REGIOSELECTIVE ADDITIONS TO 3-(OXAZOLINYL)PYRIDINE WITH ORGANOLITHIUM REAGENTS

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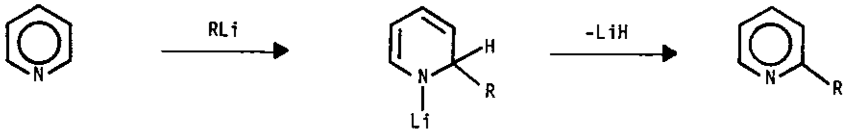
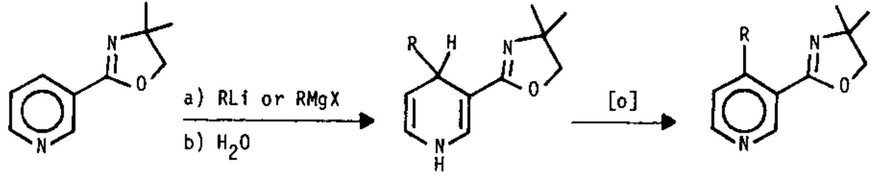
Organolithium reagents have been found to add to the 4- or 6-position in pyridines depending on the nature of the oxazoline present. Thus, methoxy-containing oxazolines lead to the 4-addition product (>95%), whereas hydroxy-containing oxazolines direct addition to the 6-position in yields as high as 95%.

Organolithium addition to pyridines has been known since 1930 when Ziegler first reported the formation of 2-(*n*-butyl)pyridine[1] (Eq. 1). Since then, a number of studies involving nucleophilic additions to pyridines have been described.[2] We[3] and others[4] have recently shown that the oxazoline moiety, through its coordination with organolithium and Grignard reagents, leads to very high yields of 4-substituted 1,4-dihydropyridines and is readily oxidized to 4-substituted pyridines (Eq. 2). The single exception to Eq. 2 was reported using *t*-butyllithium which gave the 6-*tert*-butyl derivative.[3]



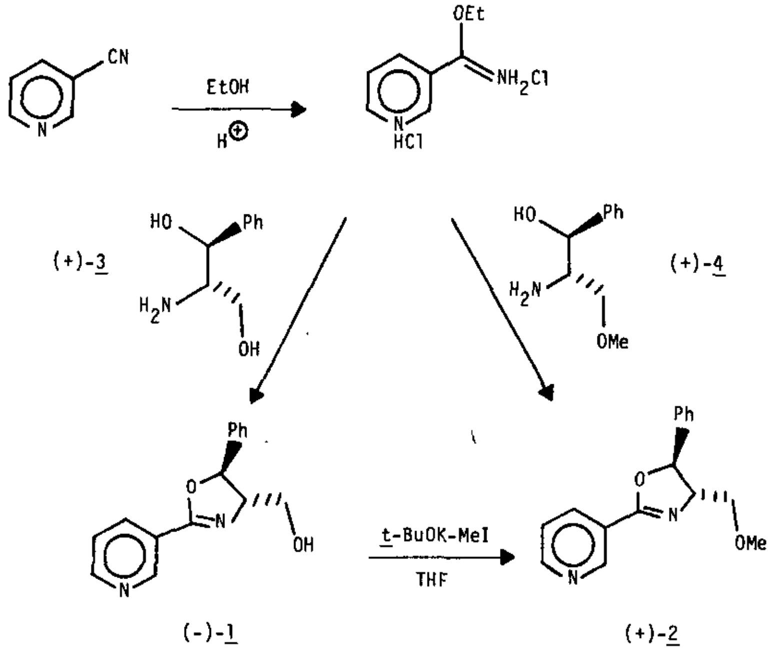
(Eq. 1)



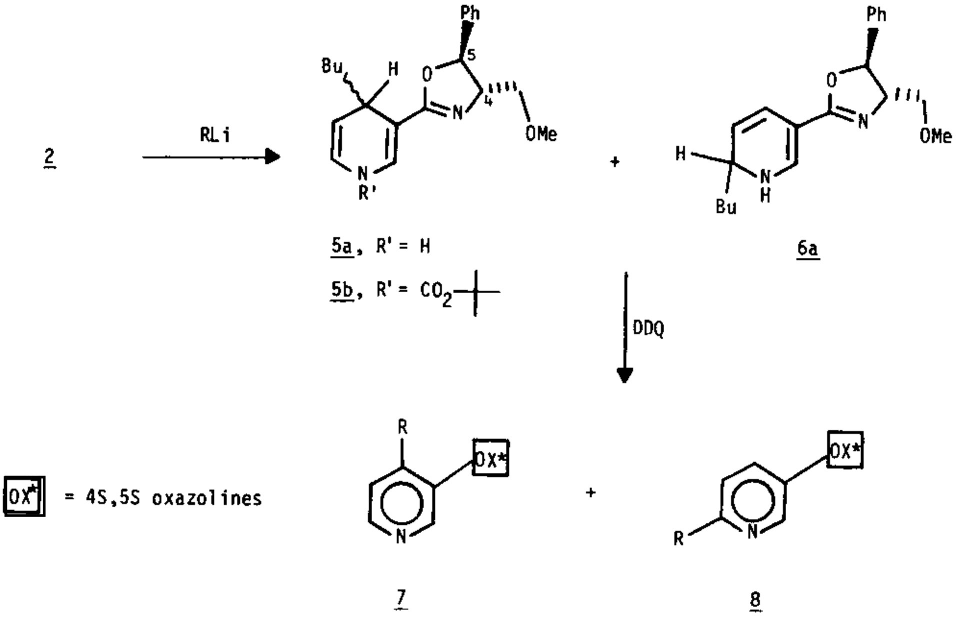
(Eq. 2)

As part of an on-going program using chiral oxazolines as auxiliary reagents for asymmetric synthesis, we now report some preliminary results using 3-pyridyloxazolines 1 and 2. These chiral pyridine systems were prepared from 3-cyanopyridine, converted to its imidate (Scheme 1), and treated either with the aminodiol 3[5] or the methoxyamino alcohol 4.[5] In this fashion 1 was formed in 89% yield by heating, to reflux, a solution of imidate, 1.0 equiv of triethylamine in dry 1,2-dichloroethane, and 1.0 equiv of (+)-aminodiol for 4 h; mp 124-125° (Et_2O), $[\alpha]_D$ -33.3° (c 10.5, $CHCl_3$). Likewise, 2 was prepared in

SCHEME 1



84% yield by stirring at room temperature a 1,2-dichloroethane solution of the imidate, triethylamine, and (+)-methoxyamino alcohol 4 for 21 h, bp 147-149° (0.13 torr), $[\alpha]_D$ +42.7° (c 7.3, CHCl$_3$). Furthermore, 1 could be transformed into 2 by treatment with t-BuOK-MeI. The intended purpose of the chiral pyridines was to assess whether addition of organometallics would lead to diastereomerically pure 1,4-dihydropyridines which would serve as chiral NADH-mimics. This area of study has recently received much attention[6] and it was felt that chiral dihydropyridines obtained via Eq. 2 would provide a facile entry into useful NADH mimics. Addition of n-butyllithium (ether, -78°) to 2 gave a mixture of *two* dihydropyridines 5a and 6a which were rather unstable and, therefore, oxidized (DDQ, toluene, 25°, 2h) to the pyridines 7 and 8. The ratio *[hplc or pmr of 6H (δ 8.6 d) or* 4H (δ 8.12 dd)] of 7:8 was nearly 1:1. After changing solvents and other parameters (Table 1), the ratio of 5a:6a and, *ultimately, 7:8 rose to greater than 97%.* Although 5a was unstable, it could be trapped as its lithio salt using t-butyl chloroformate to give the



urethane 5b (100%, oil). Nmr integration of C-2 using Eu-optishift indicated a diastereomeric ratio of 89:11. A pure diastereomer of 5b was obtained using Waters 500 Prep-LC, $[\alpha]_D$ +197° (c 1.4, $CHCl_3$). The absolute configuration of 5b and other examples of diastereoselective additions will be deferred until the study is complete. For the present purposes, however, the regioselective addition to the pyridine ring remains the central theme of this report.

As seen from Table 1, use of THF at -78° in solutions 0.005 M in 2, addition of butyl, methyl, and phenyllithium gave pure 4-addition product, since oxidation gave yields of 7 in the 60-85% range. Thus, a viable route to chiral dihydropyridines 5b or 4-substituted pyridines 7 is now available.

Table 1. Addition of Organolithiums to 2

RLi	Solvent	M, Conc. 2	T°	Ratio 7:8
BuLi	Ether	0.01	-78	48:52
BuLi	THF Et_2O-pentane (4:1:1)	0.015	-120	83:17
BuLi	THF-TMEDA[a]	0.01	-78	88:12[b]
BuLi	THF	0.10	-78	85:15
BuLi	THF	0.005	-78	97:3[b]
MeLi	THF	0.005	-78	>99:1[c]
PhLi	THF	0.005	-78	>99:1[c]

a) BuLi precomplexed with 2.0 equiv TMEDA prior to addition to a THF solution of 2.

b) HPLC ratio (refractive index) EtOAc-$CHCl_3$ (1:1).

c) Vpc analysis.

When the hydroxymethyloxazoline 1 was investigated as a source of chiral dihydropyridines, the results were surprisingly different (Table 2). Under all the conditions examined

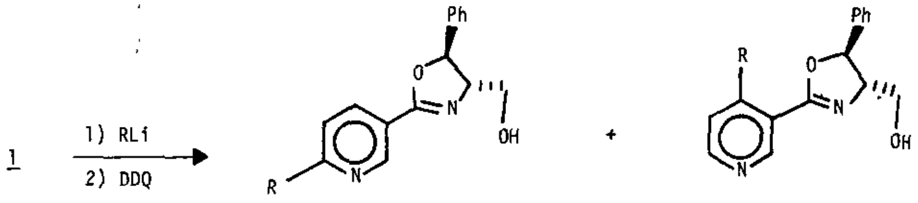


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Table 2. Addition of Organolithiums to 1.

RLi[a]	Solvent	T°	M, Conc. 1	Ratio 9:10[b,c]
BuLi	THF	-78	0.03	60:40
BuLi	THF	-78	0.20	70:30
BuLi	THF	0	0.03	86:14
BuLi	DME	-78	0.03	73:27
BuLi	DME	0	0.10	95:5
MeLi	DME	0	0.10	80:20
PhLi	DME	0	0.10	53:47

a) 2.0 equiv RLi employed.

b) Determined by nmr of 6-H and 4-H, see text.

c) Yields of all products were in the 60-95% range.

the 6-substituted pyridine 9 was the major product. By varying solvents, temperature, and concentration, it was indeed possible to generate 9 in greater than 95% yield. The optimum conditions lay in the use of dimethoxyethane as solvent and the addition temperature at 0°. Use of methyllithium or phenyllithium gave poorer regioselectivity than butyllithium. In fact, phenyllithium, on the hydroxymethyloxazoline gave virtually no selectivity as compared to phenyllithium addition to the methoxymethyloxazoline (>99%). It may be concluded by these results that the oxygen substituent on the oxazoline exhibits a profound effect on the regiochemical addition to the pyridine ring. The preponderance for 4-addition (on 2) may be due to the strong chelating effect of the methoxyl group and its effect in assisting organolithium entry to the "ortho" (4-) position.[7] No additions to the 2-position were observed in this study. On the other hand, the hydroxyoxazoline 1, after being transformed into its oxo-lithio salt, loses its coordinating ability[8] with the second equiv of organolithium and a simple Ziegler addition (Eq. 1) competes satisfactorily. With the successful addition to the 4-position of 2 giving chiral dihydropyridines 5b, the study toward chiral NADH mimics as well as other useful pyridine synthons is continuing.[9]

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7. Conjugate additions to unsaturated chiral oxazolines have been reported to give very high diastereoselectivity; A. I. Meyers, C. E. Whitten, and R. K. Smith, J. Org. Chem., 44, 2250 (1979). The present reaction may, therefore, be considered as an analogous process.

8. D. A. Evans and J. M. Takacs [Tetrahedron Letters, 21, 4233 (1980)] have also observed large variations in the course of reactions when a hydroxyl rather than a methoxyl is present in the metalation step (see also *ref.* 5).

9. All compounds gave satisfactory spectral, mass, and elemental analyses.

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