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# Enantioselective Synthesis of (2-Pyridyl)alanines via Catalytic Hydrogenation and Application to the Synthesis of L-Azatyrosine

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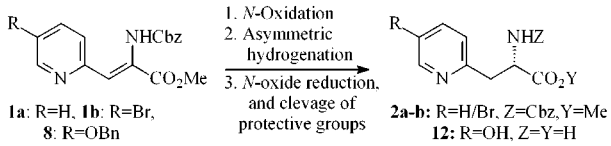
## ABSTRACT




**1a**: R=H, **1b**: R=Br, **8**: R=OBn

**2a-b:** R=H/Br, Z=Cbz, Y=Me
**12:** R=OH, Z=Y=H

**A novel method for the synthesis of (2-pyridyl)alanines 2a–b was developed by converting (2-pyridyl)dehydroamino acid derivatives 1a–b to the corresponding *N*-oxides 3a–b followed by asymmetric hydrogenation using (*R*,*R*)-[Rh(Et-DUPHOS)(COD)]$BF_4$ [(*R*,*R*)-6] catalyst and subsequent *N*-oxide reduction in 80–83% ee. This methodology was applied to the total synthesis of L-azatyrosine [(+)-12], an antitumor antibiotic, starting from (5-benzyloxy)-2-pyridylmethanol (7), in >96% enantiomeric purity.**

Interest in nonproteinogenic α-amino acids continues to arise as a result of their applications in the medicinal and biotechnological fields[1,2] and utility as chiral building blocks in organic synthesis.[3] Pyridylalanines have been used as replacements of histidine[4] and shown to function as antagonists of phenylalanines.[5] Additionally, the pyridylalanine derivative have also been studied as antiinflammatory[6] and antitumor−antibiotic agents[7] and for other pharmaceutical applications.[8] A number of methods have been developed for synthesis of pyridylalanines, e.g., enzymatic separation of racemates,[9] organometallic coupling reactions,[10] diastereoselective alkylation,[11] and by catalytic asymmetric hydrogenation.[12] Although asymmetric hydrogenation of pyridyldehydroamino acid derivatives requires high pressure and temperature[12c] or addition of nonchelating agents such as tetrafluoroboric acid,[12a,b] this protocol has a number of

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advantages over other methods available for synthesis of α-amino acids. This is due to the compatibility of a variety of groups to the reaction conditions and, more importantly, the excellent optical purity with which α-amino acids can be produced.[12e,13] However, attempts to prepare 6-unsubstituted (2-pyridyl)alanines (**2**) by asymmetric hydrogenation protocol (Figure 1) have not been successful as a result of

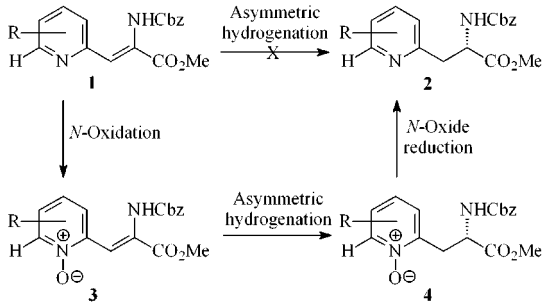
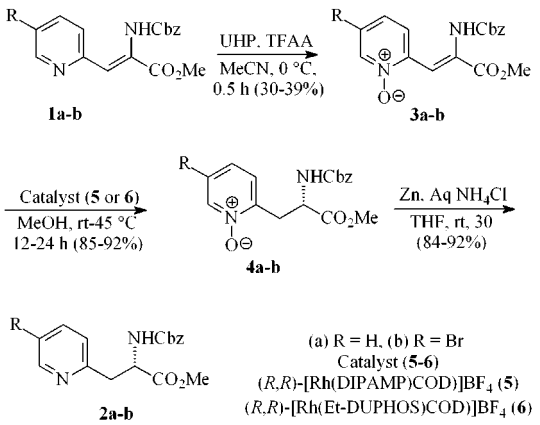



**Figure 1.** General strategy for the synthesis of (2-pyridyl)alanines (**2**) via asymmetric hydrogenation.

the participation of ring nitrogen in the formation of metal-substrate complex.[11] It is pertinent to note that when the 6-position on pyridine ring is substituted with groups such as OMe, asymmetric hydrogenation proceeds to give 2-pyridylalanines.[12e] To overcome this difficulty, we envisioned (Figure 1) that by converting the pyridine ring nitrogen to its derivatives, e.g., *N*-oxide, its participation in the formation of complex with metal catalyst could be prevented and thereby asymmetric hydrogenation of the double bond be accomplished. After the asymmetric induction step, the *N*-oxide could easily be removed by reduction under mild conditions using metals such as zinc. In this paper, we describe a general method for enantioselective synthesis of (2-pyridyl)alanine derivatives **2a**−**b** via asymmetric hydrogenation of the *N*-oxide derivatives of (2-pyridyl) dehydroamino acids **3a**−**b** and subsequent reduction of *N*-oxide. Application of this methodology to the total synthesis of L-azatyrosine (**12**), an antibiotic exhibiting interesting antitumor properties,[7,14] is also described.

To validate this strategy, our first goal was to prepare the required pyridinium *N*-oxide derivatives **3a**−**b** needed for asymmetric hydrogenation. Accordingly, (Scheme 1) the (2-pyridyl)dehydroamino acid derivatives **1a**−**b**[15] were oxidized with urea−hydrogen peroxide (UHP) complex and trifluoroacetic anhydride (TFAA) in acetonitrile[16] to afford the

**Scheme 1.** Synthesis of (2-Pyridyl)alanine Derivatives **2a**−**b** via Asymmetric Hydrogenation




corresponding *N*-oxides **3a**−**b** in 30−39% yields after purification by silica gel column chromatography. Oxidation of **1a**−**b** with *m*-CPBA was found to be very slow, and even after 6 days, only a 10% of the desired *N*-oxide (e.g., **3a**) was isolated. Asymmetric hydrogenation of *N*-oxide **3a** was initially carried out using a catalytic amount (0.05 equiv) of (*R*,*R*)-[Rh(DIPAMP)(COD)]$BF_4$ [(*R*,*R*)-**5**][17] in anhydrous MeOH at 48 °C and 60 psi. After the reaction was complete as determined by TLC, the reaction mixture was concentrated, and the crude compound was purified by silica gel column chromatography to afford (*S*)-**4a** in 89% yield. The optical purity of (*S*)-**4a** was determined by converting to Mosher's amide and found to be 20% ee (Table, entry 1).[18] Alternatively, the hydrogenation of *N*-oxide derivative **3a** using (*R*,*R*)-[Rh(Et-DUPHOS)(COD)]$BF_4$ [(*R*,*R*)-**6**] in anhydrous MeOH at room temperature and 45 psi gave (*S*)-**4a** 91% yield. To our delight, the optical purity of **4a** was found to be 83% ee (entry 2).[18,19] Hydrogenation of **3a** with (*S*,*S*)-**6** to gave (*R*)-**4a** in 83% ee (entry 3). Similarly the hydrogena-

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(15) (2-Pyridyl)dehydroamino acid derivatives **1a**−**b** were prepared from commercially available pyridine-2-carboxaldehyde and 5-bromo-pyridine-2-carboxaldehyde, respectively, in 78−89% yield by treatment with *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester in the presence of *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) in THF at room temperature for 6 h.

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(18) The optical purity (% ee) of **4a**−**b** was determined by converting **4a**−**b** to the corresponding Mosher's amide in three steps [(1) Zn, 30% aqueous $NH_4Cl$ solution, THF, rt, 30 min; (2) 10% Pd/C and 1 N aq HCl, $H_2$, 1 atm, rt, 2 h; (3) (*R*)-MTP-Cl, $Et_3N$, $CH_2Cl_2$, rt, 12 h] and analyzed by $^{19}F$ NMR.

(19) The absolute configuration of the newly generated chiral center in **4a** using (*R*,*R*)-**6** catalyst was determined to be (*S*) by cleavage of protective groups to the corresponding known α-amino acid and comparison of its rotation; see: ref 9a.

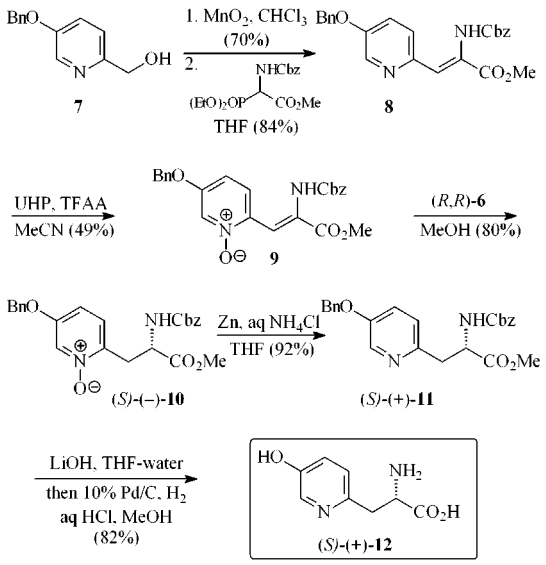
**Table 1.** Asymmetric Hydrogenation of *N*-Oxides **3a**−**b**

| entry | *N*-oxide (**3**), R = | catalyst **5**/**6** | product (**4**), R = | ee[a] |
|---|---|---|---|---|
| 1 | **3a**, R = H | (*R*,*R*)-**5** | (*S*)-**4a**, R = H | 20% |
| 2 | **3a**, R = H | (*R*,*R*)-**6** | (*S*)-**4a**, R = H | 83% |
| 3 | **3a**, R = H | (*S*,*S*)-**6** | (*R*)-**4a**, R = H | 83% |
| 4 | **3b**, R = Br | (*R*,*R*)-**6** | (*S*)-**4b**, R = Br | 80% |

[a] The optical purity (% ee) of **4a**−**b** was determined by $^{19}$F NMR of the Mosher amide (see ref 18).

tion of *N*-oxide **3b**, which contains bromine at the 5-position of the pyridine ring, with (*R*,*R*)-**6** catalyst gave (*S*)-**4b** in 85% yield and 80% ee (entry 4). It is pertinent to mention that the direct hydrogenation of (2-pyridyl)dehydroamino acid derivatives **1a**−**b** using 0.05−0.15 equiv of catalysts (*R*,*R*)-**5** or (*R*,*R*)-**6** at a higher temperature (up to 50 °C) and/or pressure (up to 60 psi $H_2$) was not successful. Thus, transformation of the pyridine ring nitrogen to its *N*-oxide derivative allowed the catalytic asymmetric hydrogenation of the double bond in **3a**−**b** using (*R*,*R*)-**6** catalyst to give **4a**−**b** in 80−83% ee's. The *N*-oxide in (*S*)-**4a,** (*S*)-**4b** was then easily reduced with activated zinc powder and 30% aqueous ammonium chloride solution in THF at room temperature.[20] Purification of the crude product by silica gel column chromatography afforded the amino acid derivatives (*S*)-**2a** and (*S*)-**2b**, respectively, in excellent yield (84−92%).

**Scheme 2.** Synthesis of L-Azatyrosine (**12**)




L-Azatyrosine [(+)-**12**] is an antibiotic isolated from *Streptomyces chibaensis*[7a] that has been shown to restore normal phenotypic behavior to transformed cells bearing oncogenic Ras genes.[14] Additionally, (*S*)-(+)-**12** has been found to inhibit chemical carcinogen-induced tumor growth in mice harboring normal human c-Ha Ras genes.[7b] The synthesis of (*S*)-(+)-**12** was accomplished (Scheme 2) via asymmetric hydrogenation protocol starting from a 5-benzyloxy-2-pyridylmethanol (**7**).[21] Accordingly, the compound **7**[21c] was oxidized using manganese dioxide in chloroform, and the resulting aldehyde was subjected to a reaction with *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester in the presence of *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) in THF. Purification of the crude product by silica gel column chromatography afforded the dehydroamino acid derivatives **8** in 84% yield. Oxidation of the dehydroamino acid derivatives **8** with urea−hydrogen peroxide (UHP) complex and trifluoroacetic anhydride gave the corresponding *N*-oxide **9** in 49% yield. Asymmetric hydrogenation of *N*-oxide **9** in the presence of (*R*,*R*)-[Rh(Et-DUPHOS)(COD)]$BF_4$ [(*R*,*R*)-**6**] catalyst in anhydrous MeOH at 48 °C and 45 psi afforded (*S*)-(−)-**10** in 80% yield and 83% ee. Crystallization of (*S*)-(−)-**10** in $CH_2Cl_2$/hexanes improved the ee to >96%.[22] The (*S*)-(−)-**10** (ee >96%) was then reduced with activated zinc powder and 30% aqueous ammonium chloride solution in THF[20] at room temperature to afford the amino acid derivative (*S*)-(+)-**11** in excellent yield (92%) after silica gel column chromatography The α-amino acid derivative (*S*)-(+)-**11** was then subjected to hydrolysis with LiOH to afford the corresponding free carboxylic acid, which was then hydrogenated in the presence of 10% Pd/C and 1 N HCl in MeOH. The crude product was purified by preparative reversed phase HPLC[23] followed by ion exchange chromatography using Dowex 50 WX4-100 resin to afford L-azatyrosine [(+)-**12**] in 82% yield, $[\alpha]^{23}_D$ +56.41 (*c* 0.78, 1 N HCl) {lit.[7a] $[\alpha]^{25}_D$ +55 (*c* 1.1, 1 N HCl)}.

In summary, a novel method was developed for enantioselective synthesis of (2-pyridyl)alanines **2a**−**b** via asymmetric hydrogenation protocol. This methodology was successfully applied to the total synthesis of L-azatyrosine [(+)-**12**], an antitumor antibiotic, in >96% enantiomeric excess and good overall yield.

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(22) The enantiomeric excess (% ee) of (*S*)-(−)-**10** before and after crystallization was determined by converting to Mosher's amide in three steps; see ref 18 for details.

(23) Preparative reversed phase HPLC was carried out on a Waters, Symmetry, C18, 7.0 μ, 40 × 100 mm column using 2:98 MeCN/0.1% aqueous trifluoroacetic acid, 25 mL/min at 225 nm.