Organocatalysis

DOI: 10.1002/anie.201407185

# Organocatalytic Asymmetric Mannich Cyclization of Hydroxylactams with Acetals: Total Syntheses of (−)-Epilupinine, (−)-Tashiromine, and (−)-Trachelanthamidine**

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***Abstract:*** *An asymmetric, organocatalytic, one-pot Mannich cyclization between a hydroxylactam and acetal is described to provide fused, bicyclic alkaloids bearing a bridgehead N atom. Both aliphatic and aromatic substrates were used in this transformation to furnish chiral pyrrolizidinone, indolizidinone, and quinolizidinone derivatives in up to 89% yield and 97% ee. The total syntheses of (−)-epilupinine, (−)-tashiromine, and (−)-trachelanthamidine also achieved to demonstrate the generality of the process.*

Naturally occurring izidine alkaloids (pyrrolizidine, indolizidine, and quinolizidine; Figure 1 A) and their synthetic variants are of considerable importance because of their diverse biological activities.[1] While the polyhydroxylated izidines inhibit glycosidase and glycosyl-transfer enzymes, and show anti-HIV, anti-dengue virus, anticancer, anti-inflammatory, and antidiabetic activities,[2] the alkylated izidines are noncompetitive blockers of nicotinic acetylcholine receptors and are known as defense chemicals used by hosts against predators.[3]

Although chiral-pool[4,5] and chiral-auxiliary-mediated[4,6] approaches have been described for the asymmetric synthesis of various izidine derivatives, they are often target directed. In contrast, approaches for the catalytic asymmetric synthesis of these skeletons are limited and izidine specific. These include chiral-rhodium-catalyzed[7] [2+2+2], [3+3], and 1,3-dipolar cycloadditions for indolizidine and quinolizidine derivatives, asymmetric hydrogenation of dihydro-β-carbolines,[8] organocatalytic cascade cyclizations,[9] formal aza-hetero-Diels–Alder reactions,[10] intramolecular annulation of oxo-isoquinolinium[11] for quinolizidine derivatives, chiral-silver-catalyzed one-pot double 1,3-dipolar cycloaddition for pyrrolizidines,[12] and asymmetric hydrogenation of indolizine by a chiral-ruthenium-catalyst[13] for indolizidine derivatives. A few other examples of enantioselective organocatalytic reactions are also known for the synthesis of indolizidine-based alkaloids.[14] However, a general method for the catalytic asymmetric synthesis of all the izidine skeletons is rare. Herein, we report the development of an asymmetric organocatalytic Mannich cyclization for the synthesis of the bicyclic skeleton of izidine alkaloids and its application to the total syntheses of (−)-epilupinine,[15] (−)-tashiromine,[16] and (−)-trachelanthamidine.[17]

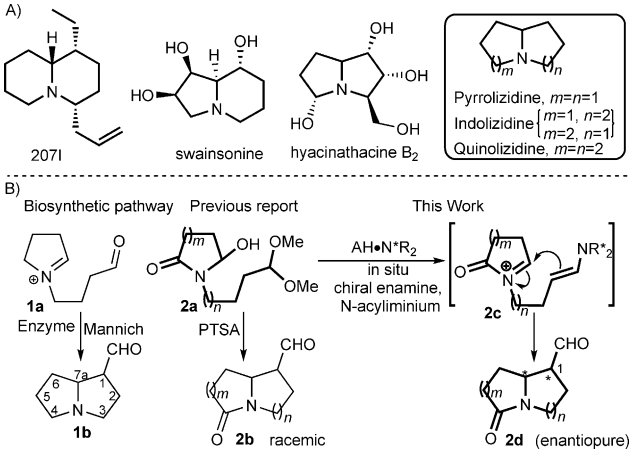


***Figure 1.*** A) Izidine alkaloids. B) Asymmetric bioinspired approach for the synthesis of the skeletons of izidine alkaloids.

Inspired by the biosynthetic pathway of pyrrolizidine alkaloids (**1a**→**1b**; Figure 1 B),[18] we recently reported the Brønsted acid catalyzed Mannich cyclization between a hydroxylactam and acetal (**2a**→(*rac*)-**2b**; Figure 1 B).[19] This reaction led us to realize that an asymmetric version of such a cyclization might be possible by using a suitable chiral catalyst. Although various chiral Brønsted acid[20] catalyzed enantioselective reactions of N-acyliminium[20,21] ions with various aromatic and heteroaromatic C nucleophiles[20,22] have been reported, these processes are unable to introduce chirality at C1. We realized that a nucleophilic addition of an asymmetric enamine[23] (generated at C1) onto an N-acyliminium ion should resolve the issue. Our efforts to remove the acetal of **2a** under various reaction conditions gave either very low yield of the linear aldehyde along with the cyclized product, or led to decomposed products. We hypothesized that a one-pot catalytic acetal removal/enamine formation/N-

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[**] This work was supported by CSIR-GenCODE (BSC0123), New Delhi. We are thankful to SAIF, CSIR-CDRI, for providing the analytical facilities, R. K. Purshottam for assistance with HPLC, Dr. Tejender S. Thakur, Molecular and Structural Biology, CSIR-CDRI for supervising the X-ray data collection and structure determination of the compound **4m**, and the Director of the Centre of Biomedical Research, Lucknow, 226014, (India) for allowing us to measure optical rotations. Y.K., K.S. thank CSIR for SRF. This is CSIR-CDRI communication no 8778.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201407185.

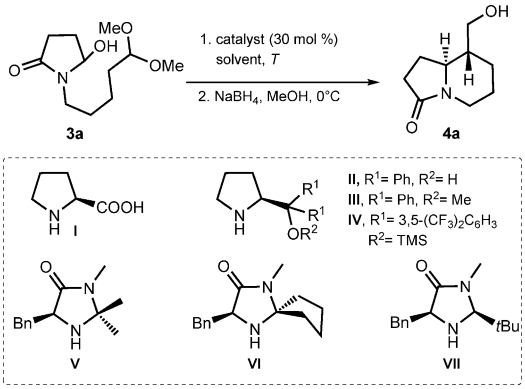
  

acyliminium formation using **2a** might be possible and provide **2c** by using a chiral amine in cooperation[24] with a Brønsted acid and water. Such a strategy, if successful, would then provide enantioenriched **2d**, from **2c**, after cyclization. However, the main challenges were to identify 1) a suitable Brønsted acid which would only catalyze the acetal removal and N-acyliminium formation, but not promote the background reaction to deliver racemic products[19] and 2) a chiral amine catalyst that will simultaneously perform cyclization via an enamine. To the best of our knowledge, an acetal has not been reported as a direct precursor to a chiral enamine, although List et al. have developed[25] the chiral Brønsted acid catalyzed asymmetric transketalization of acetals.

Given the versatile performance of pyrrolidine-[20] and imidazolidinone-based[20,26] substrates as enamine catalysts, we screened the catalysts **I**–**V** using **3a**[19] as a model substrate (Table 1). While the pyrrolidine-based catalysts **I**–**IV** (free amine) did not lead to the desired cyclization, only traces of **4a** were formed when HCl was used as an additive (see Table S1 in the Supporting Information). In contrast, although the imidazolidinone-based catalyst **V** (free amine) failed to promote the cyclization (entry 1), the salt **V**·HCl catalyzed the desired transformation enantioselectively (46%) to furnish **4a** in 74% yield after six days (entry 2). Despite having a low *ee* value, this result clearly validated our hypothesis of using an acetal and hydroxylactam as a pro-nucleophile and pro-electrophile, respectively. Surprisingly, **V**, better known as a LUMO-lowering catalyst[27] via iminium-ion formation, performed much better than **IV**. Thus, a series of Brønsted acid salts (with different p$K_a$) of the MacMillan catalyst were screened against **3a** in acetonitrile (entries 3–8). The salt of the strongest Brønsted acid (TfOH) provided good yields of **4a** with very good enantioselectivity (entry 8). This increase in the enantioselectivity could be rationalized on the basis of the strength of Brønsted acidity of the cocatalyst. A stronger acid cocatalyst facilitates a higher equilibrium content of **2c**, thereby increasing the rate of asymmetric cyclization. Notably, this result indicates that despite using a strong Brønsted acid, the desired asymmetric pathway outcompetes the undesired racemic cyclization process. Solvent screening (entries 9–13) showed acetone to be the most suitable solvent, thus allowing 90% *ee* of **4a**, presumably by favoring the transacetalization (entry 13). An additional increase in enantioselectivity was observed (entry 14) in the absence of water at 18°C. Addition of excess water disfavored the enamine formation, and therefore decreased both the yield and enantioselectivity (entries 15 and 16). However, in the presence of 4 Å molecular sieves, only traces of the cyclized product were obtained (entry 17; see Figure S2). Screening of additives (entry 18) and additional imidazolidinone catalysts (**VI** and **VII**) did not improve the enantioselectivity of the process (entries 19 and 20). Surprisingly, **VII**, having a bulky *tert*-butyl group, showed substantially low enantioselectivity (entry 20). Presumably, **VII** could not surpass the background reaction because of the steric factor.

After establishing the optimal reaction conditions, the scope and generality of this cyclization reaction were investigated (Table 2). The yields of the six-membered ring-closed products (**4b**–**g**) were in the good to very good range (63–88%) with excellent *ee* values (up to 97%). *gem*-Dialkyl-substituted substrates (**3c**–**e**) and sterically hindered acetals (**3f**,**g**) tethered with cyclopentyl and cyclohexyl groups also afforded **4c**–**g** with good yield and excellent *ee* values (up to 97%). The process has also been found useful for five-membered and seven-membered rings and provided the corresponding izidinone derivatives (**4h**–**k**) in very good yields with very good *ee* values (up to 87%). Interestingly, when **3i** was treated with **V**·HCl, the opposite sense of diastereoinduction was observed and **4i′** was obtained in good yield with good *ee* value. Although the reason is unclear to us,

***Table 1:*** Optimization of the enantioselective cyclization of **3a**[a]

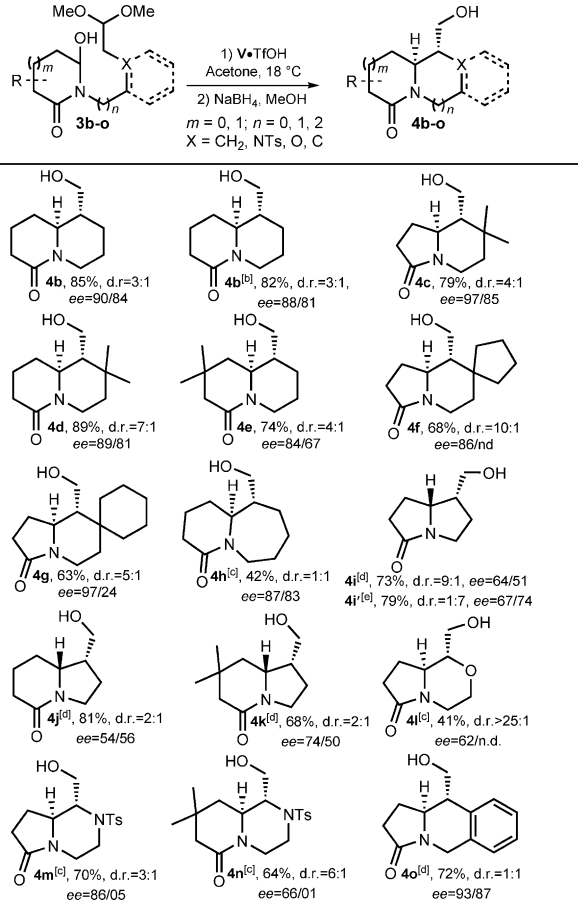



| Entry | Catalyst | Solvent | *t* [days] | Yield[b] [%] | d.r.[c] (*trans*/*cis*) | *ee* [%][d] (*trans*/*cis*) |
|---|---|---|---|---|---|---|
| 1[e] | **V** | $CH_3CN$ | 10 | trace | – | – |
| 2[e] | **V**·HCl | $CH_3CN$ | 6 | 74 | 12:1 | 46:03 |
| 3[e] | **V**·TFA | $CH_3CN$ | 5 | 69 | 9:1 | 60:72 |
| 4[e] | **V**·(+)CSA | $CH_3CN$ | 6 | 55 | 4:1 | 76:77 |
| 5[e] | **V**·(−)CSA | $CH_3CN$ | 6 | 52 | 4:1 | 76:80 |
| 6[e] | **V**·PTSA | $CH_3CN$ | 5 | 68 | 3:1 | 80:77 |
| 7[e] | **V**·$HClO_4$ | $CH_3CN$ | 5 | 85 | 3:1 | 82:74 |
| 8[e] | **V**·TfOH | $CH_3CN$ | 5 | 71 | 5:1 | 86:76 |
| 9 | **V**·TfOH | THF | 5 | 42 | 5:1 | 90:82 |
| 10 | **V**·TfOH | $CH_2Cl_2$ | 5 | 56 | 3:1 | 86:78 |
| 11 | **V**·TfOH | DMF | 7 | 27 | 4:1 | 88:80 |
| 12 | **V**·TfOH | toluene | 7 | 15 | 2:1 | 42:32 |
| 13 | **V**·TfOH | acetone | 5 | 78 | 5:1 | 90:82 |
| 14[f] | **V**·TfOH | acetone | 5 | 77 | 4:1 | 92:82 |
| 15[f,g] | **V**·TfOH | acetone | 5 | 70 | 5:1 | 86:76 |
| 16[f,h] | **V**·TfOH | acetone | 5 | 62 | 6:1 | 86:80 |
| 17[f,i] | **V**·TfOH | acetone | 7 | trace | – | – |
| 18[f,j] | **V**·TfOH | acetone | 5 | 72 | 6:1 | 86:74 |
| 19 | **VI**·TfOH | acetone | 5 | 66 | 4:1 | 84:72 |
| 20[f,k] | **VII** | acetone | 4 | 79 | 3:1 | 46:38 |

[a] Reaction conditions: 0.21 mmol of **3a**, 30 mol% catalyst, 1.5 mL of solvent at 25°C. [b] Combined yield of the isolated **4a** (two diastereomers are inseparable by silica gel column chromatography for most of the substrates). [c] Determined by $^1$HNMR analysis of the crude alcohol. [d] Determined by HPLC analysis of the benzoyl ester of **4a** using a chiral stationary phase. [e] 10 mol% of $H_2O$ was added. [f] Carried out at 18°C. [g] 1 equiv of $H_2O$ was used. [h] 4 equiv of $H_2O$ was used. [i] Carried out in presence of 4 Å molecular sieves. [j] 30 mol% of $AgSbF_6$ was used as additive. [k] 20 mol% of TfOH was added. DMF = *N*,*N*-dimethylformamide, *ee* = enantiomeric excess, PTSA = *para*-toluenesulfonic acid, TFA = trifluoroacetic acid, TfOH = trifluoromethanesulfonic acid, THF = tetrahydrofuran, TMS = trimethylsilyl.

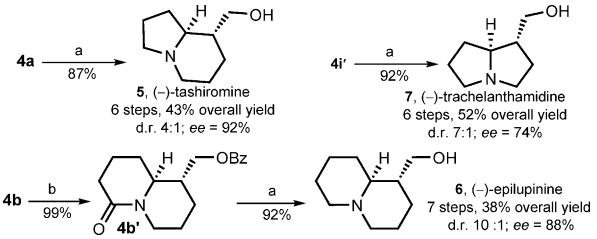
***Table 2:*** Scope with respect to **3** in the enantioselective cyclization.[a]



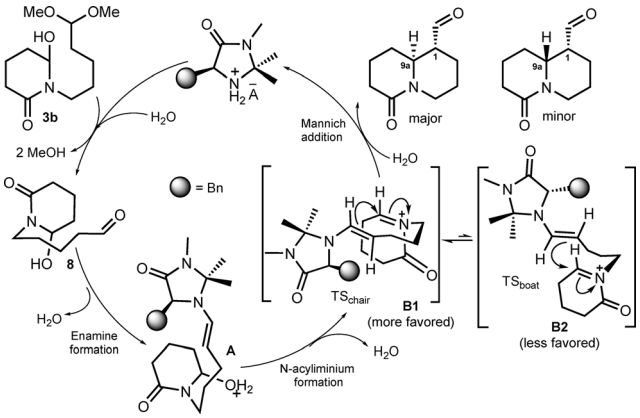

[a] Reaction conditions: 0.21 mmol of **3b–3o**, 30 mol% catalyst, 1.5 mL of solvent, 18 °C. Yield is that of the two isolated diastereomers. The d.r. value was determined by $^1$H NMR spectroscopy. The *ee* values (mentioned for both the diastereomers) were determined by HPLC analysis of the benzoyl ester (4-nitrobenzoyl ester for **4i** and **4i'**) of the substrates using a chiral stationary phase. [b] Performed on 2.04 mmol of **3b**. [c] 30 mol% of $AgSbF_6$ was used as additive. [d] Performed at 4 °C. [e] Performed using 30 mol% **V**·HCl in THF (see Scheme S1). Ts = 4-toluenesulfonyl.

such a counteranion-directed switch in diastereoselectivity was reported earlier by MacMillan et al.[28] Pleasingly, substrates with heteroatom-containing acetals afforded pyrazinopyrrolidinone (**4l**), pyrazinopiperidinone (**4m**), and oxazinopyrrolidinone (**4n**) derivatives with very good *ee* values (up to 86%). The arene substrate **3o** afforded **4o** in 72% yield in 93% *ee*, and there was no isolable product corresponding to the intramolecular Friedel–Crafts reaction.

A larger scale (500 mg, 2.04 mmol) reaction of **3b** also furnished **4b** in 82% yield with 88% *ee* (Table 2). In addition, the total syntheses of (−)-tashiromine (**5**), (−)-epilupinine (**6**), and (−)-trachelanthamidine (**7**) [representative natural products of the indolizidine, quinolizidine, and pyrrolizidine alkaloids, respectively; Scheme 1] were also achieved by using our method. The absolute configuration of **4m** was determined by X-ray crystallography[29] (see Figure S9). The optical rotation of **6** (see the Supporting Information) also matched the literature value for the natural product.[15]




***Scheme 1.*** Total syntheses of (−)-epilupinine, (−)-tashiromine, and (−)-trachelanthamidine. Reaction conditions: a) $LiAlH_4$, THF, reflux; b) PhCOCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C. DMAP = 4-(*N*,*N*-dimethylamino)pyridine.




***Scheme 2.*** Postulated mechanism for cyclization.

With regard to the mechanism, first the acetal removal for **3b** provides the aldehyde **8** (Scheme 2; see the Supporting Information). We assume that the reaction of **8** with the imidazolidinone catalyst **V** results in the *E*-enamine **A**.[27a] Upon protonation, **A** loses a water molecule and furnishes the intermediate N-acyliminium-enamine ion which cyclizes through the *Si* face of the enamine, preferably via the transition-state $TS_{chair}$ (**B1**, more favored; $TS_{boat}$ **B2** less favored) conformation to afford the *trans*-configured major product (*cis*/*trans* descriptors are with respect to the H1 and H9a). A similar hypothesis also explains why the *cis* derivative was formed as the major product in the case of the five-membered ring cyclization (see Figure S8).

In summary, we have demonstrated a mild, step-economic, catalytic enantioselective intramolecular Mannich reaction between acetals and hydoxylactams to provide N-bridgehead bicyclic scaffolds by employing MacMillan's catalyst. Our method has been generalized for the asymmetric synthesis of the entire izidine skeleton and utilized for the total synthesis of izidine alkaloids. We hope that the concept of using an acetal as the precursor to an enamine in one pot will be useful towards designing new organocatalytic cascade reactions for the synthesis of complex polycyclic scaffolds. We aim to explore this strategy further and studies are currently ongoing.

Received: July 14, 2014
Published online: ■■ ■■, ■■■■

**Keywords:** acetals · alkaloids · cyclization · natural products · organocatalysis

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# Communications

## Organocatalysis

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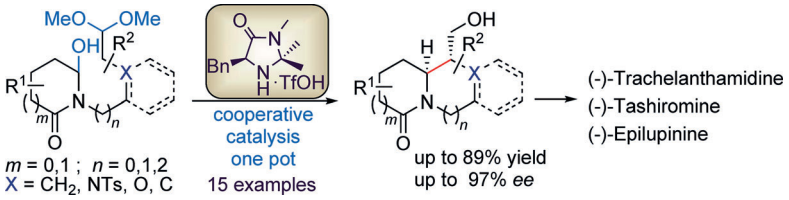
Organocatalytic Asymmetric Mannich Cyclization of Hydroxylactams with Acetals: Total Syntheses of (−)-Epilupinine, (−)-Tashiromine, and (−)-Trachelanthamidine




**Double bonanza**: The title reaction in the presence of an imidazolidinone-based catalyst furnished N-bridgehead bicyclic alkaloids bearing [3.3.0], [3.4.0], [4.4.0], and [4.5.0] skeletons. By using this protocol, the total syntheses of (−)-epilupinine, (−)-tashiromine, and (−)-trachelanthamidine were achieved.