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Grignard Addition to 1-Acyl Salts of Chiral 4-Alkoxypyridines. A New Enantioselective Preparation of 2-Alkyl-2,3-dihydro-4-pyridones

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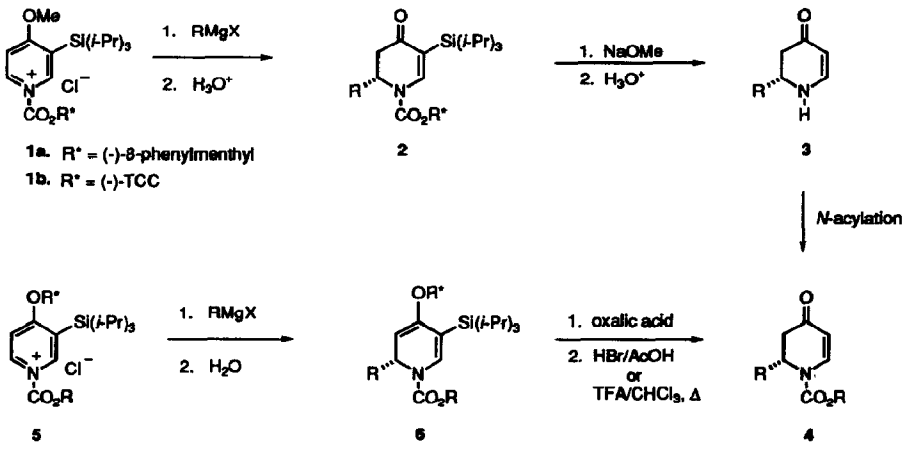
Abstract: *Several 2-alkyl-2,3-dihydro-4-pyridones were prepared by asymmetric addition of Grignard reagents to the 1-acyl salts of chiral 4-alkoxypyridines.*

The synthetic utility of 2-alkyl-2,3-dihydro-4-pyridones **3** has been amply demonstrated in our laboratories[1,2] and others.[3,4] We have developed an efficient asymmetric synthesis of **3** via addition of nucleophiles to chiral 1-acylpyridinium salt **1**, which is prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine and a homochiral chloroformate.[5] The chiral auxiliary and TIPS group can be removed from intermediate **2** by a one-pot reaction using NaOMe/MeOH followed by aqueous acid. The nitrogen of **3** can be reacylated to give the 1-acyl derivatives **4**.



The synthetic potential of heterocycles **3** and **4** has prompted us to investigate other methods for their asymmetric synthesis. One attractive strategy involved moving the chiral auxiliary from the 1-acyl group of **1** to the C-4 position, replacing the methoxy function with a homochiral ether. For example, a chiral 4-

alkoxy-3-(triisopropylsilyl)pyridine could be treated with an alkyl chloroformate to give 1-acyl salt **5** in situ. Addition of a Grignard reagent will give 1,2-dihydropyridine **6**. Purification of the major diastereomer followed by acidic hydrolysis and TIPS removal would provide enantiopure 1-acyl-2,3-dihydro-4-pyridones **4**. The chiral auxiliary could be recovered at this stage and recycled. This route avoids the NaOMe step required for auxiliary removal in our original synthesis, which may be advantageous in certain cases. We reasoned that the C-3 TIPS group of **5** is necessary to block the C-2 position against nucleophilic attack and to restrict the rotation of the C-4 chiral alkoxy oxygen-carbon bond. Molecular mechanics (MMX) suggested this approach may be fruitful, as a low energy conformation (Figure 1) was found that looked quite advantageous for favorable asymmetric induction at C-6.[6]

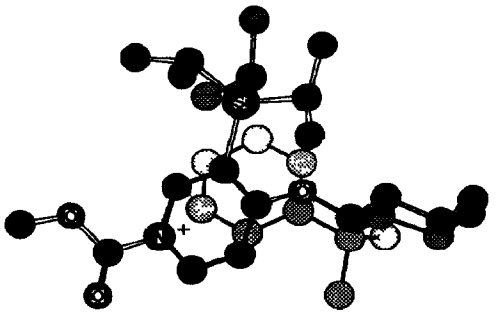
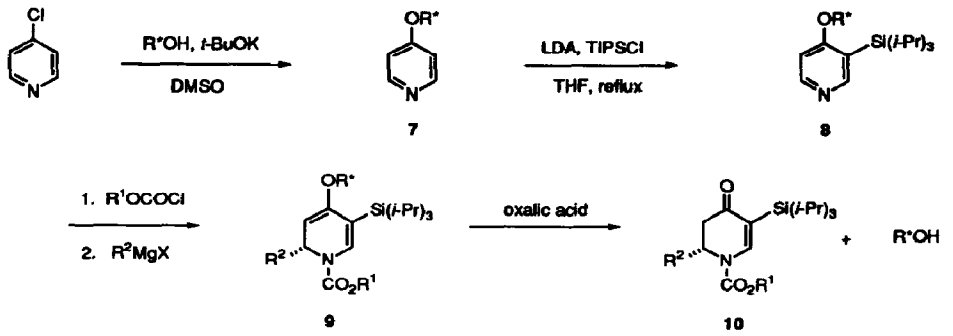


Figure 1.

Our investigation began with the preparation of the required homochiral 4-alkoxypyridines. Treatment of 4-chloropyridine with (-)-8-phenylmenthol/*t*-BuOK in DMSO gave the ether **7a** in good yield. Lithiation with LDA and in situ trapping with triisopropylsilyl chloride provided pyridine **8a**.[7] Other chiral alkoxypyridines **8** were prepared in a similar manner from various homochiral alcohols as shown in Table I.

Table I. Preparation of Chiral Alkoxypyridines **7** and **8**.

entry	R*OH	conditions (for **7**)	yield, % **7**	yield, % **8**
a	(-)-8-phenylmenthol	25 °C, 24 h	84	58
b	(+)-*trans*-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexanol	25 °C, 24 h	87	53
c	(±)-*trans*-2-[1-methyl-1-(4-biphenyl)ethyl]cyclohexanol	120 °C, 2 d	44	0
d	(+)-*trans*-2-phenylcyclohexanol	25 °C, 24 h	63	46



The chiral pyridines **8** were treated with a chloroformate and a Grignard reagent to give 1,2-dihydropyridines **9**, which were hydrolyzed with saturated oxalic acid to provide good yields of the 2,3-dihydro-4-pyridones **10** and the recovered chiral auxiliary. The yields and diastereoselectivities for the various examples studied are given in Table II.

Table II. Grignard Addition to 1-Acyl Salts of **8**

entry[a]	alkoxypyridine	R^1OCOCl (R^1)	R^2MgX	yield,[b] % **9**	de[c] **9**	yield,[d] % **10**
a	**8a**	Et	Me	86	78	86[e]
b	**8a**	Et	Ph	73	77	38[f]
c	**8a**	Ph	Me	79	71	79[e]
d	**8a**	Ph	Bu	72	72	87[f]
e	**8a**	Bn	Me	71	77	68[f]
f	**8a**	Bn	Ph	91	68	36[f]
g	**8b**	Et	Me	50	61	-
h	**8d**	Ph	Et	58	60	-

[a]The reactions were generally performed on a 0.1-mmol scale. [b]Yield of diastereomeric mixture isolated from radial PLC. [c]The diastereomeric excess (de) was determined by HPLC. [d]Satisfactory IR, ^1H and ^{13}C NMR, and microanalysis data were obtained for compounds **10**. [e]Hydrolysis was carried out by adding saturated aqueous oxalic acid and heating at reflux. [f]Hydrolysis performed by adding saturated oxalic acid in methanol and heating at reflux.

Isolation of the major diastereomers **9** by chromatography and subsequent hydrolysis provide enantiopure dihydropyridones **10**. By comparing **10** to authentic compounds of known absolute stereochemistry,[5] it was determined that the major diastereomer **9**, prepared from **8a** (R* = (-)-8-phenylmenthyl), contained the *R* configuration at C-2 (*S* configuration when R^2 = Ph). This sense of asymmetric induction was anticipated based on molecular mechanics (Figure 1). Work is underway to increase the degree of asymmetric induction through the use of more effective chiral auxiliaries. This new asymmetric synthesis of 2,3-dihydro-4-pyridones compliments our earlier work[5] and the methods developed by others.[4]

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