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Diastereoisomeric Pure 2-(1-Hydroxyalkyl)pyridines as Catalysts in the Enantioselective Addition of Diethylzinc to Aldehydes

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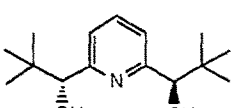
Abstract: Diastereoisomeric pure 2-(1-hydroxyalkyl)pyridines have been prepared from chiral ketones and checked as enantioselective catalysts in the addition of diethylzinc to aldehydes: enantioselectivities up to 82% were obtained

Optically active hydroxyalkylpyridines have been used in asymmetric synthesis: three derivatives of this compound class having the *tert*-butylmethanol group as common substituent have been reported. Sharpless and co-workers[1] have synthesized the optically active (R,R)-2,6-bis(2,2-dimethyl-1-hydroxypropyl)pyridine (**1**) and prepared the corresponding dioxomolybdenum(VI) and titanium(IV) complexes which were used as asymmetric oxidation catalysts. Bolm and co-workers[2,3] have prepared the (+)-(R,R)-6,6'-bis(2,2-dimethyl-1-hydroxypropyl)-2,2'-bipyridine[2] (**2**) and (S)-2-phenyl-6-(2,2-dimethyl-1-hydroxypropyl)pyridine[3] (**3**) which have been found effective enantioselective catalysts in the addition of diethylzinc to benzaldehyde and in the conjugated addition of diethylzinc to enones. The preparation of these ligands requires a step of stereoisomer differentiation: compounds **2** and **3** involve the asymmetric reduction of a prochiral ketone, whereas **1** requires a tedious resolution procedure.



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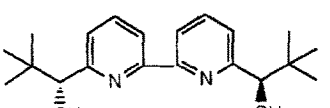

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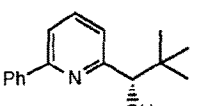

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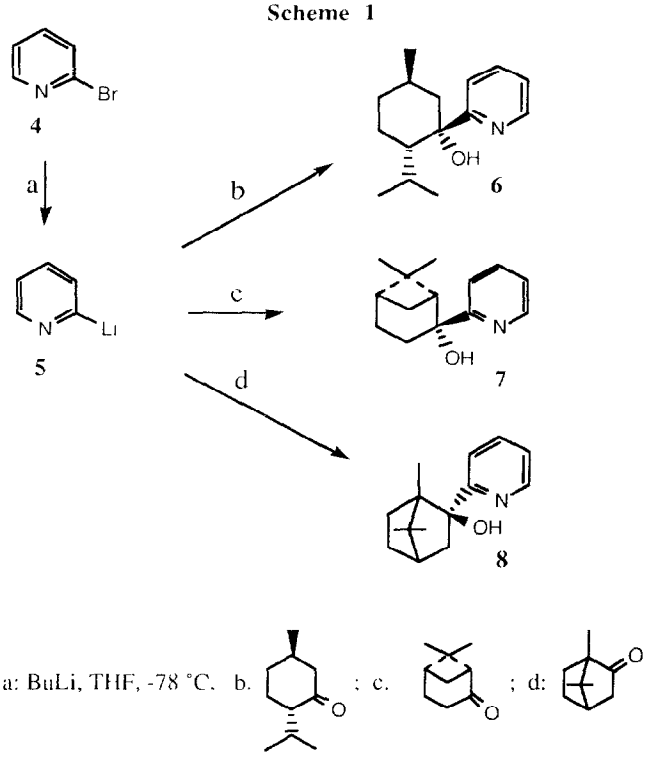
With the aim of obtaining optically active pyridine-carbinols having the same features through a more directed way we have prepared diastereoisomeric pure 2-(1-hydroxyalkyl)pyridines and checked these compounds as enantioselective catalysts in the addition of diethylzinc to aldehydes.

The 2-(1-hydroxyalkyl)pyridines **6-8** were prepared by condensation of 2-pyridyllithium (**5**) with optically active naturally occurring ketones (Scheme 1). Pyridines **6-8** were obtained as sole diastereomers[4]: configurations are reported in Scheme 1. The yield (12-60%, based on 2-bromopyridine) greatly depends upon

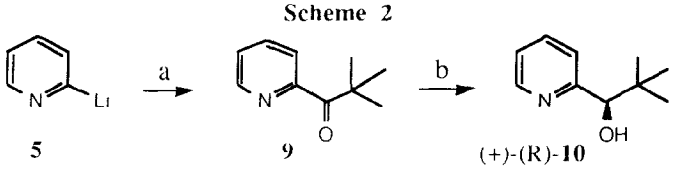
the nature of ketone, dropping on passing from the moderately sterically-crowded menthone (60%) to the very sterically-crowded camphor (12%), an intermediate situation being found in the case of nopinone (39%).

Scheme 1



We have also prepared the (+)-(R)-(2,2-dimethyl-1-hydroxypropyl)pyridine (**10**) in order to define if the enantioselective ability of 2-pyridyl-carbinols could be affected by the presence of an another substituent on 6-position of the pyridine ring, as in compounds **1-3**. Compound **10** was obtained in 53% overall yield through condensation of 2-pyridyllithium with 2,2-dimethylpropane nitrile, followed by asymmetric reduction of the ketone **9** with (-)-ß-chlorodiisopinocampheylborane[5] (Scheme 2). The alcohol (+)-(R)-**10**[6] was obtained in 91% ee, as determined by means of ^{19}F-NMR of the corresponding ester of (+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid ((+)MPTA).

Scheme 2



a: *t*-BuCN, 75 %; b: (-)-ß-chlorodiisopino-campheylborane, THF, -25 °C., 15 d, 70 %, 91 % ee;

Enantioselective additions of diethylzinc to aldehydes in the presence of catalytic amounts (3 mol%) of **6-8,10** were carried out in hexane/ether at room temperature (20 °C)[7]. The data obtained using chiral pyridines **6-8,10** are summarized in the Table.

Table: Asymmetric Addition of Diethylzinc to Aldehydes[a]

			optically active carbinol	
ligand	aldehyde	conv[b] %	$[\alpha]_D^{25}$ (*c*, solvent)	ee[c] %
6	benzaldehyde	93	-9.7 (6, $CHCl_3$)	21 (*S*)
7	benzaldehyde	93	+17.4 (5, $CHCl_3$	38 (*R*)
8	benzaldehyde	93	+20.0 (4, $CHCl_3$)	44 (*R*)
10	benzaldehyde	100	+34.0 (5, $CHCl_3$)	82 (*R*)[d]
6	3-phenylpropanal	89	+7.0 (5, EtOH)	26 (*S*)
7	3-phenylpropanal	81	-5.4 (5, EtOH)	20 (*R*)
8	3-phenylpropanal	87	-10.2 (5, EtOH)	38 (*R*)
10	3-phenylpropanal	87	-15.2 (5, EtOH)	63 (*R*)[d]
6	3-phenylpropynal	91	-1.7 (3, Et_2O)	9 (*S*)
7	3-phenylpropynal	95	+0.3 (3, Et_2O)	1 (*R*)
8	3-phenylpropynal	92	+3.9 (3, Et_2O)	21 (*R*)
10	3-phenylpropynal	90	+7.3 (3, Et_2O)	43 (*R*)[d]

a) Reaction carried out at room temperature in hexane/ether with a molar ratio Et_2Zn/aldehyde/ligand = 2/1/0.06. *b*) GLC yields of the crude products. *c*) Verified both by GLC and ^{19}F NMR of the (+)MPTA. *d*) Corrected for the minimum optical purity of (+)-(R)-**10**.

In all the examined cases, the ethyl carbinols were obtained in good chemical yields, whereas the enantioselectivity ranges from very low (1%) to moderately high (82%). The data of the Table indicate that higher asymmetric inductions are achieved with the ligand **10**. Whereas **8** appears to be, in all cases the most effective ligand among the ligands derived fron natural compounds.

It is important to note that **10** gives a lower ee with respect to compounds **2,3**. This result indicates that a predictable improvement of the stereo differentiating ability of 2-pyridyl-carbinols could be obtained by introduction of a suitable substituent on the 6-position of the pyridine ring.

Efforts to achieve a higher stereo selectivity by modification of the 2-(1-hydroxyalkyl)pyridines presented here are under study in these laboratories.

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References and Notes

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4. All new compounds gave satisfactory spectroscopic and microanalysis data. Compound **6**: mp 69-70 °C; $[\alpha]25_D$ -33.0 (*c*= 1.6, CCl_4); ^{1}H-NMR (300 MHz, $CDCl_3$, selected data) d 8.51 (m, 1H), 7.65 (m, 1H), 7.34 (d, 1H), 7.18 (m, 1H), 5.25 (broad, 1H), 0.89 (d, 3H), 0.83 (d, 3H), 0.67 (d, 3H). ^{13}H-NMR (75.4 MHz, $CDCl_3$, selected data) d 165.3, 146.9, 136.8, 121.5, 119.2, 50.6, 50.0, 33.2, 28.5, 27.4, 23.6, 22.4, 21.9, 18.8. Compound **7**: bp 120 °C (0.1 mbar); $[\alpha]25_D$ -1.9 (*c*= 1.6, CCl_4); ^{1}H-NMR (300 MHz, $CDCl_3$) d 8.51 (m, 1H), 7.65 (dt, 1H), 7.44 (d, 1H), 7.15 (m, 1H), 4.55 (s, 1H), 1.26 (s, 6H). ^{13}H-NMR (75.4 MHz, $CDCl_3$) d 166.5, 147.9, 136.3, 121.7, 119.7, 78.7, 53.2, 40.0, 38.8, 29.7, 27.7, 24.9, 23.5. Compound **8** mp 59-60 °C, $[\alpha]25_D$ -46.2 (*c*= 1.6, CCl_4); ^{1}H-NMR (300 MHz, $CDCl_3$,selected data) d 8.53 (m, 1H), 7.66 (dt, 1H), 7.43 (d, 1H), 7.17 (m, 1H), 5.28 (s, 1H), 1.26 (s, 3H), 0.92 (s, 3H), 0.82 (s, 3H). ^{13}H-NMR (75.4 MHz, $CDCl_3$) d 163.5, 147.3, 135.5, 121.6, 120.6, 82.6, 53.4, 50.5, 45.3, 44.2, 30.7, 26.9, 21.3, 21.1, 9.9.
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6. The rotatory power of obtained (+)-(R)-**10** was $[\alpha]25_D$ +16.32 (*c*= 1.6, CCl_4). Since to this value corresponds a 91 % ee (determined by means of ^{19}F-NMR of the corresponding ester of (+)MPTA) a more corrected value of the maximum rotatory power of chiral **10** is $[\alpha]25_D$ 17.8 (in CCl_4 solution) rather than 29.5 as extrapolated from previous data[8].
7. A solution of the ligand **6-8**,**10** (0.37 mmol) in ether (5 mL) was cooled at 0 °C. Diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, added with benzaldehyde (0.6 mL, 0.647 g, 6.1 mmol) then stirred for additional 20 h. The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then was extracted with ether and the organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The residue was distilled and purified by flash chromatography to afford pure (GLC) 1-phenylpropanol.
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