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Highly enantioselective [4+2] annulation *via* organocatalytic Mannich-reductive cyclization: one-pot synthesis of functionalized piperidines†

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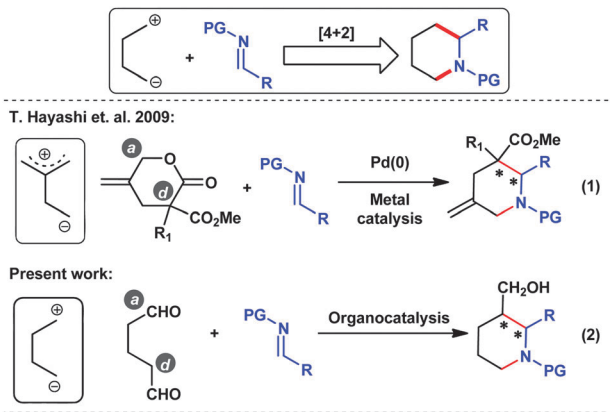
Indresh Kumar,*[a] Panduga Ramaraju,[a] Nisar A. Mir,[a] Deepika Singh,[b] Vivek K. Gupta[c] and Rajnikant[c]

A new method for one-pot synthesis of 2,3-substituted piperidine from *N*-PMP aldimine and aqueous glutaraldehyde *via* formal [4+2] cycloaddition is reported. This reaction involves organocatalytic direct Mannich reaction–reductive cyclization with high yields (up to 90%) and excellent enantioselectivities (up to >99%). The practicability of this method is also shown at a gram scale as well as through the synthesis of functionalized (−)-anabasine.

Functionalized saturated piperidines are increasingly common scaffolds widely distributed in a number of biologically active natural and synthetic compounds.[1] Among several known efforts, cycloaddition reactions are the most efficient methods for the synthesis of a cyclic ring system, because of their atom-economy.[2] Notably, [4+2] cycloaddition–annulation reactions such as (i) imino-Diels–Alder reaction,[3] and (ii) phosphine catalyzed *in situ* generated 1,4-carbon dipole and a subsequent reaction with imines[4] are the important methods to synthesize piperidines. Despite high utility, more strictly, these two methods gave only direct access to tetrahydropyridines instead of piperidines. On the other hand, complementary [4+2] annulation of suitable all-carbon 1,4-dipoles with imines to synthesize piperidines directly has not been studied extensively due to the unavailability of suitable 1,4-dipoles. To the best of our knowledge, the only report on *in situ* generation of 1,4-carbon dipole *via* the metal-catalyzed decarboxylative ring-opening of γ-methylidene-δ-valerolactones and subsequent [4+2] annulation with imines to synthesize 2,3-substituted piperidines in a *non-asymmetric* fashion was developed by Prof. T. Hayashi's group in 2009 (eqn (1), Scheme 1).[5] Hence, the development of a catalytic asymmetric method for 2,3-substituted piperidines through



Scheme 1 1,4-Carbon *donor–acceptor* approach with imine as formal [4+2] cycloaddition for piperidines.

1,4-carbon *donor–acceptor* annulation with imines, from simple and easily available materials, is still in very high demand. Additionally, a 2,3-substituted piperidine skeleton present in a number of compounds having biological significance (Fig. 1), though lengthy, and limited methods are available for the synthesis of this ring system.[6]

The last few years have witnessed the impressive growth of the organocatalytic cascade or tandem transformations, which are now considered to be the most effective ways to design new catalytic asymmetric synthetic routes.[7] Recently, a number of attractive organocatalytic cascade approaches have been reported by different groups to synthesize optically enriched piperidines.[8] Herein, we report a proficient one-pot organocatalytic Mannich-reductive

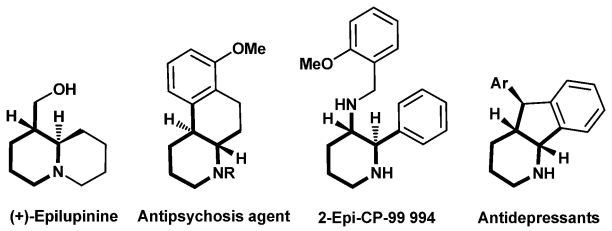


Fig. 1 Representative examples of bioactive 2,3-substituted piperidines.

[a] *Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, Rajasthan, India. E-mail: indresh.chemistry@gmail.com, indresh.kumar@pilani.bits-pilani.ac.in; Fax: +91 1596 244183; Tel: +91 1596 515707*

[b] *Instrumentation Division, IIIM-CSIR Lab, Jammu 180 001, India*

[c] *X-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu 180 006, India*

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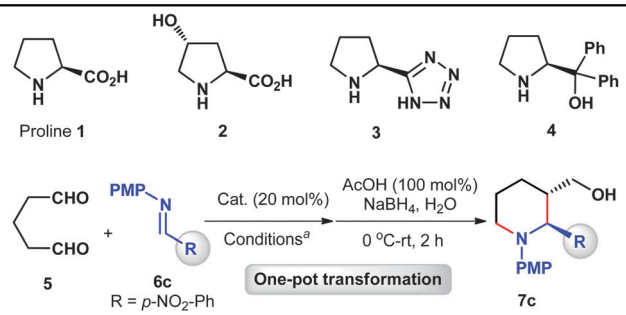
cyclization sequence for the asymmetric synthesis of 2,3-substituted piperidines from imines and aqueous glutaraldehyde **5** (eqn (2), Scheme 1). Although glutaraldehyde **5** has been used earlier for *N*-substituted piperidine synthesis[9] it has recently been employed in several other organocatalytic transformations.[10]

In continuation of our interests in nitrogen heterocyclic compounds,[11] we have recently presented the organocatalytic [3+2] annulation between succinaldehyde and *N*-PMP aldimines for the synthesis of substituted pyrrolidines and pyrroles.[12] Here, we anticipated that glutaraldehyde **5**, a synthetically useful 1,5-dicarbonyl compound, could be explored as an *in situ* 1,4-carbon *donor–acceptor* precursor with imines **6** to synthesize piperidines. This reaction involves a proline catalyzed direct Mannich reaction and acid catalyzed intramolecular reductive cyclization as one pot formal [4+2] cycloaddition. The screening of catalysts, solvents, and temperature with *N*-PMP aldimine **6c** as a model substrate was investigated and is summarized in Table 1.

Our initial experimentations showed that among the amine catalysts that were screened (entries 1–4, Table 1), proline **1** efficiently catalyzed the direct Mannich reaction of aqueous glutaraldehyde **5** (25% sol.) with imine **6c**, which on acid catalyzed reductive cyclization afforded substituted piperidine **7c** with good yield and selectivity (entry 1, Table 1). Solvent screening (entries 5–11, Table 1) revealed that polar aprotic solvents were optimal for this one-pot transformation and particularly DMSO was preferred as the solvent. Gratifyingly, enhancement in the yield (90%) and enantioselectivity (98%) was observed, when the reaction was carried out at 10 °C (entry 12, Table 1). Further decreasing the reaction temperature (entry 13, Table 1) and catalyst loading (entry 14, Table 1) led to the prolonged reaction with reduced yields. Thus, we preferred to perform this one-pot cascade sequence with optimized conditions (entry 12, Table 1).

With the optimal conditions in hand, we further explored the scope of the proline **1** catalyzed asymmetric [4+2] annulation reaction with regard to a variety of preformed *N*-PMP aldimines **6** and the results are summarized in Table 2. In general, all the *N*-PMP aldimines derived from corresponding aromatic aldehydes worked well and provided a series of 2,3-substituted piperidines **7** in moderate to high yields (up to 90%) with high diastereo- (>25 : 1) and excellent enantioselectivities (up to >99% ee) under optimized conditions (Table 2). In the case of electron-deficient aryl-imines, reactions proceeded very well (entries 1–14, Table 2), however the reactions were rather slow in the case of imines preformed from 2-substituted aldehydes (entries 1, 4, 7, and 10, Table 2) and naphthaldehydes (entries 16 and 17, Table 2) leading to lower yields, possibly because of the steric crowding. In addition, imines derived from hetero-aromatic aldehydes also resulted in the corresponding products in good yields and enantioselectivities (entries 18–22, Table 2). In the case of an alkenyl imine **6w**, derived from α-β-unsaturated aldehyde, the reaction proceeded with good yields and low enantioselectivity (entry 23, Table 2). A clean transformation to highly functionalized **7x** was observed

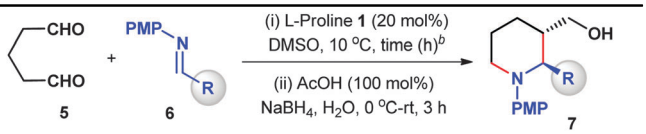
Table 1 Optimization of reaction conditions[a]



Entry	Cat.	Conditions[a]	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1**	DMSO, rt, 4 h	81	>20 : 1	94
2	**2**	DMSO, rt, 5 h	72	>20 : 1	93
3	**3**	DMSO, rt, 7 h	65	>20 : 1	82
4	**4**	DMSO, rt, 10 h	n.r.	n.d.	n.d.
5	**1**	Toluene, rt, 12 h	n.r.	n.d.	n.d.
6	**1**	CH_3CN, rt, 8 h	58	10 : 1	90
7	**1**	THF, rt, 7 h	40	10 : 1	85
8	**1**	CH_2Cl_2, rt, 12 h	n.r.	n.d.	n.d.
9	**1**	1,4-Dioxane, rt, 10 h	46	10 : 1	88
10	**1**	DMF, rt, 6 h	71	>20 : 1	92
11	**1**	NMP, rt, 5 h	65	>20 : 1	95
12	**1**	**DMSO, 10 °C, 6 h**	**90**	>25 : **1**	**98**
13	**1**	DMSO, 5 °C, 10 h	75	>25 : 1	98
14[e]	**1**	DMSO, 10 °C, 9 h	68	>25 : 1	96

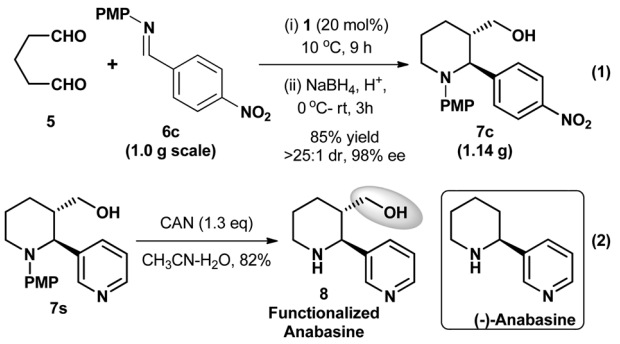
[a] (i) Imine **6c** (0.3 mmol), **5** (25% aqueous sol., 0.9 mmol), catalyst (20 mol%), solvent (3.0 mL) (ii) H_2O (2.0 mL). [b] Isolated yield refer to **7c** (after two steps in one pot operation). [c] Determined by ^{1}H-NMR. [d] Determined by HPLC analysis using a CHIRALPAK-IA column using iPrOH–hexane as solvents. [e] Catalyst **1** (10 mol%).

Table 2 Generality of formal [4+2] cycloaddition for piperidine synthesis



Entry[a]	R	Time[b] (h)	7	Yield[c] (%)	dr[d]	ee[e]
1	2-$NO_2C_6H_4$	9	**7a**	72	>25 : 1	>99
2	3-$NO_2C_6H_4$	8	**7b**	81	>25 : 1	>99
3	4-$NO_2C_6H_4$	6	**7c**	90	>25 : 1	98
4	2-FC_6H_4	9	**7d**	79	>25 : 1	92
5	3-FC_6H_4	8	**7e**	83	>25 : 1	91
6	4-FC_6H_4	8	**7f**	80	>25 : 1	75
7	2-Cl-C_6H_4	9	**7g**	69	>25 : 1	96
8	3-ClC_6H_3	8	**7h**	80	>25 : 1	89
9	4-ClC_6H_4	8	**7i**	79	>25 : 1	88
10	2-BrC_6H_4	10	**7j**	68	>25 : 1	96
11	3-BrC_6H_4	9	**7k**	75	>25 : 1	97
12	4-BrC_6H_4	9	**7l**	81	>25 : 1	90
13	3-Br-4-FC_6H_3	8	**7m**	62	>25 : 1	92
14	4-CNC_6H_4	8	**7n**	82	>25 : 1	97
15	Ph	9	**7o**	61	>25 : 1	73
16	1-Naphthyl	9	**7p**	58	>25 : 1	81
17	2-Naphthyl	9	**7q**	64	>25 : 1	94
18	2-Pyridyl	8	**7r**	72	>25 : 1	80
19	3-Pyridyl	9	**7s**	65	>25 : 1	81
20	4-Pyridyl	8	**7t**	81	>25 : 1	90
21	4-Thiophene	9	**7u**	72	>25 : 1	80
22	4-Furan	8	**7v**	63	>25 : 1	68
23	(*E*)-$CHCHC_6H_4$	10	**7w**	61	>25 : 1	68
24[f]	CO_2Et	6	**7x**	90	>25 : 1	99
25	4-Ome-C_6H_4	20	**7y**	n.r.	n.d.	n.d.
26[g]	Me	20	**7z**	n.r.	n.d.	n.d.

[a] (i) Imine **6** (0.3 mmol), **5** (25% aqueous sol., 0.9 mmol), **1** (20 mol%), DMSO (3.0 mL), (ii) H_2O (2.0 mL). [b] Time for the Mannich reaction catalyzed by **1** (20 mol%). [c] Isolated yield refer to **7**. [d] Determined by ^{1}H-NMR. [e] Determined by HPLC analysis using CHIRALPAK-IA and IB columns using iPrOH–hexane as solvents. [f] Reaction was carried out without water. [g] Aldimine was prepared *in situ*.



Scheme 2 Application at gram-scale synthesis (1); synthesis of functionalized (−)-anabasine (2).

with high yields (90%) and excellent selectivities (>25 : 1 dr, 99% ee), when activated imine **6x** was utilized without water (entry 24, Table 2). The reactions failed in the case of electron-rich arylimine and *in situ* generated alkyl imine from acetaldehyde, similar to our previous results (entries 25 and 26, Table 2).[12a]

The relative stereochemistry of C2 and C3 as *trans*- and absolute as (2*S*, 3*S*) was confirmed by determination of the coupling constant and comparing the $[\alpha]_D$ of one of our compounds **7o** with literature data (see ESI†).[6e] Single crystal X-ray study of **7t** further confirmed the stereochemical outcome,[13] as expected through the L-proline **1** catalyzed *syn*-Mannich reaction, followed by cyclization; the stereochemistry of all other products was assigned through analogy. A plausible mechanism has been proposed, which rationalizes the high stereochemical outcome of this transformation (see ESI†).

To demonstrate the practical utility of our [4+2] annulation protocol, we examined the reaction on a gram scale. While, a somewhat longer reaction time was required, aldimine **6c** (1.0 g scale) could be transformed into **7c** (1.14 g) without much reduction in yields and with the same selectivity (eqn (1), Scheme 2). These substituted piperidines are versatile building blocks in organic synthesis and can be readily converted into important products. For example, compound **7s** contains the basic skeleton of anabasine, a tobacco alkaloid obtained from *Nicotiana tobacum*, known to possess nicotinic receptor agonist activity,[14] which was easily converted to functionalized (−)-anabasine **8** (eqn (2), Scheme 2).

In conclusion, we have developed the first organocatalytic asymmetric two component direct synthesis of 2,3-substituted piperidines. The present one-pot cascade sequence involves a direct Mannich reaction of glutaraldehyde with various *N*-PMP aldimines, followed by acid catalyzed reductive cyclization, through a 1,4-carbon *donor–acceptor* strategy as formal [4+2] cycloaddition under very mild conditions. The viability of this method was established through (i) the reaction proceeding efficiently at a gram scale, and (ii) one step synthesis of a basic skeleton of (−)-anabasine alkaloid. Further applications of this methodology for the synthesis of related alkaloids are currently under investigation and will be presented in due course.

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