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Synthesis of Optically Active Hydroxyalkylpyridines and Related Pyridyl Amines

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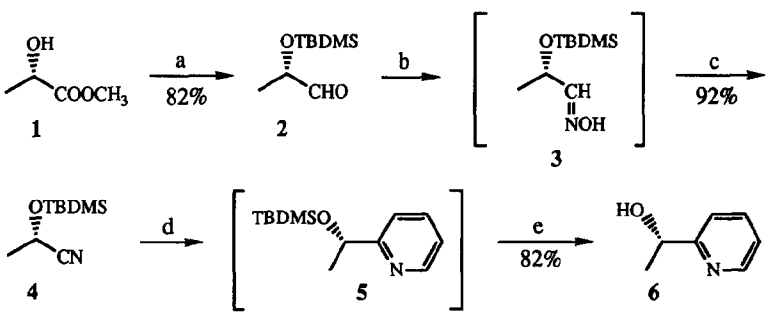
Abstract: 2-(1-Hydroxyalkyl)pyridines have been prepared by cobalt(I)-catalyzed cocyclotrimerization reaction of O-protected α-hydroxynitriles with acetylene. From these compounds the related pyridyl amines have been obtained.

Optically active pyridyl alcohols[1] and amines[2] have recently attracted attention because of their utility as chiral ligands in metal complexes for stereoselective catalysis. Chiral 2-(1-hydroxyalkyl)pyridines have been prepared in three ways: a) asymmetric reduction of the corresponding ketones by diisopinocampheylborane chloride (DIP-Cl)[1d]; b) catalytic biotransformations[3]; c) resolution of racemic alcohols.[1c] However these synthetic approaches are not always successful for instance several attempts to prepare the optically active 2-(1-hydroxyethyl)pyridine by reduction of the 2-acetylpyridine with DIP-Cl failed. These results prompted us to search for a practical synthetic methodology to obtain chiral pyridyl alcohols and amines from easily accessible chiral compounds. In this paper we report a generalizable procedure for the preparation of 2-(1-hydroxyalkyl)pyridines through cobalt(I)-catalyzed cocyclotrimerization reaction of O-protected α-hydroxynitriles with acetylene. Access to the related pyridyl amines has also been evaluated. The commercial (S)-2-hydroxypropanoic acid methyl ester (1) was selected as a prototype from which to develop the basic methodology.

Scheme 1

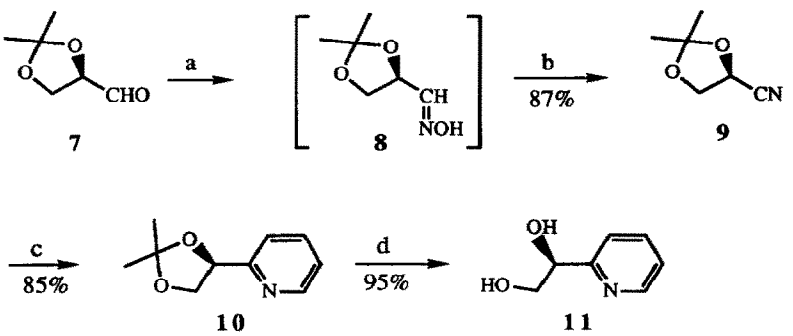


a: literature; b: NH_2OH HCl,10% K_2CO_3, MeOH; c: N,N'-carbonyldiimidazole, CH_2Cl_2 2h, r.t.; d: CpCo(COD), acetylene, toluene, 120 °C, 14 atm.; e: 10 % HCl

The aldehyde **2**, prepared from **1** by a literature procedure,[4] was converted into the nitrile **4** *via* the formation of the corresponding oxime followed by dehydration with N,N'-carbonyldiimidazole. Cobalt catalyzed cocyclotrimerization of nitrile **4** with acetylene[5] afforded the unisolated pyridine **5** which by treatment with 10 % hydrochloric acid gave the hydroxy pyridine **6** in 60 % overall yield based on **1** and 100 % enantiomeric excess.[6]

We decided to extend this procedure to the preparation of hydroxy pyridines containing other functional groups. 2,3-O-(Isopropylidene)-D-glyceraldehyde (**7**), easily obtained from D-mannitol,[7] appeared to be an interesting starting compound. Thus, starting from **7** and following the above procedure the pyridine **10** was obtained in 85 % yield. Deprotection of the acetonide group afforded the 2-(1,2-dihydroxyethyl)pyridine **11** in 81 % overall yield (based on **7**) and 98 % enantiomeric excess.[6]

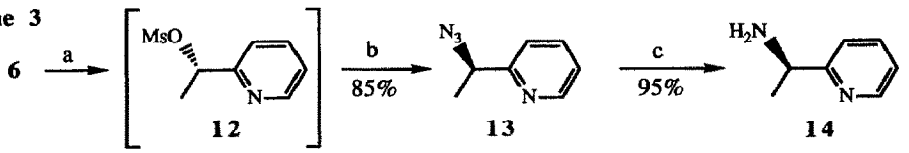
Scheme 2



a: NH_2OH HCl,10% K_2CO_3, MeOH; b: N,N'-carbonyldiimidazole, CH_2Cl_2, 2h, r.t.; c: CpCo(COD), acetylene, toluene, 120 °C, 14 atm.; d: 6 % HCl;

With hydroxy pyridines **6** and **11** in hand we considered the possibility of obtaining the corresponding amino pyridines. Compound **6** was converted into the azide **13** *via* the unisolated mesylate **12** (Scheme 3). This compound was reduced by hydrogen on Pd/C to give the 2-(1-aminoethyl)pyridine (**14**) in 71 % overall yield based on **6** and 66 % enantiomeric excess.[6]

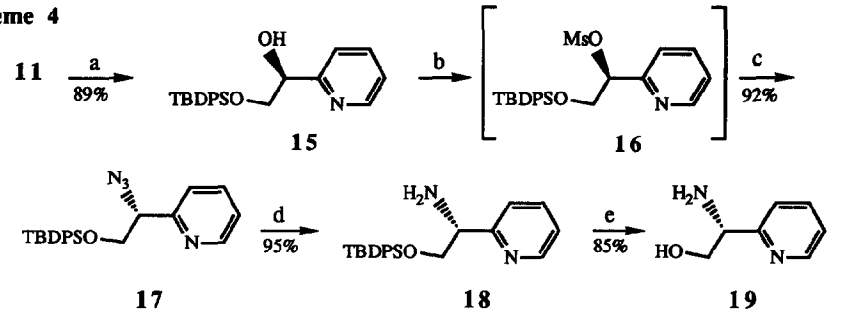
Scheme 3



a: MsCl, Et_3N, DMPA, CH_2Cl_2; b: NaN_3, DMF, r.t., 24h.; c: Pd/C, H_2

For the transformation of glycol **11** into the amine **19** (Scheme 4) the selective protection of the primary hydroxy group was necessary. Thus, starting from **15** and following the above procedure the amine **18** was obtained. Removal of the protective group by 10 % hydrofluoric acid gave the hydroxyamine **19** in 66 % overall yield based on **11** and 92 % enantiomeric excess.[6]

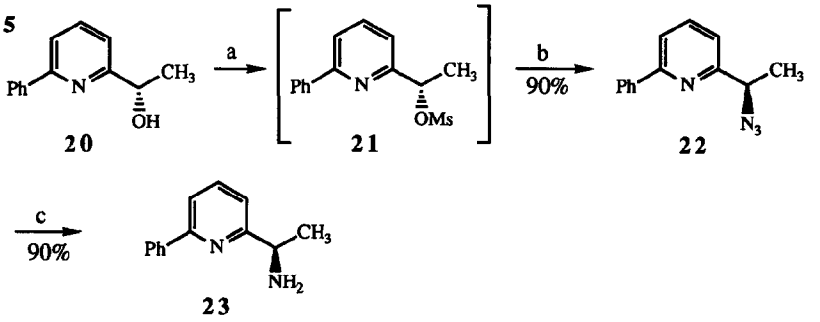
Scheme 4



a: (*t*-Bu)Ph_2SiCl, Et_3N, DMPA, CH_2Cl_2; b: MsCl, Et_3N, DMPA, CH_2Cl_2;
c: NaN_3, DMF, r.t., 24h.; d: Pd/C, H_2; e: 10% HF

Moreover, the pyridyl amine **23** was prepared in order to investigate the enantioselection in the nucleophilic displacement of the mesyloxy group by the azido group. Thus, the carbynol **20**, prepared according to a reported procedure in 85 % enantiomeric excess,[1d] was converted in the usual way into the pyridine **23**. This compound was obtained in 85 % overall yield (based on **20**) and 77 % enantiomeric excess[6] (Scheme 5).

Scheme 5



a: MsCl, Et_3N, DMPA, CH_2Cl_2; b: NaN_3, DMF, r.t., 24h.; c: Pd/C, H_2

In conclusion it has been demonstrated that cobalt(I)-catalyzed cocyclotrimerization of chiral O-protected α-hydroxynitriles with acetylene affords a convenient method for the preparation of pyridyl alcohols with high enaniomeric excess. This procedure is extremely straightforward since enantiomerically pure cyanohydrins are readily available by the catalytic asymmetric addition of hydrogen cyanide to carbonyl compounds.[8] Moreover, it has been shown that homochiral pyridyl alcohols can be converted into the corresponding amines in good overall yields, but partial inversion of configuration is found in the nucleophilic substitution of the mesyloxy group by the azido group.The use of pyridyl alcohols as starting points for the preparation of other pyridine derivatives is under investigation in our laboratory.

Experimental section

Boiling point are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The ^1H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical

rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin-Elmer 240 B analyzer.

(2S)-2-[(*tert*-Butyldimethylsilyl)oxy]propanal (**2**)[4], 2,3-O-(isopropylidene)-D-glyceraldehyde (**7**)[7] and (S)-1-6-phenyl-2-(1-hydroxyethyl)pyridine (**20**)[1d] were prepare according to reported procedures.

(2S)-2-[(*tert*-Butyldimethylsilyl)oxy]propanenitrile (4). A solution of hydroxylamine hydrochloride (5.85 g, 84 mmol) in 10% Na_2CO_3 (38 ml) was added to a solution of (2S)-2-[(*tert*-butyldimethylsilyl)oxy]propanal (**2**) (14.1 g, 0.075 mol) in methanol (100 ml). The mixture was stirred at room temperature for 24 h. The methanol was evaporated and the residue taken up in CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4) and concentrated under reduced pressure to give **3** (14.2 g) which was used in the next step without further purification.

1,1'-Carbonyldiimidazole (11.3 g, 0.07 mol) in CH_2Cl_2 (100 ml) was added dropwise to a solution of **3** in CH_2Cl_2 (70 ml). The mixture was stirred for 3 h and the solvent evaporated. The residue was distilled to give pure **4**: 12.75 g (92 %); $[\alpha]^{21}_D$ -46.2 (*c*, 2.3 $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 4.54 (q, 1H), 1.53 (s, 3H), 0.89 (s, 6H), 0.16 (d, 9H). *Elem. Anal.*, found % (calcd. for $C_9H_{19}NOSi$) C, 58.56 (58.32), H, 10.45 (10.33), N, 7.60 (7.56), Si, 15.15 (15.15).

(S)-2-(1-Hydroxyethyl)pyridine, 6. π-(Cyclopentadienyl)cobalt-1,5-cyclooctadiene (500 mg) was placed in a stainless-steel autoclave (200 ml). The autoclave was rocked and the air removed (0.1 atm). A solution of **5** (11.1 g, 0.6 mol) in toluene (100 ml) was introduced by suction. The reaction vessel was pressurized with acetylene up to 14 atm and then rocked and heated at 120 °C. After 24 h the autoclave was cooled and the residual gas released. The reaction mixture was filtered and the solution taken up with 10 % hydrochloric acid (50 ml). The aqueous solution was stirred at room temperature for 5h and then made alkaline with 10 % sodium hydroxide. The solution was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), the solvent evaporated and the residue distilled to give pure **6**: 12 g (84 %); $[\alpha]^{25}_D$ - 56.5 (*c*, 3.4 EtOH) {literature:[9] $[\alpha]^{25}_D$ - 49.8 (*c*, 3.1 EtOH) for (S)-**6**:(R)-**6** = 94:6}; ^{1}H-NMR ($CDCl_3$) δ 8.53 (d, 1H), 7.70 (t, 1H), 7.32 (d, 1H), 7.19 (t, 1H), 3.92 (q, 1H), 4.50 (s, 1H), 1.52 (d, 3H). *Elem. Anal.*, found % (calcd. for C_7H_9NO) C, 68.46 (68.27); H, 7.53 (7.37); N, 11.23 (11.37).

(S)-4-Cyano-2,2-dimethyl-1,3-dioxolane, 9. The procedure reported for the preparation of **6** was followed. From 2,3-O-(isopropylidene)-D-glyceraldehyde (**7**) (6.0 g, 46.2 mmol) the compound **9** was isolated by distillation : 4.7 g (87 %); bp 100 °C (15 mm); $[\alpha]^{25}_D$ +1.46 (*c*, 2.2 $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 4.78 (dd, 1H), 4.29 (dd, 1H), 4.20 (dd, 1H), 1.56 (s, 3H), 1.39 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_6H_9NO_2$) C, 56.46 (56.68); H, 7.23 (7.13); N, 11.23 (11.02).

(S)-4-(2-Pyridyl)-2,2-dimethyl-1,3-dioxolane, 10. π-(Cyclopentadienyl)cobalt-1,5-cyclooctadiene (250 mg) was placed in a stainless-steel autoclave (200 ml). The autoclave was rocked and the air removed (0.1 atm). A solution of **9** (4.7 g, 37 mmol) in toluene (30 ml) was introduced by suction. The reaction vessel was pressurized with acetylene up to 14 atm and then rocked and heated at 120 °C. After 24 h the autoclave was cooled and the residual gas released. The reaction mixture was filtered, the solvent evaporated and the residue purified by chromatography on silica gel (petrolium ether:ethyl acetate/7:3) to give pure **10**: 5.6 g (85 %); bp 70 °C (0.3 mm); $[\alpha]^{25}_D$ +93.6 (*c*, 2.9 $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.53 (d, 1H), 7.69 (t, 1H), 7.53 (d, 1H), 7.19 (t, 1H), 5.20 (t, 1H), 4.46 (t, 1H), 3.94 (t, 1H), 1.49 (s, 3H), 1.45 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_{10}H_{13}NO_2$) C, 67.26 (67.0); H, 7.23 (7.32); N, 8.65 (7.82).

(S)-2-(1,2-Dihydroxyethyl)pyridine, 11. A solution of **10** (5.6 g, 31.3 mmol) in 6% hydrochloric acid 950 ml) was stirred at room temperature for 5h and then made alkaline with 10 % sodium hydroxide. The

aqueous solution was extracted exaustively with ethyl acetate. The organic solution was dried (Na_2SO_4), the solvent evaporated and the solid residue cristallyzed from acetone to give pure **11**: 4.2 g (97 %); $[\alpha]^{25}_D$ + 80.6 (c, 1.6 EtOH); ^{1}H-NMR ($CDCl_3$) δ 8.49 (d, 1H), 7.77 (t, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.85 (dd, 1H), 3.92 (dd, 1H), 3.75 (dd, 1H). *Elem. Anal.*, found % (calcd. for $C_7H_9NO_2$) C, 60.46 (60.40); H, 6.53 (6.52); N, 10.23 (10.07).

(R)-2-(1-Azidoethyl)pyridine, 13. Methanesulfonyl chloride (1.73 g, 15 mmol) in CH_2Cl_2 (10 ml) was added at 0 °C to a solution of **6** (1.23 g, 10 mmol), triethylamine (3.2 ml), 4-(dimethylamino)pyridine (142 mg) in CH_2Cl_2 (30 ml). The resulting solution was stirred at 0 °C for 10 min and then at room temperature for 24 h. The reaction mixture was poured into a $NaHCO_3$ solution, the organic phase separated, washed with H_2O, dried on Na_2SO_4 and the solvent removed under reduced pressure. The residue was used in the next step without further purification. The crude mesyloxy compound **12** (2.3 g) was taken up in N,N-dimethyl formamide (20 ml) and sodium azide (1.95 g, 30 mmol) was added a portion. After 24 h at room temperature the solvent was evaporated under reduced pressure and the residue purified by chromatography on silica gel (petroleum ether:ethyl acetate/7:3) to give pure **13**: 1.26 g (85 %); $[\alpha]^{22}_D$ +40.75 (*c*, 2.1 $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.59 (d, 1H), 7.71 (dt, 1H), 7.34 (d, 1H), 7.23 (dt, 1H), 4.68 (q, 1H), 1.61 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_7H_8N_4$) C, 57.26 (57.12); H, 4.63 (4.80); N, 38.15 (38.09).

(R)-2-(1-Aminoethyl)pyridine, 14. A mixture of **13** (0.74 g, 5 mmol) and 10 % Pd/C (74 mg) in methanol (15 ml) was reduced by H_2 at atmospheric pressure and room temperature for 24h. The solvent was evaporated under reduced pressure and the residue distilled to give pure **14**: 0.58 g (95 %); bp 70 °C (10 mm); $[\alpha]^{22}_D$ +15.7 (*c*, 2.4 $CHCl_3$); $[\alpha]^{25}_D$ +18.7 (*c*, 5.1 EtOH) {literature:[10] $[\alpha]^{25}_D$ +26.25 (EtOH) for (R)-**14**:(S)-**14** = 97:3}; ^{1}H-NMR ($CDCl_3$) δ 8.53 (d, 1H), 7.63 (dt, 1H), 7.29 (d, 1H), 7.13 (dt, 1H), 4.14 (q, 1H), 1.82 (s, 2H), 1.42 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_7H_{10}N_2$) C, 68.26 (68.20); H, 8.43 (8.26); N, 22.65 (22.94).

(R)-2-{2-[(*tert*-Butyldiphenylsilyl)oxy]-1-hydroxyethyl}pyridine, 15. A solution of **11** (1.55 g, 11.15 mmol), 4-(dimethylamino)pyridine (50 mg), triethylamine (3.38 g, 34 mmol) and *tert*-butyldiphenylchlorosilane (3.37 g, 12.27 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 48h. The solution was washed with 10 % $NaHCO_3$, H_2O and the organic phase dried (Na_2SO_4). After evaporation of the solvent the residue was purified by chromatography on silica gel (ethyl acetate) to give pure **15**: 3.74 g (89 %); ^{1}H-NMR ($CDCl_3$) δ 8.52 (d, 1H), 7.67 (dt, 1H), 7.61-7.17 (m, 12H), 4.85 (q, 1H), 4.12 (d, 1H), 3.87 (d, 2H), 1.02 (s, 9H). *Elem. Anal.*, found % (calcd. for $C_{23}H_{27}NO_2Si$) C, 73.26 (73.17); H, 7.33 (7.21); N, 13.85 (13.93); Si, 65.90 (7.44).

(R)-2-{2-[(*tert*-Butyldiphenylsilyl)oxy]-1-azidoethyl}pyridine, 17. The procedure reported for the preparation of **13** was followed. From **15** (3.5 g, 9.26 mmol) the mesyloxy compound **16** was obtained (4.5 g). Sodium azide (1.95 g, 30 mmol) was added a portion to a solution of crude **12** (4.5 g) in N,N-dimethyl formamide (13 ml). After 24 h at room temperature the solvent was evaporated under reduced pressure and the residue purified by chromatography on silica gel (petrolium ether:ethyl acetate/7:3) to give pure **17**: 3.42 g (92 %). ^{1}H-NMR ($CDCl_3$) δ 8.53 (d, 1H), 7.70-7.16 (m, 13H), 4.74 (t, 1H), 4.08 (dd, 1H), 3.94 (dd, 1H), 1.05 (s, 9H). *Elem. Anal.*, found % (calcd. for $C_{23}H_{26}N_4OSi$) C, 68.46 (68.62); H, 6.53 (6.52); N, 13.73 (13.93); Si, 6.86 (6.96).

(R)-2-{2-[(*tert*-Butyldiphenylsilyl)oxy]-1-aminoethyl}pyridine, 18. The procedure reported for the preparation of **14** was followed. From **17** (3.0 g, 7.5 mmol) the compound **18** was obtained: 32.7 g (95 %); ^{1}H-NMR ($CDCl_3$) δ 8.53 (d, 1H), 7.67-7.12 (m, 13H), 4.16 (t, 1H), 3.88 (dd, 1H), 3.77 (dd, 1H), 1.94

(s, 2H), 1.01 (s, 9H). *Elem. Anal.*, found % (calcd. for $C_{23}H_{28}N_2OSi$) C, 73.55 (73.37); H, 7.53 (7.50); N, 20.30 (20.28); Si, 7.66 (7.44).

(R)-2-(1-Amino-2-hydroxyethyl)pyridine, 19. A solution of **18** (1.12 g, 3 mmol) in Et_2O (10 ml) was treated with 10 % aqueous hydrofluoric acid and then stirred at room temperature for 2h. The separated aqueous solution was extracted with Et_2O, made alkaline with 10 % NaOH, saturated with Na_2CO_3 and extracted with ethyl acetate (5 x 30 ml). The organic phase was dried (Na_2SO_4), the solvent evaporated and the residue distiled to give pure **19**: 0.35 g (85 %), bp 120 (0.3 mm); $[\alpha]^{25}_D$ -36.1 (*c*, 1.9 MeOH); ^{1}H-NMR ($CDCl_3$) δ 8.52 (dd, 1H), 7.68 (dt, 1H), 7.34 (d, 1H), 7.19 (dt, 1H), 4.07 (dd, 1H), 3.84 (dd, 1H), 3.70 (dd, 1H), 2.89 (broad, 3H). *Elem. Anal.*, found % (calcd. for $C_7H_{10}N_2O$) C, 60.76 (60.85); H, 7.23 (7.30); N, 20.33 (20.27).

(R)-2-(1-Azidoethyl)-6-phenylpyridine, 22. The procedure reported for the preparation of **13** was followed. From **20** (1 g, 5 mmol) the mesyloxy compound **21** was obtained 1.4 g. Sodium azide (0.33 g, 15 mmol) was added a portion to a solution of crude **21** (1.4 g) in N,N-dimethylformamide (12 ml). After 24 h at room temperature the solvent was evaporated under reduced pressure and the residue purified by chromatography on silica gel (petroleum ether:ethyl acetate/7:3) to give pure **22**: 1.01 g (90 %); $[\alpha]^{12}_D$ +7.36 (*c*, 2.4 $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.05 (d, 1H), 7.73 (t, 1H), 7,66 (d, 1H), 7.52-7.38 (m, 4H), 7.23 (d, 1H), 4.63 (q, 1H), 1.66 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_{13}H_{12}N_4$) C, 69.46 (69.62); H, 6.53 (5.39); N, 13.73 (13.93); Si, 6.86 (6.96).

(R)-2-(1-Aminoethyl)-6-phenylpyridine, 23. The procedure reported for the preparation of **14** was followed. From **22** (0.9 g, 4 mmol) the compound **23** was obtained: 0.71 g (90 %); $[\alpha]^{22}_D$ +2.0 (*c*, 2.0 EtOH); ^{1}H-NMR ($CDCl_3$) δ 9.00 (s broad, 2H), 8.10 (d, 2H), 7.75 -7.18 (m, 6H), 4.65 (s broad, 1H), 2.71 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_{13}H_{14}N_2$) C, 78.76 (78.75); H, 7.23 (7.12); N, 14.33 (14.13).

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References and Notes

1. a) Chelucci, G., *Gazz. Chim. Ital.*, **1992**, *122*, 89. b) Chelucci, G., Soccolini, F., *Tetrahedron: Asymmetry*, **1992**, *3*, 1235. c) Ishizaki, M., Fuijta, K., Shimamoto, M., Hoshino, O., *Tetrahedron: Asymmetry*, **1994**, *5*, 411. d) Bolm, C., Edwald, M., Felder, M., Schlingloff, G., *Chem. Ber.*, **1992**, *125*, 1169.
2. Cabras, M.A., Chelucci, G., Giacomelli, G., Soccolini, F., *Gazz. Chim. Ital.*, **1994**, *124*, 23 and references therein.
3. a) Bailey, D., O'Hagan, D., Dyer, U., Lamont, R.B., *Tetrahedron: Asymmetry*, **1993**, *4*, 1258 and references therein. b) Seemayer, R., Schneider, M.P., *Tetrahedron: Asymmetry*, **1992**, *3*, 827 and references therein.
4. Massad, S.K., Hawkins, L.D., Baker, D.C., *J. Org. Chem.*, **1983**, *48*, 5180
5. For a review on the cobalt-catalyzed synthesis of pyridines see: Bonnemann, H., *Angew. Chem.*, 1985, **97**, 264; *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 248.
6. The enantiomeric excess (ee) of compounds **6**, **14**, **20**, **23** was calculated from ^{1}H and ^{19}F NMR spectrum of the corresponding (R)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester. The ee of **11** and **18** was presumed to be the same of their derivatives **15** and **19** respectively, whose ee was determined in the same way.
7. Schmid, C.R., Bryant, J.D., Dowlatzedah, M., Phillips, J.L., Prather, E.D., Schantz, R.D., Sear, N.L., Vianco, C.S., *J. Org. Chem.*, **1991**, *56*, 4056.
8. For a review: North, M., *Synlett*, **1993**, 807
9. Imuta, M., Kawai, K., Ziffer, H., *J. Org. Chem.*, **1980**, *45*, 3352.
10. Mi, A., Xiao, X., Wu, L., Jiang, Y., *Synth.Commun.*, **1991**, *21*, 2207.

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