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# Biomimetic Organocatalytic Asymmetric Synthesis of 2-Substituted Piperidine-Type Alkaloids and Their Analogues

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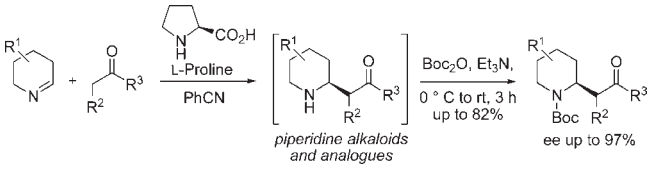
## ABSTRACT




**Natural substances such as pelletierine and its analogues have been prepared in up to 97% ee and good yield by a protective-group-free, biomimetic approach. Usage of benzonitrile or acetonitrile as solvents effectively prevents product racemization.**

Six-membered ring nitrogen heterocycle alkaloids are widespread in nature, and given their useful biological activity, significant effort has been devoted to their preparation.[1] In particular, (−)-pelletierine, *ent*-**1a**, isolated in 1878,[2] has been a popular target since its first total synthesis reported in 1961, which confirmed its structure.[3a] Through the years, new methodologies have been specifically ideated to obtain this molecule and its analogues,[3b−j] and one of the most effective strategies is the asymmetric lithiation of *N*-protected heterocycles by means of chiral amines and their subsequent functionalization with electrophiles.[4a−g] This procedure requires noncommercially available chiral bases, air- and moisture-sensitive reagents such as organolithium species, and low temperatures, generally below −50 °C. Recently, Carter and coworkers accessed these structures in good enantioselectivity (up to 95% ee), in six steps and 37% yield starting from an acyclic precursor[5] via an asymmetric organocatalytic approach. Significantly, the asymmetric preparation of the core structure **1** would easily give access to a set of natural substances *via* *N*-methylation and/or diastereoselective partial or complete carbonyl reduction.[6]

Furthermore, chiral nonracemic pelletierine **1a** (Figure 1) could also be the starting material for the asymmetric

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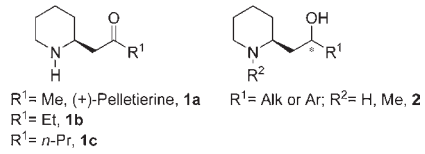
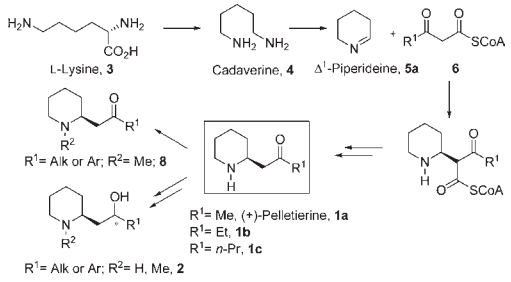



**Figure 1.** Structure of some six-membered ring alkaloids.

preparation of more complex alkaloid-type natural substances, such as *rac*-vertine, recently synthesized in 11 steps from *rac*-pelletierine by Künding and co-workers[7a] or a citrinadin B analog by Sorensen and co-workers.[7b]

The biosynthesis of these natural substances derives from the metabolism of L-lysine **3**, which is decarboxylated to the achiral diamine cadaverine **4**, cyclized to the unsaturated heterocycle $\Delta^1$-piperideine **5a** and then attacked by acylacetyl-CoA **6**. Subsequently, the side chain undergoes further elaboration, to afford the simplest members of this alkaloid family, pelletierine **1a** or its superior homologues **1b**–**c**. Reduction of the carbonyl function and *N*-methylation give a variety of naturally occurring molecules such as compounds **2** or **8** (see Scheme 1).[1b]

**Scheme 1.** Biosynthesis of 2-Substituted Six-Membered Nitrogen Heterocyclic Natural Substances **1**, **2**, and **8**




Inspired by Nature's approach, we envisaged that the organocatalyzed Mannich-type addition reaction[8] of activated ketones to $\Delta^1$-piperideine **5a** could be the most straightforward and direct synthesis possible for many of these molecules, accessing them in a single step, in an asymmetric way and without the need of protective groups.[9]

The Mannich addition reaction of acetone and other ketones to cyclic imines is reported only for two peculiar substrate types, the 9-tosyl-3,4-dihydro-$\beta$-carboline by Ohsawa and Itoh[10a–c] and, more recently, thiazines and oxazines as described by Martens.[10d] The asymmetric addition of nucleophiles to $\Delta^1$-piperideines is, to the best of our knowledge, unreported.

We prepared $\Delta^1$-piperideine **5a** (via piperidine *N*-chlorination and base-mediated HCl elimination)[11] and employed this electrophile in the reaction with carbonyl compounds **9a**–**b** (see Table 1, entries 1–2).

$\Delta^1$-Piperideine **5a**, such as other cyclic imines presented later in this work, exists in solution as a complex diastereoisomeric mixture of a trimeric (major component) and monomeric form.[11a] However, during the reaction with nucleophiles, the latter component is constantly removed from the equilibrium, and the final reaction outcome is consistent with if only the monomer would be present. No background reaction was observed when acetone **9a** ($pK_{a[DMSO]}$ = 26.5) was employed as the nucleophile (Table 1, entry 1). Ethyl acetoacetate **9b** ($pK_{a[DMSO]}$ = 14.2),[12,13] which upon hydrolysis and decarboxylation could lead to a one-pot, two-step synthesis of the alkaloid pelletierine **1a**, readily reacted with $\Delta^1$-piperideine **5a** in the absence of any additive (entry 2) because the unsaturated heterocycle could itself act as the catalyst, suggesting that the development of a tertiary amine asymmetric approach to this peculiar reaction could be, at the state-of-the-art, unfeasible.

The reaction was therefore run with acetone **9a** via enamine activation[14] employing organocatalysts **I**–**V**. In particular, with TMS ether **I**[15] none of the desired compound could be obtained (entry 3). Only catalysts bearing a deprotonable functional group such as **II**[16]–**V** were effective in this transformation, leading to complete conversion of $\Delta^1$-piperideine **5a**, in moderate yield and with no stereoselection employing catalyst **II** (entry 4) and in low yield and 42% *ee* with catalyst **III** (entry 5). (L)-Proline **IV** (entry 6) and azetidine **V** (entry 7) gave satisfactory yields and good enantioselectivities.[17] After aqueous workup, the $^1$H and $^{13}$C NMR spectra of the crude material showed the formation of (+)-pelletierine **1a**[2–4] with only some minor

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(12) Racemic synthesis of pelletierine **1a** exploiting this strategy: ref 3d.

(13) Rouchaud and Braekman recently reported that ethyl acetoacetate **9b** reacts with the dimer form of **5a** to give the racemic skeleton of tetraponerine-type alkaloids. With our conditions, we only observed the reaction of monomer **5a** with the nucleophile tested; see ref 11a.

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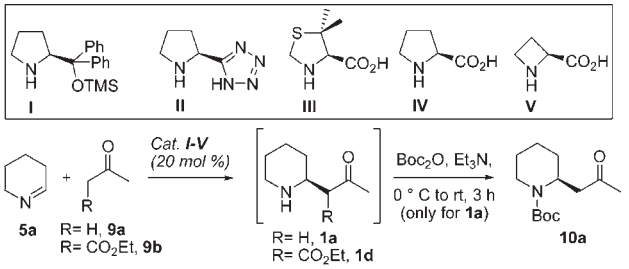
(17) Amino acids **III**–**IV** were employed in the pioneering paper describing the asymmetric intermolecular aldol reaction: List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

impurities, but in order to perform HPLC analysis, the secondary nitrogen moiety was protected *in situ* ($Boc_2O$) and the compound was purified by FC affording the protected amine **10a**.[18]

**Table 1.** Optimization of Conditions for Organocatalytic Synthesis of *N*-Boc-pelletierine **10a**

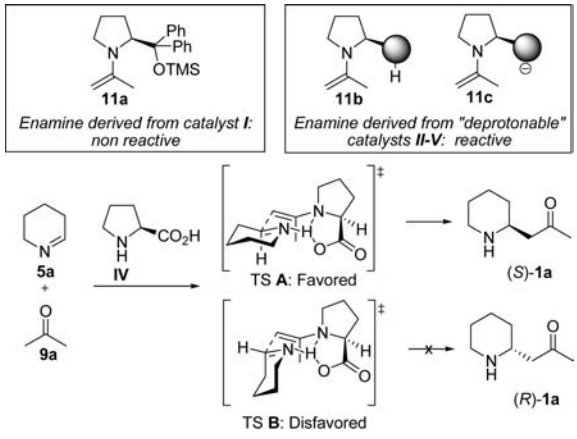



| entry[a] | catalyst | solvent | $T$, °C | $t$ | yield, %[b] | ee, %[c] |
|---|---|---|---|---|---|---|
| 1[d] | none | DCM | rt | 24 h | NR | – |
| 2[e] | none | DCM | rt | 24 h | 95[f] | – |
| 3[d] | **I** | $CH_3CN$ | rt | 2 d | NR | – |
| 4[d] | **II** | $CH_3CN$ | rt | 2 d | 60 | <5 |
| 5[d] | **III** | $CH_3CN$ | rt | 2 d | 22 | 42 |
| 6[d] | **IV** | $CH_3CN$ | rt | 2 d | 67 | 79 |
| 7[d] | **V** | $CH_3CN$ | rt | 2 d | 65 | 85 |
| 8[d] | **IV** | $CH_3CN$ | −20 | 5 d | 68 | 87 |
| 9[d] | **V** | $CH_3CN$ | −20 | 5 d | 65 | 87 |
| 10[d] | **IV** | *n*-PrCN | −20 | 7 d | 45 | 93 |
| **11**[d] | **IV** | **PhCN** | **−20** | **7 d** | **82** | **95** |
| 12[d] | **IV** | DMSO/$H_2O$[g] | rt | 2 h | 92 | 76 |

[a] Reactions are run employing 50 mg (0.6 mmol) of $\Delta^1$-piperideine **5a**, nucleophile **9a**–**b**, 0.85 mL of solvent, and 20 mol % catalyst **I**–**V**. [b] Isolated yield of **9a**–**b** determined after purification via FC. [c] Ee determined by HPLC on chiral stationary phase, for **10a**/hexane/*i*-propanol 98.5:1.5, IA Chiralpack + IB Chiralpack columns, flow 0.9 mL/min. [d] Acetone, R = Me, **9a**, 6 equiv (0.3 mL). [e] Nucleophile: ethyl acetoacetate, R = $CO_2Et$, **9b**, 2 equiv. [f] Yield of **1d**. [g] 4 mL of DMSO/$H_2O$ 8:1. rt = room temperature; NR = no reaction. ND = not determined. See Supporting Information for a full list of conditions and catalysts tested.

After the reaction temperature was lowered to −20 °C, *N*-Boc pelletierine **10a** was obtained in very good enantioselectivity (89–95% ee, entries 8–11). The reaction conditions originally developed by Ohsawa and Itoh[10a–c] (DMSO/$H_2O$, entry 12) for their analogous Mannich reaction afforded the desired compound in shorter reaction times and good yield; however, in these specific conditions we observed racemization of the product **1a** (see Supporting Information (SI) for details; Table 3). It is well-known that compounds such as **1a** racemize through a retro aza-Michael process.[1b] Nitriles as solvents led to longer reaction times, but they significantly prevented racemization. We believe that the superior reactivity of organocatalysts **II**–**V** presenting a free carboxyl group or its isoster, with respect to catalyst **I**, is due to the deprotonation of the enamine **11b** by the reagent or the product, which, as documented recently,[19] leads to the more activated intermediate **11c** (Scheme 2, top). The absolute configuration of **10a** was determined by optical rotation comparison with literature data,[5] and the stereochemical outcome is consistent with a Zimmerman–Traxler transition state (Scheme 2).[17]

**Scheme 2.** Activation of Enamines via Deprotonation (Top) and Rationalization of the Stereochemical Outcome of the Reaction (Bottom)




We then extended the scope of our reaction to different combinations of unsaturated cyclic amines and ketones (Table 2). First, we examined the electrophiles **5b**–**c**, in the reaction with acetone. The cyclic imine **5b**, which presents a protected carbonyl functionality, gave results comparable to $\Delta^1$-piperideine **5a** (Table 2, entry 1, 94% ee, 56% yield). The isoquinoline-derived electrophile **5c** allowed the preparation of adduct **10c** in good yield, but with low stereoselectivity (16% ee, entry 2).

The enhanced reactivity of carbonyl compounds in these conditions rendered possible extending this reaction to several ketones different from acetone (entries 3–11).[20]

These reactions were high yielding at room temperature but proceeded in poor enantioselectivity (compound **10e**,

(18) The Boc protection reaction, although necessary for analytical purposes and compound purification via FC, has a yield ≤ 80% and is responsible for the moderate overall yield reported in Table 2.

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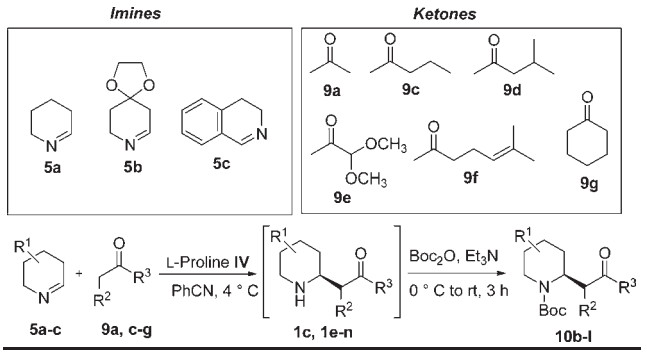
**Table 2.** Synthesis of Pelletierine Analogues **10b**–**l** by the Combination of Cyclic Imines **5a**–**c** and Ketones **9a,c**–**g**




| entry[a] | | reagents | | product | IV, mol % | t, day | yield, %[b] | ee, %[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | | **9a** | **5b** | **10b** | 20 | 7 | 56 | 94 |
| 2 | | **9a** | **5c** | **10c** | 20 | 7 | 54 | 16 |
| 3 | | **9c** | **5a** | **10d** | 20 | 7 | 25 | 97 |
| 4 | a[d] | **9d** | **5a** | **10e** | 20 | 7 | 71 | 36 |
| | b | | | | 20 | 10 | 12 | 90 |
| | c | | | | 45 | 30 | 35 | 84 |
| 5 | a | **9e** | **5a** | **10f** | 20 | 7 | 22 | 88 |
| | b | | | | 45 | 20 | 33 | 92 |
| 6 | a | **9f** | **5a** | **10g** | 20 | 10 | 15 | 92 |
| | b | | | | 45 | 30 | 49 | 92 |
| 7 | a[e] | **9g** | **5a** | **10h** | 20 | 14 | 39 | 92/99[f] |
| | b | | | | 45 | 7 | 25 | 87/94[f] |
| 8 | | **9c** | **5b** | **10i** | 45 | 30 | 72 | 86 |
| 9 | | **9d** | **5b** | **10j** | 100 | 30 | 36 | 93 |
| 10 | | **9e** | **5b** | **10k** | 100 | 30 | 14 | 96 |
| 11 | | **9g** | **5b** | **10l** | 20 | 7 | 37 | 90/–[g] |

[a] Reactions are run employing 0.6 mmol of electrophiles **5a**–**c**, 6 equiv of nucleophile **9a,c**–**g**, 0.85 mL of PhCN, and catalyst **IV**. [b] Isolated yield of **10b**–**l** determined after purification via FC. [c] Ee determined by HPLC on chiral stationary phase; see Supporting Information. [d] Reaction run at rt. [e] Reaction run at −20 °C. [f] Dr = 1:1 stereochemistry not determined. [g] Dr = 2:1, ee of major diastereoisomer; stereochemistry not determined. See Supporting Information for details.

8 entry 4a, 71% yield but only 36% ee). The lowering of the temperature to 4 °C led to excellent enantiomeric excesses, but at the expense of the yield (see Table 2, entries 3–11, low conversion after few days). This dilemma was solved employing in some cases a higher catalyst loading of the cheap and widely available (L)-proline **IV**. For ketones different from acetone, DMSO/$H_2O$ mixtures as solvent led to better yields but to low enantioselectivity due to racemization (see SI). With these improved conditions and the usage of benzonitrile as solvent which prevented racemization, it was finally possible to obtain in moderate yields but excellent enantioselectivity the desired adducts. Cyclic ketones such as **9g** reacted in high enantioselectivity (entries 7 and 11) without significant diastereoselection.

In conclusion, herein we report a new synthetic methodology for the direct and asymmetric introduction of six-membered heterocycles in ketones. Reactions proceed in good yield and elevated stereoselectivity employing as a chiral mediator the cheap organocatalyst (L)-proline **IV**. We prepared (+)-pelletierine **1a** in a single step. We strongly believe that electrophiles **5** could be successfully exploited in several other asymmetric reactions.

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**Supporting Information Available.** Characterization of new compounds and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.