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Asymmetric synthesis of highly enantioenriched 2-substituted piperidines and 6-substituted piperidine-2-ones by a combination enantioselective hydrazone allylation with ring closing metathesis

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ABSTRACT

An efficient method for the asymmetric synthesis of highly optically pure 2-substituted piperidines and 6-substituted piperidine-2-ones from aldehydes was developed by a sequence of enantioselective hydrazone allylation and ring closing metathesis. This method was found to be effective for a variety of substrates, showing substrate generality. The method's synthetic utility was illustrated in concise synthesis of the alkaloid (*R*)-(−)-coniine.

1. Introduction

The optically pure 2-substituted piperidine skeleton is ubiquitous in a wide range of natural products and medicinal drugs.[1] It has been used as a building block in the synthesis of biologically active compounds. Stereoselective construction of a chiral carbon center adjacent to the ring nitrogen atom in 2-substituted piperidines has been an important issue in organic synthesis.[2] Among strategies reported in the literature, one reliable route to enantio-enriched 2-substituted piperidines is ring closing metathesis of chiral dienes.[3] The ring closing metathesis reaction has been widely used in organic synthesis and provides a powerful synthetic method for producing nitrogen-containing heterocycles. The route to chiral 2-substituted piperidines by ring closing metathesis requires chiral homoallylamines (Scheme 1). Various methods have been reported for asymmetric homoallylamine synthesis.[4] The asymmetric addition of allylindium reagents into C=N bonds has been a powerful method for the synthesis of chiral homoallylamines because allylindium reagents have low basicity, high chemoselectivity, and low toxicity. However, many of these synthesis reactions rely on chiral auxiliaries and a stoichiometric amount of chiral reagents to establish the desired stereochemistry at the chiral center adjacent to the nitrogen atom.[5,6] To the best of our knowledge, only a few procedures have operated in a catalytic enantioselective manner.[7] We reported recently that a stereogenic center adjacent to the nitrogen atom was readily established by indium-mediated enantioselective allylation of *N*-benzoylhydrazones derived from aldehydes in the presence of a catalytic amount of protonated chiral amine (PCA) with a high level of enantioselectivity (Scheme 2).[8] The present work continues our research on developing asymmetric synthetic methods for optically pure compounds.[9] Here, we present the asymmetric synthesis of highly optically pure 2-substituted piperidines and 6-substituted 2-piperidinones by combining highly enanatioselective allylation of hydrazones with ring closing metathesis.

2. Results and discussion

As outlined in Scheme 1, the chiral dienes used for ring closing metathesis were accessed by a synthetic sequence of enantioselective hydrazone allylation, *N*–*N* bond cleavage, and *N*-allylation. Enantioselective addition of allylindium reagent (3 equiv) to aldehyde-derived *N*-benzoylhydrazones in the presence of protonated chiral amine (0.33 equiv) gave the corresponding homoallylamines in high chemical yields with high enantioselectivities (Table 1). Optically pure homoallylamines from aryl aldehyde-

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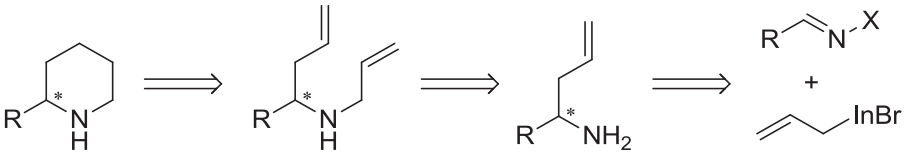
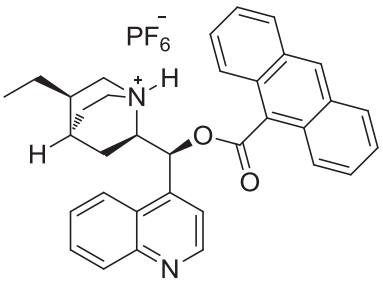


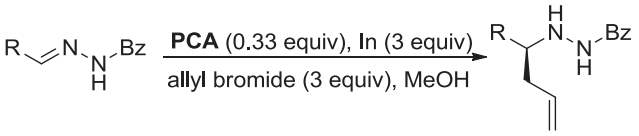
Scheme 1. Retrosynthesis for 2-substituted piperidines.



PCA

Scheme 2. Structure of PCA.

Table 1
Enantioselective allylation of aldehyde-derived *N*-benzoylhydrazones in the presence of protonated chiral amine **PCA**



1 **2**

Entry	Substrate	R	Temp (°C)	Time (h)	Product	Yield (%)[a]	ee (%)[b]
1	**1a**	Ph–	rt	12	**2a**	91	99 (*S*)[c]
2	**1b**	4-F–Ph–	rt	12	**2b**	91	99 (*S*)[c]
3	**1c**	4-NO_2–Ph–	rt	12	**2c**	93	99 (*S*)[c]
4	**1d**	3-Cl–Ph–	rt	12	**2d**	92	99 (*S*)[c]
5	**1e**	2-Br–Ph–	rt	12	**2e**	92	99 (*S*)[c]
6	**1f**	2-MeO–Ph–	rt	12	**2f**	92	99 (*S*)[c]
7	**1g**	$CH_3(CH_2)_2$–	rt	12	**2g**	92	80 (*R*)
8	**1g**	$CH_3(CH_2)_2$–	−30	58	**2g**	93	99 (*R*)
9	**1h**	$(CH_3)_3C$–	−30	58	**2h**	92	99 (*S*)
10	**1i**	CH_3CH=CH–	−30	58	**2i**	93	99 (*S*)

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA) with hexane–isopropanol as solvent.
[c] From Ref. [8].

derived *N*-benzoylhydrazones were synthesized, regardless of substituent positions and whether the substituent was electron-withdrawing or electron-donating (entries 1–6). *N*-benzoylhydrazones derived from aliphatic aldehydes underwent allylation at room temperature with relatively low enantioselectivity (entry 7). To improve the optical purity of homoallylamines, the reaction was performed at −30 °C. This resulted in increased enantioselectivity up to 99% ee, although prolonged reaction times were required to complete the corresponding addition transformation (entry 8). Interestingly, sterically hindered pivalaldehyde also afforded the corresponding addition product in 92% yield with 99% ee (entry 9). An α,ß-unsaturated aldehyde-derived *N*-benzoylhydrazone exclusively gave the 1,2-addition product in high yield with high enantioselectivity (entry 10). The reaction of organometallic reagents with imines derived from aliphatic aldehydes with α-hydrogen is complicated by poor stereoselectivity due to enamine formation. The present method represents the best example to date of indium-mediated catalytic enanatioselective allylation of substrates with alkyl chains.[7]

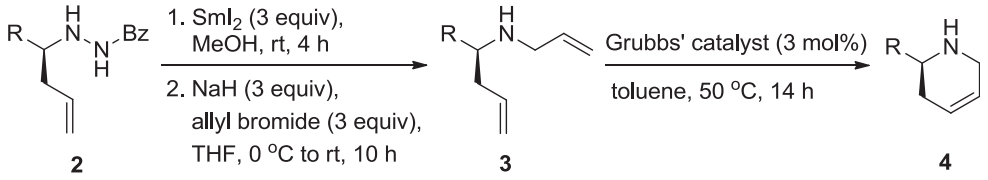
We reasoned that the high enantioselectivity is the consequence of the interaction of PCA with *N*-benzoylhydrazone via hydrogen bonding and π–π interaction, providing a chiral environment. The allylindium nucleophile generated in situ attacks at the less hindered *Si*-face of the C=N bond.

After obtaining the optically pure amines, the next synthesis step was investigated. Compound **3** was obtained by *N*–*N* bond cleavage of compound **2** performed with SmI_2 and followed by allylation.[10] The results are summarized in Table 2. Deprotected amines were converted into the corresponding dienes **3** by reaction with allyl bromide in the presence of sodium hydride. The subsequent reactions afforded dienes **3** in more than 80% yield in all cases. The dienes **3** obtained were then subjected to ring closing metathesis. Free amines are known to be detrimental to Grubbs' catalyst.[11] However, when the ring closing metathesis reaction of dienes **3** in dichloromethane in the presence of benzylidene bis(tricyclohexylphosphine)-dichlororuthenium (Grubbs' second generation catalyst) was carried out, the desired products **4** were obtained in more than 91% yield and showed generality of substrates. Optical purity was examined with HPLC analysis using a chiral column, proving not altering the stereochemistry at the sterogenic center. To the best of our knowledge, the levels of enantioselectivity and substrate generality reported herein are the highest among all those previously reported.[3]

The reaction scope was then extended to asymmetric synthesis of 6-substituted piperidine-2-ones, which are important building blocks for the synthesis of 2-substituted piperidines[12] and bioactive molecules.[13] The results are summarized in Table 3. After *N*–*N* bond cleavage using SmI_2, homoallylamine acylation with acryloyl chloride in the presence of triethylamine afforded the corresponding amides in more than 80% yields in all cases over two steps. The resulting amides **5** were then subjected to ring closing metathesis with Grubbs' catalyst to afford enantioenriched 6-substituted piperidine-2-one motifs in high yields. The optical purity of homoallylamines was retained in compound **6**.

To illustrate the utility of the methodology, (*R*)-(−)-coniine was prepared by hydrogenation of compound **4g**. (*R*)-(−)-Coniine is a poisonous alkaloid found in poison hemlock and a neurotoxin that disrupts the peripheral nervous system.[14] Catalytic

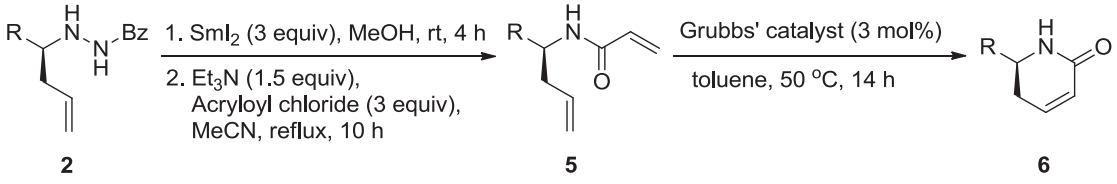
Table 2
N–N bond cleavage, *N*-allylation, and ring closing metathesis



Entry	Substrate	R	Product **3**	Yield (%)[a]	Product **4**	Yield (%)[a]	ee (%)[b]
1	**2a**	Ph–	**3a**	81	**4a**	91	99 (*S*)
2	**2b**	4-F–Ph–	**3b**	81	**4b**	91	99 (*S*)
3	**2c**	4-NO_2–Ph–	**3c**	83	**4c**	93	99 (*S*)
4	**2d**	3-Cl–Ph–	**3d**	82	**4d**	92	99 (*S*)
5	**2e**	2-Br–Ph–	**3e**	80	**4e**	92	99 (*S*)
6	**2f**	2-MeO–Ph–	**3f**	81	**4f**	92	99 (*S*)
7	**2g**	$CH_3(CH_2)_2$–	**3g**	81	**4g**	92	99 (*R*)
8	**2h**	$(CH_3)_3C$–	**3h**	80	**4h**	93	99 (*S*)
9	**2i**	CH_3CH=CH–	**3i**	80	**4i**	91	99 (*S*)

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA) with hexane–isopropanol as solvent.

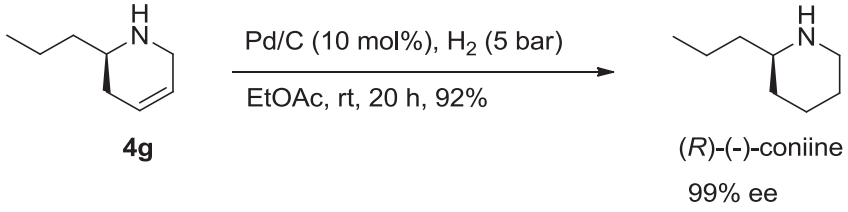
Table 3
N–N bond cleavage, acylation, and ring closing metathesis



Entry	Substrate	R	Product **5**	Yield (%)[a]	Product **6**	Yield (%)[a]	ee (%)[b]
1	**2a**	Ph–	**5a**	81	**6a**	93	99 (*S*)
2	**2b**	4-F–Ph–	**5b**	80	**6b**	94	99 (*S*)
3	**2c**	4-NO_2–Ph–	**5c**	81	**6c**	93	99 (*S*)
4	**2d**	3-Cl–Ph–	**5d**	81	**6d**	93	99 (*S*)
5	**2e**	2-Br–Ph–	**5e**	81	**6e**	93	99 (*S*)
6	**2f**	2-MeO–Ph–	**5f**	82	**6f**	93	99 (*S*)
7	**2g**	$CH_3(CH_2)_2$–	**5g**	81	**6g**	92	99 (*R*)
8	**2h**	$(CH_3)_3C$–	**5h**	80	**6h**	93	99 (*S*)
9	**2i**	CH_3CH=CH–	**5i**	81	**6i**	91	99 (*S*)

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA) with hexane–isopropanol as solvent.

hydrogenation of **4g** with Pd/C in ethyl acetate at room temperature gave 92% yield of (*R*)-(−)-coniine. The enantiomeric purity was determined to be 99% ee by HPLC analysis using a chiral column Scheme 3.



Scheme 3. Synthesis of (*R*)-(−)-coniine.

3. Conclusions

In conclusion, we have developed an efficient method for the asymmetric synthesis of highly optically pure 2-substituted piperidines and 6-substituted piperidine-2-ones from aldehydes. This method involves a sequence of enantioselective hydrazone allylation and ring closing metathesis with excellent yields. This approach was found to be effective for a variety of substrates, showing generality of substrates. The process provides a pathway for the synthesis of optically pure bioactive alkaloids that contain piperidine skeletons with a stereogenic center adjacent to the ring nitrogen atom.

4. Experimental section

4.1. General

Unless otherwise specified, chemicals were purchased from commercial suppliers and used without further purification. Column chromatography was performed using silica gel (230–400 mesh, Merck). TLC was performed on glass sheets pre-coated with

silica gel (Kieselgel 60 PF_{254}, Merck). Mps were determined with a Fisher–Johns melting point apparatus and were uncorrected. The ^1H- and ^{13}C NMR spectra were generated using a Bruker 400 NMR spectrometer operated at 400 MHz for ^1H and 100 MHz for ^{13}C nuclei. The spectra were internally referenced to residual protio solvent signals. Chemical shifts were reported in parts per million (ppm). IR spectra were collected on a Perkin–Elmer 16 PC FTIR spectrometer. Specific rotations were measured on a JASCO P-2000 polarimeter. Microanalyses were performed on a CE instrument EA1110 elemental analyzer. High performance liquid chromatography (HPLC) analyses were performed using a Younglin SP930D instrument with a Daicel Chiralpak IA column (250×4.6 mm). UV absorption was monitored at 254 nm. PCA and **2a**–**f** were synthesized by using the previously reported methods.[8] **4a**,[3a] **4g**,[15] **6a**,[3b] and **6b**[3b] were reported in literature.

4.1.1. General procedure for allylation of N-benzoylhydrazones.[8] A mixture of **PCA** (194 mg, 0.30 mmol) and *N*-benzoylhydrazones **1** (0.90 mmol) in methanol (4 mL) was stirred at room temperature or −30 °C for 1 h under argon. Allyl bromide (0.23 mL, 2.67 mmol) and indium powder (306 mg, 2.67 mmol) were added to the above mixture, which was then stirred under argon at either room temperature or -30 °C. The reaction was monitored by TLC and proceeded for the indicated time. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, and dried over anhydrous $MgSO_4$. After solvent filtration and evaporation, the residue was purified by flash chromatography on silica gel, affording the corresponding addition products **2**. Enantiomeric excess was determined by chiral HPLC analysis and compared with the authentic racemic material.

*4.1.2. (R)-N′-(Hept-1-en-4-yl)benzohydrazide (**2g**).* Following the general procedure above, **2g** was obtained as a yellow oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=2/8) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=95/5, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=15.2 min, t_r (minor)=12.3 min]. $[\alpha]_D^{20}$=+68.4 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.88 (t, *J*=7.2 Hz, 3H), 1.39–1.56 (m, 4H), 2.24–2.36 (m, 2H), 3.54 (t, *J*=7.2 Hz, 1H), 5.03–5.20 (m, 3H), 5.91–5.99 (m, 1H), 7.01(s, 1H), 7.35–7.66 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=167.7, 133.4, 132.1, 129.0, 127.4, 117.6, 60.0, 33.1, 32.2, 30.2, 29.6; IR (neat) ν 3300, 1639, 1579, 1315, 872 cm^{-1}; Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.74; H, 8.33; N, 12.14.

*4.1.3. (S)-N′-(2,2-Dimethylhex-5-en-3-yl)benzohydrazide (**2h**).* Following the general procedure above, **2h** was obtained as a yellow oil in 92% yield after flash chromatography (silica gel: ethyl acetate/hexane=2/8) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=95/5, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=14.4 min, t_r (minor)=11.3 min]. $[\alpha]_D^{20}$=+72.4 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.98 (s, 9H), 2.10–2.16 (m, 1H), 2.37–2.42 (m, 1H), 2.42–2.73 (m, 1H), 5.02–5.12 (m, 2H), 5.21 (s, 1H), 5.97–6.01 (m, 1H), 7.33–7.71 (m, 5H), 8.11(s, 1H); ^{13}C NMR ($CDCl_3$) δ=167.0, 136.3, 132.8, 131.6, 128.5, 126.7, 117.0, 64.3, 29.3, 18.5, 17.5; IR (neat) ν 3302, 1636, 1577, 1312, 862 cm^{-1}; Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.38; H, 8.69; N, 11.44.

*4.1.4. (S,E)-N′-(Hepta-1,5-dien-4-yl)benzohydrazide (**2i**).* Following the general procedure above, **2i** was obtained as a yellow oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=2/8) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=95/5, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=15.5 min, t_r (minor)=12.5 min]. $[\alpha]_D^{20}$=+76.7 (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.65 (d, *J*=7.2 Hz, 3H), 2.24–2.29 (m, 2H), 3.49–3.50 (m, 1H), 5.07–5.14 (m, 3H), 5.29–5.35 (m, 1H), 5.60–5.65 (m, 1H), 5.79–5.82 (m, 1H), 7.38–7.73 (m, 5H), 8.03(s, 1H); ^{13}C NMR ($CDCl_3$) δ=170.0, 138.2, 135.8, 134.2, 131.7, 129.8, 117.8, 112.2, 60.0, 38.0, 14.5; IR (neat) ν 3306, 1649, 1578, 1316, 859 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.38; H, 7.48; N, 12.14.

4.1.5. General procedure for N–N bond cleavage and N-allylation of homoallylamines. Hydrazine derivatives **2** (0.6 mmol) were dissolved in MeOH (1 mL) and treated with SmI_2 (18 mL, 1.8 mmol, 0.1 M THF solution) at room temperature for 4 h under argon. After reaction completion, the mixture was diluted with CH_2Cl_2, washed with distilled water, and dried over anhydrous $MgSO_4$. After solvent filtration and evaporation, the product was used for the next step without further purification.

4.1.6. General procedure for N-allylation of homoallylamines. NaH (55 mg, 1.35 mmol, 60% dispersion in mineral oil) was suspended in dry THF (10 mL) and cooled to 0 °C under argon. A solution of the homoallylamines (0.45 mmol) in dry THF (5 mL) was added and the reaction mixture was allowed to warm to room temperature. After 30 min, allyl bromide (0.12 mL, 1.35 mmol) was added and stirred for 10 h. After reaction completion, the product was diluted with CH_2Cl_2, washed with saturated NH_4Cl, and dried over anhydrous $MgSO_4$. After solvent filtration and evaporation, the residue was purified by flash chromatography on silica gel affording the corresponding products **3**.

4.1.7. General procedure for acylation of homoallylamines. A solution of homoallylamines (0.6 mmol), acryloyl chloride (0.15 mL, 1.80 mmol), and triethylamine (0.13 mL, 0.9 mmol) in acetonitrile (5 mL) was heated to reflux for 10 h under argon. After reaction completion, the solution was diluted with CH_2Cl_2, washed with saturated NH_4Cl, and dried over anhydrous $MgSO_4$. After solvent filtration and evaporation, the residue was purified by flash chromatography on silica gel affording the corresponding products **5**.

4.1.8. General procedure for ring closing metathesis. A solution of **3** or **5** (0.6 mmol) and Grubbs' catalyst (15.3 mg, 0.017 mmol) in dry toluene (5 mL) was stirred at 50 °C for 14 h under argon. After the reaction finished, the product was diluted with CH_2Cl_2, washed with distilled water, and dried over anhydrous $MgSO_4$. After solvent filtration and evaporation, the residue was purified by flash chromatography on silica gel affording the corresponding products **4** or **6**. Enantiomeric excess was determined by chiral HPLC analysis and was compared with the authentic racemic material.

*4.1.9. (2S)-2-(4-Fluorophenyl)-1,2,3,6-tetrahydropyridine (**4b**).* Following the general procedure above, **4b** was obtained as a yellow oil in 91% yield after flash chromatography (silica gel: ethyl acetate/hexane=5/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=46.4 min, t_r (minor)=43.3 min]. $[\alpha]_D^{20}$=−91.4 (*c*=0.01, $CHCl_3$). ^1H NMR ($CDCl_3$) δ=2.29 (m, 1H), 2.36 (m, 1H), 3.54 (m, 1H), 3.63 (m, 1H), 3.87 (dd, *J*=3.5, *J*=10.0 Hz, 1H), 5.69 (m, 1H), 5.74 (s, 1H), 5.85 (m, 1H), 7.23–7.46 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=165.3, 131.8, 130.3, 127.3, 125.7, 114.7, 57.6, 43.1, 25.8; IR (neat) ν 3412, 3008, 1516, 908 cm^{-1}; Anal. Calcd for $C_{11}H_{12}FN$: C, 74.55; H, 6.83; N, 7.90. Found: C, 74.95; H, 6.52; N, 7.93.

*4.1.10. (2S)-2-(4-Nitrophenyl)-1,2,3,6-tetrahydropyridine (**4c**).* Following the general procedure above, **4c** was obtained as a yellow oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=45.2 min, t_r (minor)=42.4 min]. $[\alpha]_D^{20}$=−89.5 (*c*=0.01, $CHCl_3$). ^1H NMR ($CDCl_3$) δ=2.21 (m, 1H), 2.27 (m, 1H), 3.58 (m, 1H), 3.67 (m, 1H), 3.82 (t, *J*=8.6 Hz, 1H), 5.79 (m, 1H), 5.85 (m, 1H), 5.91

(s, 1H), 7.26–7.43 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=142.2, 135.3, 128.8, 128.5, 128.4, 127.0, 59.3, 37.6, 32.0; IR (neat) ν 3421, 3011, 1602, 1208 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.98; H, 5.52; N, 13.77.

*4.1.11. (2S)-2-(3-Chlorophenyl)-1,2,3,6-tetrahydropyridine (**4d**).* Following the general procedure above, **4d** was obtained as a yellow oil in 92% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=46.0 min, t_r (minor)=42.5 min]. $[\alpha]_D^{20}$=−78.6 (c=0.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.29 (m, 1H), 2.34 (m, 1H), 3.59 (m, 1H), 3.68 (m, 1H), 3.87 (m, 1H), 5.79 (m, 1H), 5.87 (m, 2H), 7.23–7.49 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=142.1, 135.3, 132.9, 131.9, 128.7, 128.4, 128.4, 125.9, 59.2, 37.5, 34.3; IR (neat) ν 3424, 3014, 1621, 889 cm^{-1}; Anal. Calcd for $C_{11}H_{12}ClN$: C, 68.22; H, 6.25; N, 7.23. Found: C, 68.62; H, 5.92; N, 7.30.

*4.1.12. (2S)-2-(2-Bromophenyl)-1,2,3,6-tetrahydropyridine (**4e**).* Following the general procedure above, **4e** was obtained as a yellow oil in 92% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=46.3 min, t_r (minor)=43.4 min]. $[\alpha]_D^{20}$=−82.6 (c=0.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.38 (m, 1H), 2.49 (m, 1H), 3.54 (m, 1H), 3.67 (m, 1H), 3.91 (t, J=7.2 Hz, 1H), 5.79 (m, 1H), 5.88 (m, 1H), 5.91 (s, 1H), 7.23–7.41 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=138.3, 134.2, 132.4, 131.2, 128.1, 127.6, 127.2, 126.3, 63.2, 39.9, 28.0; IR (neat) ν 3429, 3014, 1578, 936 cm^{-1}; Anal. Calcd for $C_{11}H_{11}BrN$: C, 55.48; H, 5.08; N, 5.88. Found: C, 55.68; H, 4.69; N, 6.04.

*4.1.13. (2S)-2-(2-Methoxyphenyl)-1,2,3,6-tetrahydropyridine (**4f**).* Following the general procedure above, **4f** was obtained as a yellow oil in 92% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=45.2 min, t_r (minor)=42.4 min]. $[\alpha]_D^{20}$=−90.4 (c=0.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.29 (m, 1H), 2.36 (m, 1H), 3.54 (m, 1H), 3.67 (m, 1H), 3.80 (s, 3H), 3.84 (t, J=8.6 Hz, 1H), 5.64 (m, 1H), 5.76 (m, 1H), 6.60 (s, 1H), 7.26 -7.51 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=167.2, 143.8, 138.9, 134.8, 133.1, 131.9, 127.0, 118.1, 63.8, 40.5, 28.6, 15.6; IR (neat) ν 3431, 3014, 1548, 1146 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.53; H, 7.57; N, 7.41.

*4.1.14. (S)-2-tert-Butyl-1,2,3,6-tetrahydropyridine (**4h**).* Following the general procedure above, **4h** was obtained as a colorless oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=40.3 min, t_r (minor)=37.6 min]. $[\alpha]_D^{20}$=+61.5 (c 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.97 (s, 9H), 2.18 (m, 1H), 2.20 (s, 1H), 2.23 (m, 1H), 2.98 (t, J=7.2 Hz, 1H), 3.26 (m, 1H), 3.34 (m, 1H), 5.61 (m, 1H), 5.69 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=129.9, 128.0, 69.5, 64.7, 59.6, 41.4, 38.9; IR (neat) ν 3234, 1544, 802 cm^{-1}; Anal. Calcd for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 78.01; H, 11.95; N, 10.07.

*4.1.15. (S,E)-2-(Prop-1-enyl)-1,2,3,6-tetrahydropyridine (**4i**).* Following the general procedure above, **4i** was obtained as a colorless oil in 91% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=42.3 min, t_r (minor)=39.5 min]. $[\alpha]_D^{20}$=+58.6 (c 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=2.04 (d, J=7.2 Hz, 3H), 2.18 (m, 2H), 2.32 (s, 1H), 3.34 (m, 1H), 3.44 (m, 1H), 3.62 (t, J=7.2 Hz, 1H), 5.06 (m, 1H), 5.59 (m, 1H), 5.69 (m, 1H), 5.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=136.1, 132.3, 129.1, 127.5, 60.1, 38.1, 32.3, 14.6; IR (neat) ν 3228, 1546, 828 cm^{-1}; Anal. Calcd for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37. Found: C, 78.02; H, 10.67; N, 11.31.

*4.1.16. (S)-5,6-Dihydro-6-(4-chlorophenyl)pyridin-2(1H)-one (**6c**).* Following the general procedure above, **6c** was obtained as a colorless oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=47.2 min, t_r (minor)=44.4 min]. $[\alpha]_D^{20}$=−107.6 (c=0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.50 (m, 1H), 2.66 (m, 1H), 4.77 (t, J=6.9 Hz, 1H), 6.03 (d, J=7.2 Hz, 1H), 6.28 (s, 1H), 6.65 (m, 1H), 7.35–7.41 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=166.2, 140.5, 133.4, 131.8, 127.5, 127.5, 62.8, 39.2; IR (neat) ν 3387, 2930, 1670, 1611, 1493, 1089, 823 cm^{-1}; Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.87; H, 4.24; N, 12.84.

*4.1.17. (S)-5,6-Dihydro-6-(3-chlorophenyl)pyridin-2(1H)-one (**6d**).* Following the general procedure above, **6d** was obtained as a colorless oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=46.4 min, t_r (minor)=43.5 min]. $[\alpha]_D^{20}$=−125.6 (c=0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.50 (m, 1H), 2.66 (m, 1H), 4.77 (t, J=6.9 Hz, 1H), 6.03 (d, J=8.6 Hz, 1H), 6.26 (s, 1H), 6.65 (m, 1H), 7.35–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=166.8, 133.5, 129.2, 128.3, 126.6, 126.5, 115.2, 115.0, 57.4, 37.7; IR (neat) ν 3358, 2960, 1680, 1620, 1510, 1060, 820 cm^{-1}; Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.98; H, 4.48; N, 6.73.

*4.1.18. (S)-5,6-Dihydro-6-(2-bromophenyl)pyridin-2(1H)-one (**6e**).* Following the general procedure above, **6e** was obtained as a colorless oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=47.3 min, t_r (minor)=44.4 min]. $[\alpha]_D^{20}$=−131.2 (c=0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.50 (m, 1H), 2.60 (m, 1H), 4.77 (t, J=8.6 Hz, 1H), 6.00 (d, J=6.9 Hz, 1H), 6.60 (m, 1H), 6.17 (s, 1H), 7.09–7.47 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=168.9, 136.7, 136.2, 133.5, 130.5, 130.2, 128.4, 119.5, 117.1, 45.9, 31.2; IR (neat) ν 3387, 2930, 1670, 1611, 1493, 1089, 823 cm^{-1}; Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.65; H, 3.87; N, 5.56.

*4.1.19. (S)-5,6-Dihydro-6-(2-methoxyphenyl)pyridin-2(1H)-one (**6f**).* Following the general procedure above, **6f** was obtained as a colorless oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=46.2 min, t_r (minor)=43.4 min]. $[\alpha]_D^{20}$=−127.8 (c=0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.50 (m, 2H), 3.79 (s, 3H), 4.67 (t, J=7.2 Hz, 1H), 5.96 (d, J=6.9 Hz, 1H), 6.10 (s, 1H), 6.60 (m,1H), 6.99–7.37 (m, 4H); ^{13}C NMR ($CDCl_3$) 168.0, 160.0, 135.5, 132.7, 129.7, 129.6, 127.7, 118.9, 114.9, 56.2, 41.3, 30.6; IR (neat) ν 3442, 2980, 1682, 1615, 1516, 1250, 1060, 846 cm^{-1}; Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.31; H, 6.34; N, 6.95.

*4.1.20. (R)-6-Propyl-5,6-dihydropyridin-2(1H)-one (**6g**).* Following the general procedure above, **6g** was obtained as a colorless oil in 92% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=41.3 min, t_r (minor)=38.4 min]. $[\alpha]_D^{20}$=+89.5 (c 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.09 (t, J=7.2 Hz, 3H), 1.44 (m, 4H), 2.04 (m, 1H), 2.39 (m, 1H), 3.14 (t, J=7.2 Hz, 1H), 5.71 (m, 1H), 5.78 (m, 1H), 5.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=161.7, 134.9, 126.9, 53.4,

32.0, 31.3, 22.7, 14.2; IR (neat) ν 3218, 1687, 1546, 798 cm^{-1}; Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.32; H, 9.59; N, 10.21.

*4.1.21. (S)-6-tert-Butyl-5,6-dihydropyridin-2(1H)-one (**6h**).* Following the general procedure above, **6h** was obtained as a colorless oil in 93% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=38.2 min, t_r (minor)=35.5 min]. $[\alpha]_D^{20}$=+91.8 (*c* 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.17 (s, 9H), 1.41–1.49 (m, 1H), 2.45–2.50 (m, 1H), 3.96 (t, *J*=7.2 Hz, 1H), 5.36–5.46 (m, 2H), 5.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=167.2, 145.2, 123.7, 54.3, 36.2, 30.6, 27.9; IR (neat) ν 3214, 1656, 1546, 814 cm^{-1}; Anal. Calcd for $C_9H_{15}N$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.24; H, 10.69; N, 9.07.

*4.1.22. (S,E)-6-(Prop-1-enyl)-5,6-dihydropyridin-2(1H)-one (**6i**).* Following the general procedure above, **6i** was obtained as a colorless oil in 91% yield after flash chromatography (silica gel: ethyl acetate/hexane=4/6) and in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=44.3 min, t_r (minor)=41.5 min]. $[\alpha]_D^{20}$=+95.6 (*c* 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.22 (d, *J*=7.2 Hz, 3H), 1.84–1.92 (m, 1H), 2.88–2.94 (m, 1H), 4.03–4.11 (m, 1H), 4.35–4.39 (m, 1H), 4.57–4.62 (m 1H), 5.80–5.89 (m, 2H), 6.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=168.2, 142.7, 135.5, 128.7, 127.8, 54.4, 30.7, 17.0; IR (neat) ν 3224, 1675, 1546, 812 cm^{-1}; Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.02; H, 8.07; N, 10.31.

4.2. Synthesis of *R*-(−)-coniine

A mixture of compound **4g** (100 mg, 0.80 mmol) and 10% palladium on charcoal (85.1 mg, 0.80 mmol) in ethyl acetate (5 mL) was stirred at room temperature under 5 bar of hydrogen for 20 h. The mixture was filtered through Celite pad and the solvent was removed by evaporation to give the title compound (93.6 mg, 92%) in 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/^{i}PrOH=80/20, 0.7 mL min^{-1}, λ=254 nm, t_r (major)=36.3 min, t_r (minor)=33.4 min]. $[\alpha]_D^{20}$=−7.8 (*c* 0.10, $CHCl_3$); [lit.[16] $[\alpha]_D^{20}$=−9.7 (*c* 0.93, $CHCl_3$) All other spectroscopic data as reported.

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Supplementary data

HPLC analysis data are available as supplementary data. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.061.

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