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Diastereoselective Addition of Organocuprates on 1,4-Dihydropyridine-3-carboxaldehydes. Synthesis of Chiral 1,4-Dihydropyridyl-3-alcohols and Pyridyl-3-alcohols

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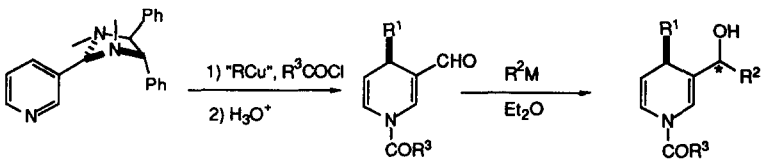
Abstract : Chiral 1,4-dihydropyridyl-3-alcohols are obtained via a diastereoselective (de 90% -> 95%) 1,2 addition of organocuprates on chiral 1,4-dihydropyridine-3-carboxaldehydes and are transformed into chiral pyridyl-3-alcohols (90% - >95%).

We recently reported an asymmetric synthesis of 1,4-dihydropyridine-3-carboxaldehydes **1** starting from nicotinaldehyde by using chiral diamines of C_2 symmetry.[1] As a part of a program directed towards the synthetic uses of such dihydropyridines **1** in synthesis, we elected to investigate the possibility of diastereoselective transformation of the aldehyde into a secondary alcohol by addition of an organometallic reagent (scheme 1).

Initially, Grignard reagent (CH_3MgBr)[2] was added in ether on the dihydropyridine **1** (R^1 = Et, R^3 = OCH_3, entry 1, Table 1). The corresponding alcohol **2** was obtained in good yield, but with a poor diastereoselectivity (measured by ^1H NMR). In contrast, the use of Me_2CuLi,[3] in ether at - 20°C, afforded the same alcohol with an excellent diastereoselectivity (d.e. > 95%) and a good yield when the work up was performed with an aqueous solution of NH_4Cl. No product resulting from a 1,4 addition was isolated. Several dihydropyridines **1** were used, and as shown in the Table1, the diastereoselectivity was independent of the nature of R^1. With Bu_2CuLi, the same result was obtained (entry 4). In the case of Ph_2CuLi (entry 7), the reaction afforded only the racemic alcohol **3**.



1 R^3 = OCH_3 or R^4 2

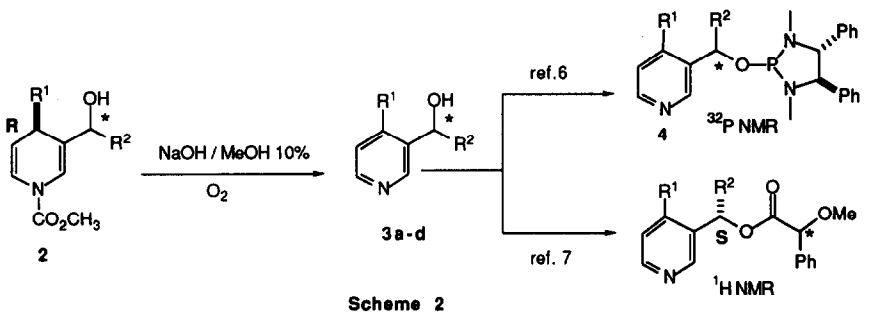
Scheme 1

Table 1 Addition of Organometallic Reagents on Aldehydes **1** ($R^3 = OCH_3$)

Entry	R^1	R^2M	Yield(%)	d.e.[a](%)	$[\alpha]_D(CHCl_3)$[b]
1	Et	MeMgBr	90	35	-
2	Et	Me_2CuLi	70	>95	-33 (c = 19)
3[c]	Me	Me_2CuLi	80	90	-49 (c = 5)
4	Et	Bu_2CuLi	87	95	-63 (c = 8)
5	$CH_2=CH_2$	Me_2CuLi	71	>95	-127 (c = 5)
6	Ph	Me_2CuLi	78	95	-128 (c = 3)
7	Et	Ph_2CuLi	-	-	-

a) Determined by ^1H NMR (400 MHz).
b) Starting from a (R) dihydropyridine **1**.
c) In THF, the same d.e. was obtained in 28 % yield
d) Racemic alcohol **3** (R^1 = Ph) was isolated in 35% yield.

Dihydropyridines **2** were converted into pyridyl alcohols **3** (table 2) by alcaline treatment (scheme 2) followed by aromatization of the dihydropyridine ring.[4] Indeed, such chiral alcohols are attractive auxiliaries used for the resolution of carboxylic acids and in the synthesis of natural products.[5] The optical purity of the alcohols **3** was determined by ^{31}P NMR of the corresponding diazaphospholidines[6] **4** (scheme 2) and found to be the same that the starting aldehyde **1**.Therefore, no racemization occurs during all the procedure. The absolute configuration of the new stereogenic center was determined on alcohol **3a** according Trost's procedure[7] and found to be (S) starting from (R) dihydropyridine **1**.



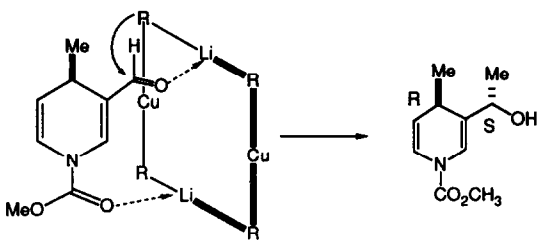
Scheme 2

Table 2 Preparation of Pyridylalcohols **3**

R^1	R^2	alcohol	Yield(%)[a]	e.e.(%)[b]	$(\alpha]_D(CHCl_3)$
Me	Me	**3a**	68	90	-29 (c = 1)
Et[c]	Me	**3b**	65	84	-27 (c = 1.9)
Et[c]	Bu	**3c**	75	80	-8.4 (c = 5.2)
Vinyl	Me	**3d**	40	>95	-37 (c = 3.7)

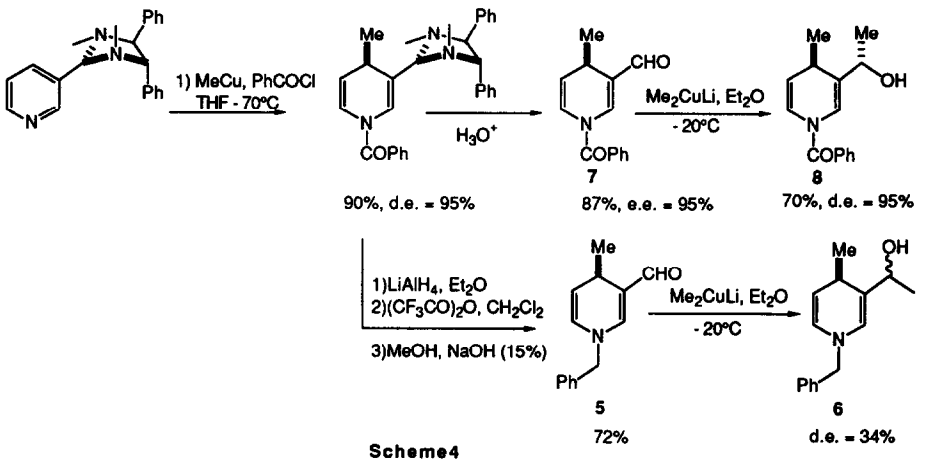
a) Not optimized
b) Determined according ref.[6].
c) Starting from 1 of 86% e.e.

In order to explain the stereochemistry of the reaction, a chelation [8] of the square planar dimeric cuprate[9] by the aldehyde and the oxygen atom of the carbamate was postulated (scheme 3). Such a chelation block the aldehyde in the conformation shown in scheme 3 and the cuprate adds on the less hindered face of the aldehyde according a Bürgi-Dunitz trajectory.[10]



Scheme 3

The influence of the oxygen atom of the carbamate was demonstrated by addition of Me_2CuLi, in ether, to aldehyde **5** prepared according scheme 4.[11] The diastereomeric composition of the unstable alcohol **6** was measured by ^1H NMR and found to be low (34%). In contrast, the same reaction performed on aldehyde **7** afforded the corresponding alcohol with an excellent diastereoselectivity (d.e. > 95%). Therefore, the presence of a carbamate (or amide) function is necessary for the diastereocontrol.



Scheme4

In conclusion, we have shown that 1, 2 addition of organocuprates on 1,4-dihydropyridine-3-carboxaldehydes occurs with a high diastereoselectivity.The obtained alcohols are good precursors of the corresponding 3-pyridyl alcohols.Work is in progress to exploit alcohols **2** in synthesis.

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