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

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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**

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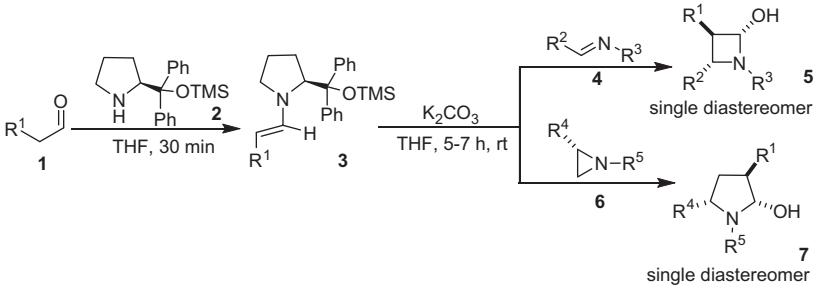
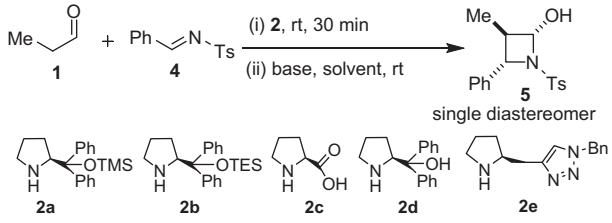


Scheme 1. Synthesis of 2-hydroxyazetidines **5** and 2-hydroxypyrrolidines **7**.

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



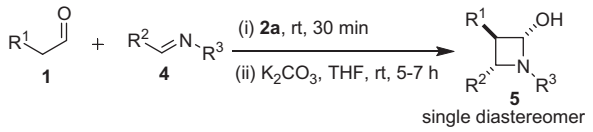
Entry	Catalyst **2** (mol %)	Base additive (equiv)	Solvent	Yield[b] (%)
1	**2a** (15)	K_2CO_3 (1.0)	THF	76
2	**2a** (20)	K_2CO_3 (1.0)	THF	85
3	**2a** (25)	K_2CO_3 (1.0)	THF	85
4	**2a** (20)	K_2CO_3 (1.0)	1,4-Dioxane	59
5	**2a** (20)	K_2CO_3 (1.0)	CH_2Cl_2	54
6	**2a** (20)	K_2CO_3 (1.0)	CH_3CN	46
7	**2a** (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-

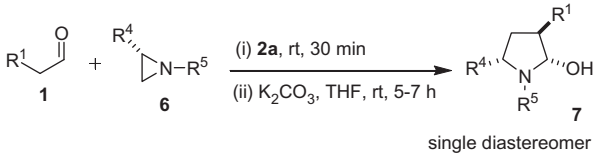
Table 2
Synthesis of 2-hydroxyazetidines **5**[a]



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%.

reomer of **5a** was formed as determined by ^{1}H NMR analysis of the crude product.

Having established the optimal reaction conditions for formation of **5** and **7**, we have surveyed the scope of reaction by using various aldehydes **1** and aldimines **4**/aziridines **6** and results are summarized in Tables 2 and 3. It was found that the nature of a substituent on the phenyl ring did not affect the diastereoselectivity.

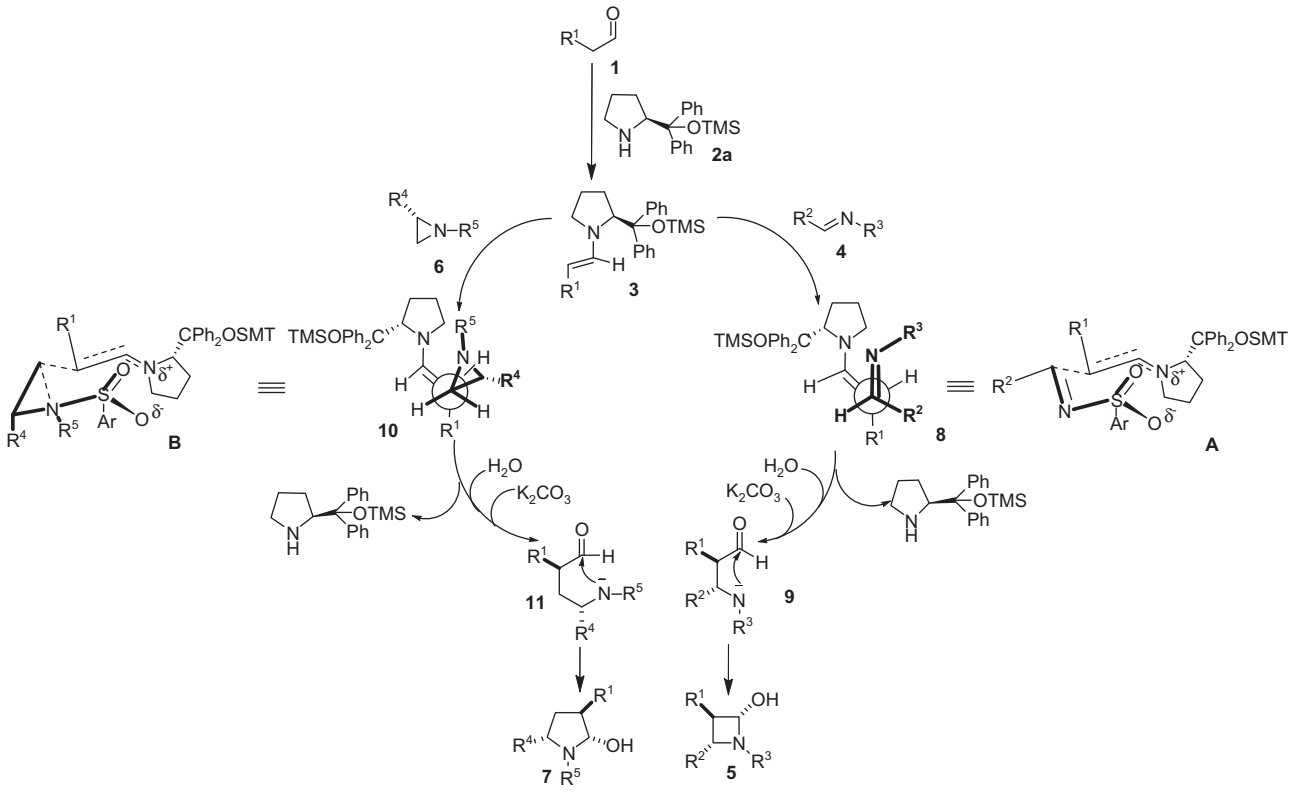
A plausible mechanism for the formation of 2-azetidinols **5** and 2-pyrrolidinols **7** is depicted in Scheme 2. In the first step, the catalyst diphenylprolinol trimethylsilyl ether **2a** activates aldehyde **1** by enamine formation which then stereoselectively adds to aldimine **4**. In the second step, the adduct undergoes intramolecular cyclization promoted by K_2CO_3 leading to the product 2-azetidinols **5**. Similarly, when aziridines **6** are used, enamine reacts with them followed by intramolecular cyclization to furnish 2-pyrrolidinols **7**.

It may be mentioned here that the chiral carbon of aziridine **6** appears to be the main driving force for the formation of a single stereoisomer **7**. However, in the presence of the catalyst **2a** a significant increase in the yield of **7** was observed (Table 3, footnote e).

In case of aziridines **6**, the regioselective ring opening may follow either electronic or steric control giving different compounds. Usually, the aziridine ring opening, takes place by a nucleophilic attack on the benzylic carbon following the electronic control,[22a,b] but the nucleophile prefers to attack the terminal carbon rather than the benzylic carbon following the steric control.[18c,22c–g] Here, presumably due to bulky nature of the attacking nucleophile, steric factor predominates over electronic effect to afford products **7** and **11**.

The C–C bond formation between the β-C-atom of enamine **3** and imino-carbon of **4** or CH_2 of aziridine ring through the TS **8** and **10**, respectively, is the enantiomeric-differentiating step (Scheme 2). This takes place from the *Si*-face of the *trans*-enamine because the bulky $(Me_3SiO)Ph_2C$ group covers the *Re*-face, hence high enantioselectivity is achieved. The TS models **8** and **10** are similar to those originally proposed by Seebach and Golinski.[23a,b] Moreover, the relative configuration of the products 2-azetidinols **5** and 2-pyrrolidinols **7** can be deduced from the mechanistic pathway if we look at the TS as shown in **A** and **B** (cf. TS suggested by Seebach et al.)[23c] because **A** bearing 1,2-diequatorial (*trans*) substituents and **B** having 1,3-equatorial, axial (*cis*) substituents are stabler conformations due to minimum repulsive interactions in the TS. Thus, **A** and **B** lead to **9** and **11**, respectively. The reactions were clean and all the synthesized products were characterized by their IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. It was gratifying that the formation of 2-azetidinols/2-pyrrolidinols was entirely diastereoselective in favour of 2,4-*cis*/2,5-*cis* isomers, respectively as determined by ^{1}H NMR of crude products **5** and **7**. The *cis*-stereochemistry of 2-azetidinols **5** was assigned and supported by comparison of $J_{trans\mathrm{H/H}}$ values of 2-H and 3-H, 3-H and 4-H of the heterocycle, which are in the range of 6.5–7.7 Hz and comparable with those reported in the literature.[24] Similarly, 2,3-*trans*-stereochemistry of 2-pyrrolidinols **7** was assigned and supported by comparison of $J_{trans\mathrm{H/H}}$ values of 2-H and 3-H of the heterocycle, which are in the range of 6.0–6.9 Hz and are comparable with those reported in the literature.[25] The relative stereochemistry of **5** and **7** are further established by NOE experiments as shown in Figure 1. A strong NOE (7.9%) at 2-H/4-H was observed in 2,4-*cis*-azetidinols **5**. Similarly, in pyrrolidinols **7** 2-H and 5-H are located on the same face of the molecule as indicated by the observation of a strong NOE between (11.4%) them. Thus, 2-azetidinols **5** and 2-pyrrolidinols **7** have 2,4-*cis* and 2,5-*cis* configurations, respectively.

In summary, we have developed a novel one-pot procedure for a highly stereoselective synthesis of 2-azetidinols and 2-pyrrolidinols via a [2+2] annulation of aldehydes and aldimines, and [2+3] annulation of aldehydes and aziridines, respectively. The synthetic protocol presents the first chiral amine triggered synthesis of 2-azetidinols and 2-pyrrolidinols via an anionic domino process,



Scheme 2. Plausible mechanism for the formation of 2-hydroxyazetidines **5** and 2-hydroxypyrrolidines **7**.

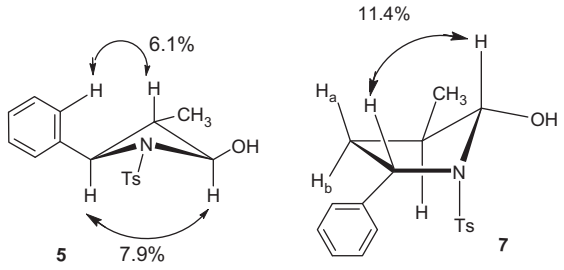


Figure 1. NOE for 2-hydroxyazetidines **5a** and 2-hydroxypyrrolidines **7a**.

thereby it also widens the scope of synthetic utility of organocatalysis. No by-product formation, atom-economy, operational simplicity, ambient temperature and high stereoselectivity are the salient features of the present protocol, which would enhance the scope of chemical and pharmaceutical applications of 2-azetidinol and 2-pyrrolidinol families of compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.013.

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26. *General procedure for the synthesis of 2-hydroxyazetidines* ***5****:* A round-bottomed flask was charged with a solution of aldehyde **1** (0.4 mmol) and the catalyst diphenylprolinol trimethylsilyl ether **2a**, (20 mol %) in THF (2 mL) previously dried over 4 Å molecular sieves, and stirred for 30 min at rt. To this was added aldimine **4** (0.4 mmol) followed by K_2CO_3 (0.4 mmol) in THF (2 mL) and stirred at rt until complete consumption of aldimine **4** (5–7 h) as indicated by TLC. Then, brine (2 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue thus obtained was purified by flash column chromatography (silica gel, 300–400 mesh; hexane/EtOAc, 95:5 as eluent) to afford an analytically pure sample of **5** (Table 2).
General procedure for the synthesis of 2-hydroxypyrrolidines ***7****:* A round-bottomed flask was charged with a solution of aldehyde **1** (0.4 mmol) and the catalyst diphenylprolinol trimethylsilyl ether **2a**, (20 mol %) in THF (2 mL) previously dried over 4 Å molecular sieves, and stirred for 30 min at rt. To this was added aziridine **6** (0.4 mmol) followed by K_2CO_3 (0.4 mmol) in THF (2 mL) and stirred at rt until complete consumption of aziridine **6** (5–7 h) as indicated by TLC. Then, brine (2 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue thus obtained was purified by flash column chromatography (silica gel, 300–400 mesh; hexane/EtOAc, 95:5 as eluent) to afford an analytically pure sample of **7** (Table 3).