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An organocatalytic approach to stereoselective synthesis of 2-hydroxyazetidines and 2-hydroxypyrrolidines

Ankita Rai, Lal Dhar S. Yadav *

Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211 002, India

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ABSTRACT

A straightforward asymmetric synthesis of a new series of 2-hydroxyazetidines/2-hydroxypyrrolidines with excellent diastereoselectivity was developed via enamine catalysis using diphenylprolinol silyl ether. The Mannich-type reaction of chiral enamines with various aldimines/aziridines under mild conditions followed by intramolecular hemiaminalization affords the desired products 2-hydroxyazetidines and 2-hydroxypyrrolidines, respectively, in a one-pot operation. The scope and generality of the reaction was adequately investigated and the conditions were optimized extensively.

Nitrogen heterocycles are of immense importance not only as key components of a range of bioactive compounds, both naturally occurring and synthetic, but also as synthetic precursors to a variety of pharmaceutically and industrially relevant nitrogen-containing compounds.[1] In particular, azetidines[1e] and pyrrolidines[2] are ubiquitous in nature, and the search for new synthetic methodologies for their substituted and chiral ring systems would be of significant value. Substituted azetidines are unique heterocycles that have a wide range of synthetic applications,[1,3,4] remarkable biological activities[1,3–6] and are prevalent in natural products.[1,3–7] However, in contrast to the homologous small ring saturated nitrogen heterocycles[8] the synthetic approaches to enantioenriched azetidines are far less in number and generally involve multistep processes.[1,9] Again, 3-azetidinols[10] have been obtained by the reduction of β-lactams, cyclization of 3-amino-1,2-diols and nucleophilic substitution of L-threitol and 3-amino-1-chloroalkan-2-ols but 2-azetidinols are hitherto unknown compounds although they might interest synthetic and medicinal chemists.

Similarly, the literature survey revealed that the hydroxy pyrrolidine ring system is present in many biologically active alkaloids[11] and these type of compounds were also exploited as catalysts in asymmetric syntheses such as stereoselective reduction of ketones and Diels–Alder reaction.[12] Apart from these, 2-hydroxypyrrolidines are also used as intermediates for the synthesis of various substituted pyrrolidines.[13,14] Moreover, in spite of their chemical and biological importance only a few and tedious methods are available for their synthesis.[12,13] Owing to the fast growing chiral drug industry,[15] currently interest is focussed on stereoselective syntheses, especially those of heterocyclic systems.[16–18] In this connection, we herein, report the first example of the catalytic, stereoselective and efficient synthesis of 2-hydroxyazetidines (2-azetidinols) and 2-hydroxypyrrolidines (2-pyrrolidinols) as depicted in Scheme 1.

The present study is in continuation of our ongoing efforts to develop synthetically useful organocatalytic processes,[18] including the synthesis of small ring heterocycles.[17,19] The Mannich reaction is a classic method for C–C bond forming strategies in organic synthesis using asymmetric catalysis.[20] Realizing the concept of organocatalyzed addition of enamines formed in situ to imines as acceptors, Hayashi et al.[21a,b] and others[21c,d] have already reported the formation of β-amino compounds. Differing from those, our synthetic approach relies on the asymmetric Mannich reaction for the C–C bond formation followed by diastereoselective hemiaminalization and is applied to intramolecular cyclization of β-amino compounds obtained from in situ generated enamines and aldimines as well as aziridines. Thus, we have explored the scope of enamine catalysis for the synthesis of 2-hydroxyazetidines and 2-hydroxypyrrolidines employing a pyrrolidine-based chiral catalyst as the key point of the proposed strategy.

With the aim of identifying a novel and efficient process to synthesize 2-azetidinols, a model reaction of propionaldehyde with *N*-tosylaldimine was investigated in detail. We began our studies by examining the influence of a range of pyrrolidine based-catalysts **2a–e** (Table 1) on the reaction. Among the catalysts tested, **2a**

* Corresponding author. Tel.: +91 532 2500652; fax: +91 532 2460533.
E-mail address: ldsyadav@hotmail.com (L.D.S. Yadav).

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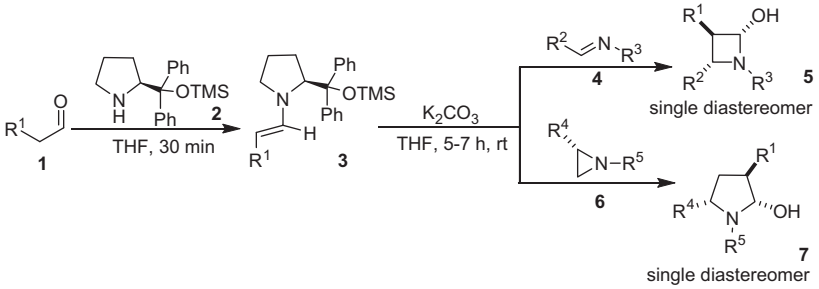
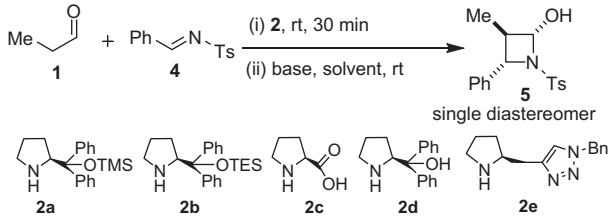


Scheme 1. Synthesis of 2-hydroxyazetidines **5** and 2-hydroxypyrrolidines **7**.

Table 1
Optimization of the reaction conditions for the synthesis of 2-azetidinol **5a**[a]



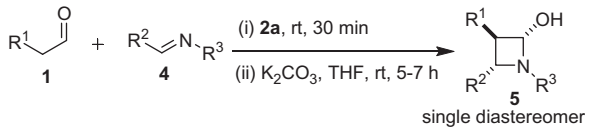
Entry	Catalyst **2** (mol %)	Base additive (equiv)	Solvent	Yield[b] (%)
1	**2a** (15)	K_2CO_3 (1.0)	THF	76
2	**2a** (20)	K_2CO_3 (1.0)	THF	85
3	**2a** (25)	K_2CO_3 (1.0)	THF	85
4	**2a** (20)	K_2CO_3 (1.0)	1,4-Dioxane	59
5	**2a** (20)	K_2CO_3 (1.0)	CH_2Cl_2	54
6	**2a** (20)	K_2CO_3 (1.0)	CH_3CN	46
7	**2a** (20)	K_2CO_3 (1.5)	THF	85
8	**2a** (20)	K_2CO_3 (0.5)	THF	67
9	**2a** (20)	Na_2CO_3 (1.0)	THF	60
10	**2a** (20)	Pyridine (1.0)	THF	9
11	**2a** (20)	$NaHCO_3$ (1.0)	THF	15
12	**2a** (20)	DABCO (1.0)	THF	40
13	**2a** (20)	DBU (1.0)	THF	53
14	**2a** (20)	Et_3N (1.0)	THF	43
15	**2b** (20)	K_2CO_3 (1.0)	THF	56
16	**2c** (20)	K_2CO_3 (1.0)	THF	42
17	**2d** (20)	K_2CO_3 (1.0)	THF	62
18	**2e** (20)	K_2CO_3 (1.0)	THF	64
19	—	K_2CO_3 (1.0)	THF	—
20	**2a** (20)	—	THF	—

[a] For the experimental procedure, see Ref. 26.
[b] Yield of isolated and purified product **5a**.

was found to be the best for triggering the reaction (Table 1, entries 2 and 15–18) through enamine catalysis. It neither interferes with the reaction leading to side reactions nor forms any zwitterionic entities. The reaction proceeds smoothly at ambient temperature with optimum catalyst loading of **2a** (20 mol %) to afford a single diastereomer. The solvent effect was next examined, and THF was found to be the best reaction medium in terms of the yield (Table 1, entries 2 and 4–6).

Again, the presence of a base is a prerequisite for the success of the hemiaminalization step. Several bases were examined, and it was found that stronger bases such as DABCO, DBU and Et_3N gave moderate yields (Table 1, entries 12–14), whereas $NaHCO_3$ and pyridine gave poor yields (Table 2, entries 10 and 11). However, K_2CO_3 (1.0 equiv) was found to be the best base additive (Table 1, entry 2). In the same manner, we utilized these optimized reaction conditions for the synthesis of 2-pyrrolidinols **7** using aldehyde **1** and aziridines **6**, and to our delight, promising results were again obtained in terms of yield and stereoselectivity. Only one diaste-

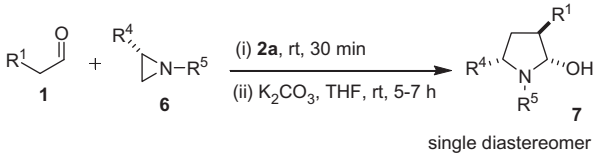
Table 2
Synthesis of 2-hydroxyazetidines **5**[a]



Entry	R^1	R^2	R^3	Product	Time[b] (h)	Yield[c,d] (%)
1	Me	Ph	Ts	**5a**	6	85
2	Me	4-MePh	Ts	**5b**	7	82
3	Me	4-MeOPh	Ts	**5c**	6	80
4	Me	4-ClPh	Ts	**5d**	6	89
5	Et	2-ClPh	Ts	**5e**	5	87
6	Me	4-NO_2Ph	Ts	**5f**	5	90
7	$PhCH_2$	2-MePh	$PhSO_2$	**5g**	7	81
8	$PhCH_2$	2-MeOPh	4-$MeOPhSO_2$	**5h**	6	79

[a] For the exprerimental procedure, see Ref. 26.
[b] Time required for completion of step (ii).
[c] Yield of isolated and purified product.
[d] All compounds gave C, H and N analyses within ±0.38% and satisfactory spectral (IR, ^1H NMR, ^{13}C NMR and EIMS) data.

Table 3
Synthesis of 2-hydroxypyrrolidines **7**[a]



Entry	R^1	R^4	R^5	Product	Time[b] (h)	Yield[c,d] (%)
1	Me	Ph	Ts	**7a**	5	84[e]
2	Me	4-MePh	Ts	**7b**	5	80
3	Me	4-*t*-BuPh	Ts	**7c**	7	79
4	Me	4-ClPh	Ts	**7d**	6	90
5	Et	2-MePh	Ts	**7e**	7	78
6	Me	Ph	$PhSO_2$	**7f**	7	88
7	Me	Ph	4-$MeOPhSO_2$	**7g**	6	80
8	$PhCH_2$	Ph	$PhSO_2$	**7h**	5	89

[a] For the experimental procedure, see Ref. 26.
[b] Time required for completion of step (ii).
[c] Yield of isolated and purified product.
[d] All compounds gave C, H and N analyses within ±0.38% and satisfactory spectral (IR, ^1H NMR, ^{13}C NMR and EIMS) data.
[e] Other conditions being the same as in Ref. 26 except the absence of **2a**, the yield for **7a** was found to be 49%, whereas in the presence of **2a** it was 84%.