

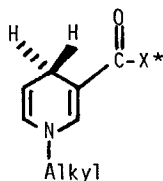
CHIRAL 1,4-DIHYDROPYRIDINES.  
SYNTHESIS AND ABSOLUTE CONFIGURATION.

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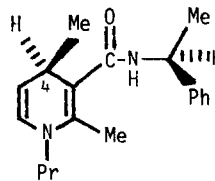
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Summary: Addition of organometallics to chiral 3-pyridyl oxazolines gave high diastereoselectivity at the 4-position of the pyridine nucleus. Absolute configuration was determined by x-ray analysis.

The extensive activity in recent years to develop NADH mimics has resulted in a number of synthetic approaches to chiral 1,4-dihyronicotinamides.<sup>1</sup> All of these routes gave 4-unsubstituted dihyronicotinamides with chiral amine or ester moieties 1 except for the work of Ohno<sup>2</sup> which produced the 4-methyl derivative 2 by resolution. Use of 1 or 2 as hydride transfer



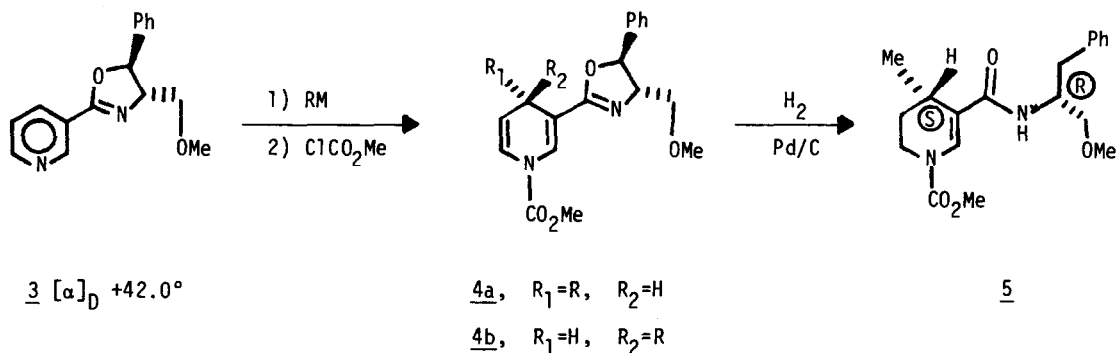
1 X\* = Chiral, non-racemic  
amines or esters



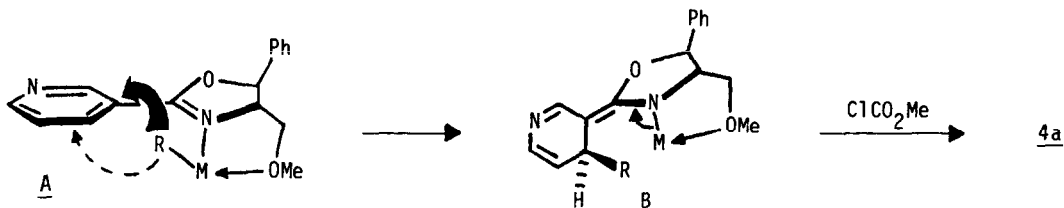
2

reagents has led to ketone reductions in very high ee's, especially for the (4R)-4-methyl derivative. The excellent stereoselectivity observed by Ohno for 2 prompted us to examine an asymmetric route to 4-substituted-1,4-dihydropyridines which, based upon our earlier studies on achiral analogs,<sup>3</sup> should provide an efficient entry into this important class of compounds.

The synthesis was initiated by conversion of 3-cyanopyridine to the chiral oxazoline 3.<sup>4</sup> Addition studies, using organolithium and Grignard reagents reported earlier, shows that 4- or 6-addition can be readily controlled.<sup>4</sup> For the case at hand only 4-addition was considered



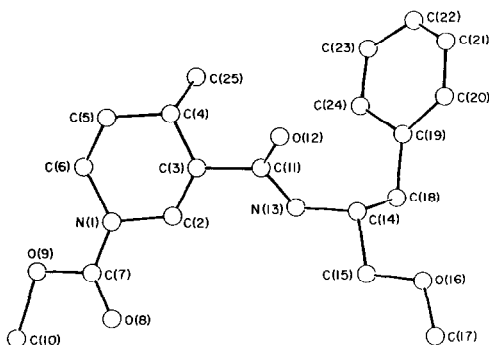
important and this was accomplished by treatment with various organometallics (THF, 0°) followed by trapping the metal salt with  $\text{ClCO}_2\text{Me}$ . This procedure gave  $\underline{4a}$  and  $\underline{4b}$  in ratios of >95:5, respectively. The ratios were assessed using hplc (10% ethylacetate-hexane, Table 1). The major



diastereomer was purified, free of the minor diastereomer, using preparative liquid chromatography (20% EtOAc-hexane). The yields and physical data are presented in the table. In all cases examined, the diastereomeric ratios of the addition products were quite high and stereochemically pure material was obtained by similar chromatographic techniques.

The absolute configuration of the 4-position in  $\underline{4}$  for the major product could not be readily determined by x-ray techniques due to their physical nature (oils, foam, or microcrystalline material). Degradation studies, as described by Ohno<sup>2</sup>, gave inconclusive results. However, pure  $\underline{4a}$  ( $R=\text{Me}$ ) was hydrogenated (10% Pd/C, 3 atm, EtOH) to give the tetrahydro derivative  $\underline{5}$  containing an open chain amide due to hydrogenolysis of the oxazoline ring.<sup>5</sup> The crystalline nature of  $\underline{5}$  allowed its structure to be determined by single-crystal x-ray analysis<sup>6</sup> and showed that the 4-position possessed the S-configuration ( $\underline{4a}$ ,  $R=\text{Me}$ , Fig. 1).<sup>7</sup>

Figure 1



From Table 1 it is clear that the stereoselective addition to 3 is rather general and also insensitive to the temperature of the addition. This efficient process may be envisioned as the organometallic initially complexing to the nitrogen and methoxyl groups (A) followed by entry of

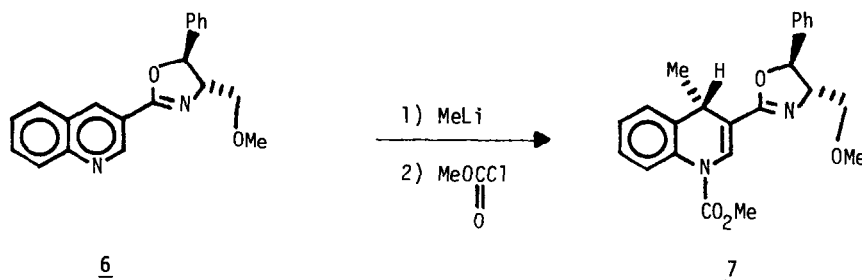
Table 1 Addition of organometallics to 3 in THF

RM	Add'n. T°	Diast. Ratio <u>4a</u> : <u>4b</u>	% Yield <sup>a</sup> (pure <u>4a</u> )	m/e	$[\alpha]_D^{25}$ (conc.) CHCl <sub>3</sub> <sup>c</sup>
MeLi	-40°	93:7	79	342	+196° (1.55)
	-78°	94:6	79 (63)	"	"
MeMgCl	0°	91:9	88	"	"
BuLi	-78°	97:3	(92)	384	+219° (1.93)
BuMgCl	0°	95:5	98	"	"
EtMgBr	0°	92:8	63	b	+177° (4.61)
PhLi	-78°	92:8	94	404	+108° (1.62)

a) All products possessed correct elemental analyses. Reactions performed in THF at concentrations of 0.005 to 0.02 M in 3 using 1.0-1.1 equiv of organometallic; b) Not determined; c) Rotations are for pure diastereomer after separation on mplc (20% ethylacetate-hexane).

the R-group to the topside plane of the pyridine ring. This is consistent with earlier asymmetric additions to alkenyl oxazolines.<sup>8</sup> Underside addition (dotted line in A) would lead to the opposite stereochemistry, 4b. After addition has occurred, the proposed lithio or magnesio salt, B, is acylated with methyl chloroformate to produce 4a. In a related experiment, the quinoline system 6<sup>9</sup> was treated with MeLi (-78°, THF) followed by MeCO<sub>2</sub>Cl and gave the 4-methyl dihydroquinoline 7 in 84% yield as a 98:2 mixture of diastereomers. Purification (mplc) gave pure 7,  $[\alpha]_D^{25}$  +274° (c 1.96, CHCl<sub>3</sub>), m/e 392, yield 70%.<sup>10</sup>

These experiments indicate that generating a new chiral center in the 4-position<sup>11</sup> of pyridines and quinolines with high enantiomeric purity is now a feasible process and further investigation of these materials is currently underway.



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## REFERENCES

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2. A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, J. Am. Chem. Soc., **101**, 7036 (1979).
3. A. I. Meyers and R. Gabel, Heterocycles, **11**, 133 (1978); A. Hauck and C. S. Giam, J. Chem. Soc. Perkin I 2070 (1980).
4. A. I. Meyers and N. R. Natale, Heterocycles (1981) in press. In this study, it was found that 4- or 6-addition may be realized by use of the hydroxy or methoxy oxazolines, respectively.
5. Mp 96-98° [ $\alpha$ ]<sub>D</sub><sup>25</sup> +18.3° (c 1.49, CHCl<sub>3</sub>).
6. Preliminary x-ray photographs showed monoclinic symmetry and accurate lattice parameters of  $\underline{a} = 11.741(2)$ ,  $\underline{b} = 4.967(1)$ ,  $\underline{c} = 17.755(3)\text{\AA}$  and  $\underline{\beta} = 112.59(1)^\circ$  in space group P2<sub>1</sub>. All unique diffraction maxima with  $2\theta \leq 114^\circ$  were collected on a four-circle diffractometer using Ni-filtered CuK $\alpha$  radiation (1.54178 $\text{\AA}$ ) and a variable speed, 1°  $\omega$ -scan. After correction for Lorentz, polarization and background effects, 1268 (86%) were judged observed ( $|F_o| \geq 3\sigma(F_o)$ ). The structure was solved using a multiresolution weighted tangent formula approach and refined by full-matrix least squares methods using anisotropic nonhydrogen atoms and isotropic hydrogens to a standard, unweighted residual of 0.056 for the observed data. Crystallographic programs are described in J. Am. Chem. Soc., **103**, 1243 (1981).
7. Figure 1 is a computer generated perspective drawing of the final x-ray model. The enantiomer shown was selected to make C(14) have the known R absolute configuration. The stereochemistry at C(4) is S. In general bond distances and angles agree well with generally accepted values. Crystallographic data have been deposited with the Cambridge crystallographic Data Center.
8. A. I. Meyers, C. E. Whitten, and R. K. Smith, J. Org. Chem., **44**, 2250 (1979).
9. Oil, purified by distillation (Kugelrohr), 105° (0.05 torr), [ $\alpha$ ]<sub>D</sub><sup>25</sup> +100° (c 9.6 CHCl<sub>3</sub>).
10. Absolute configuration tentatively assigned by analogy with 4a.
11. Dilution experiments for this addition (3 to 4) were studied to assess their effect on the % diastereomeric excess in 4. The only changes noted (0.1-0.005M in 3) was a higher proportion of 6-addition at higher concentrations. The % DE, however for the 4-addition product remained constant in the range 0.02-0.005 (see ref. 4).

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