5	74	>25:1	98
2	3-$NO_2C_6H_4$	**3b**	3.5	65	>25:1	98
3	4-CNC_6H_4	**3c**	3.5	63	>25:1	98
4	2-ClC_6H_4	**3d**	24	51	>25:1	94
5	3-ClC_6H_4	**3e**	5	61	>25:1	94
6	4-ClC_6H_4	**3f**	5	61	>25:1	92
7	2-BrC_6H_4	**3g**	24	39	>25:1	95
8	4-BrC_6H_4	**3h**	5	55	>25:1	94
9	2-FC_6H_4	**3i**	5	61	>25:1	>99
10	3-FC_6H_4	**3j**	5	60	>25:1	96
11	2-naphthyl	**3k**	5	54	>25:1	91
12	4-MeC_6H_4	**3l**	6	43	>25:1	85
13	Ph	**3m**	5	56	>25:1	92
14	(*E*)-$PhCH_2CH$	**3n**	5	21	19:1	69
15	*n*-C_3H_7	**3o**	6	<10	n.d.	n.d.
16	2-$NO_2C_6H_4$	**3p**	24	<10	n.d.	n.d.

[a] The reactions were carried out with **1** (0.5 mmol), **2** (50% in water,1.5 mmol), and L-proline (20 mol%) in DMSO (5.0 mL) at room temperature.
[b] Isolated yield after flash chromatography.
[c] Determined by ^{1}H NMR analysis of crude products.
[d] Determined by chiral-phase HPLC analysis (OD column).



Scheme 1. Proposed mechanism for the cascade reaction.

tions, the unstable intermediate **13** undergoes a dehydration reaction to afford the final optically active tetrahydropyridine **3**.

In summary, we have developed an enantioselective synthetic method for substituted tetrahydropyridines *via* a proline-mediated cascade Mannich-type/intramolecular cyclization, in which easily prepared *N*-PMP aldimines and inexpensive aqueous tetrahydro-2*H*-pyran-2,6-diol are employed as the starting materials. It is a noteworthy advantage of the organocatalyst that the Mannich-type reaction proceeds efficiently with excellent diastereo- and enantioselectivity in the presence of water. This strategy will easily provide access to structurally diverse *N*-PMP piperidines. We are currently applying this methodology to the synthesis of small natural alkaloids.

Experimental Section

General Experimental Procedure

Glutaraldehyde solution **2** (50% in water, 0.26 mL, 1.5 mmol) was added to a mixture of preformed *N*-PMP aldimine **1** (0.5 mmol) and L-proline (11.5 mg, 0.1 mmol) in DMSO (5.0 mL) under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature until the imine was consumed as monitored by TLC. The reaction was worked up by addition of saturated NH_4Cl solution and extracted with EtOAc. The combined organic fractions were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EtOAc) to afford the corresponding tetrahydropyridine **3**.

Supporting Information

Detailed experimental procedures, NMR spectra data for new compounds, and HPLC analyses are available in the Supporting Information.

Acknowledgements

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