

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

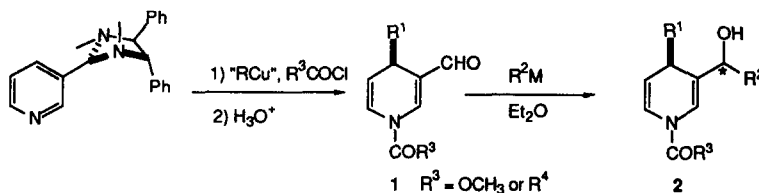
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Abstract : Chiral 1,4-dihydropyridyl-3-alcohols are obtained via a diastereoselective (de 90% -> 95%) 1,2 addition of organocuprates on chiral 1,4-dihydropyridine-3-carboxaldehydes and are transformed into chiral pyridyl-3-alcohols (90% -> 95%).

We recently reported an asymmetric synthesis of 1,4-dihydropyridine-3-carboxaldehydes **1** starting from nicotinaldehyde by using chiral diamines of C₂ 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 (CH₃MgBr)² was added in ether on the dihydropyridine **1** (R¹ = Et, R³ = OCH₃, 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 Me₂CuLi,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 NH₄Cl. No product resulting from a 1,4 addition was isolated. Several dihydropyridines **1** were used, and as shown in the Table 1, the diastereoselectivity was independent of the nature of R¹. With Bu₂CuLi, the same result was obtained (entry 4). In the case of Ph₂CuLi (entry 7), the reaction afforded only the racemic alcohol **3**.



Scheme 1

Table 1 Addition of Organometallic Reagents on Aldehydes **1** ($R^3 = \text{OCH}_3$)

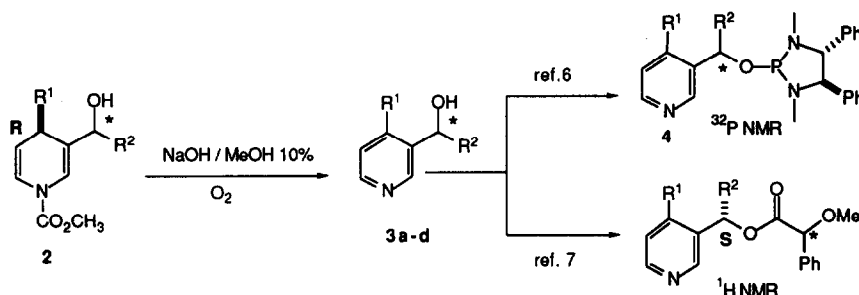
Entry	R^1	$R^2\text{M}$	Yield(%)	d.e. ^{a)} (%)	$[\alpha]_D(\text{CHCl}_3)^b)$
1	Et	MeMgBr	90	35	-
2	Et	Me ₂ CuLi	70	>95	-33 (c = 19)
3 ^{c)}	Me	Me ₂ CuLi	80	90	-49 (c = 5)
4	Et	Bu ₂ CuLi	87	95	-63 (c = 8)
5	CH ₂ =CH ₂	Me ₂ CuLi	71	>95	-127 (c = 5)
6	Ph	Me ₂ CuLi	78	95	-128 (c = 3)
7	Et	Ph ₂ CuLi	-	-	-

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** ($R^1 = \text{Ph}$) was isolated in 35% yield.

Dihydropyridines **2** were converted into pyridyl alcohols **3** (table 2) by alkaline 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 ³¹P NMR of the corresponding diazaphospholidines⁶ **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 procedure⁷ and found to be (S) starting from (R) dihydropyridine **1**.



Scheme 2

Table 2 Preparation of Pyridylalcohols **3**

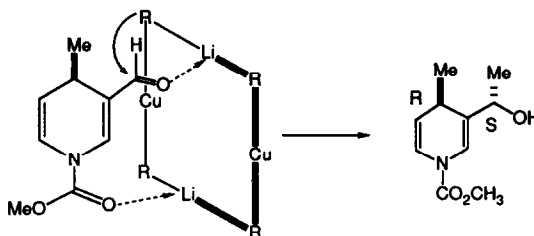
R^1	R^2	alcohol	Yield(%) ^{a)}	e.e.(%) ^{b)}	$[\alpha]_D(\text{CHCl}_3)$
Me	Me	3a	68	90	-29 (c = 1)
Et ^{c)}	Me	3b	65	84	-27 (c = 1.9)
Et ^{c)}	Bu	3c	75	80	-8.4 (c = 5.2)
Vinyl	Me	3d	40	>95	-37 (c = 3.7)

a) Not optimized

b) Determined according ref. 6.

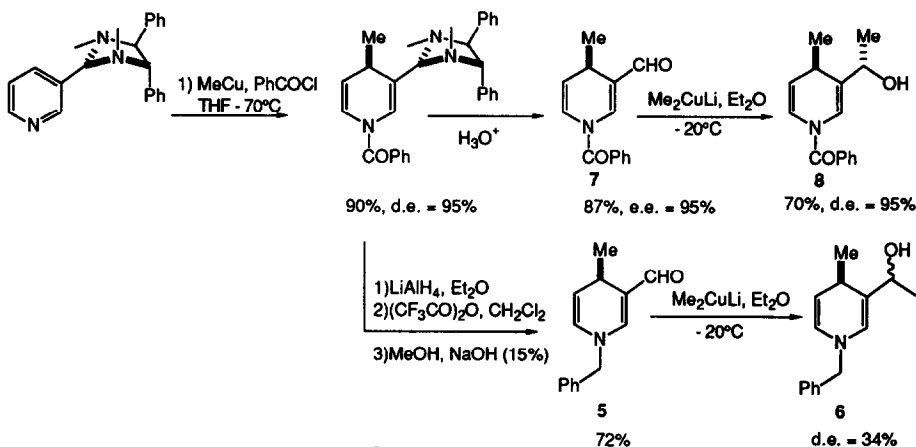
c) Starting from **1** of 86% e.e.

In order to explain the stereochemistry of the reaction, a chelation⁸ of the square planar dimeric cuprate⁹ 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.



Scheme 4

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.

REFERENCES and NOTES.

- 1 Gosmini, R. ; Mangeney, P. ; Alexakis, A. ; Commerçon, M. ; Normant, J.F., *Synlett*, **1991**, 111.
- 2 The use of MeLi afforded a H-N-1,4-dihydropyridine-3-carboxaldehyde resulting from a cleavage of the carbamate.
- 3 Organocopper reagents react with aldehydes at low temperature : Posner, G.H., Whitten, C.E.; McFarland, P.E., *J.Am.Chem.Soc.*, **1972**, *94*, 5106.
- 4 An alkaline work up afforded 3-pyridyl alcohols :
Comins, D.L.; Myoung, Y.C., *J.Org.Chem.*, **1990**, *55*, 292.
- 5 For synthesis and use of chiral pyridyl alcohols see : Uskokovic, M.R.; Lewis, R.L.; Partridge, J.J.; Despreaux, C.W.; Pruess, D.L., *J.Am.Chem.Soc.*, **1979**, *101*, 6742. Soai, K.; Hori, H.; Niwa, S., *Heterocycle*, **1989**, *29*, 2065. Seemayer, R.; Schneider, M.P., *Tetrahedron Asym.*, **1992**, *3*, 827.
- 6 Alexakis, A.; Mutti, S.; Mangeney, P., *J.Org.Chem.*, **1992**, *57*, 1224.
- 7 Trost, B.M.; Belletire, J.L.; Godleski, S., Mc Dougal, P.G.; Balkovec, J.M., *J.Org.Chem.*, **1986**, *51*, 2370.
- 8 For chelated mediated addition of copper reagents to aldehydes see: a) Still, W.C.; Schneider, J.A., *Tetrahedron Lett.*, **1980**, *21*, 1035. b) Kunz, T.; Reissig, H.U., *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 269. c) Janowitz, A.; Kunz, T.; Handke, G.; Reissig, H.U., *Synlett*, **1989**, *24*. d) Kozikowski, A.P.; Lee, J., *J.Org.Chem.*, **1990**, *55*, 863. e) Alexakis, A.; Sedrani, R.; Normant, J.F.; Mangeney, P., *Tetrahedron Asym.*, **1990**, *1*, 283. f) Baldwin, S.W., McIver, J.M., *Tetrahedron Lett.*, **1991**, *32*, 1937. d) Burke, S.D.; Piscopio, A.D.; Marron, B.E.; Matulenko, M.A., Pan, G., *Tetrahedron Lett.*, **1991**, *32*, 857. e) Molander, G.A.; Haar, J.H., Jr, *J.Am.Chem.Soc.*, **1993**, *115*, 40 and ref. cited therein.
- 9 Van Koten, G., *J.Organomet.Chem.*, **1990**, *400*, 283.
- 10 Bürgi, H.B.; Dunitz, J.D.; Shefter, E., *J.Am.Chem.Soc.*, **1973**, *95*, 5065.
- 11 Mangeney, P. ; Gosmini, R. ; Alexakis, A., *Tetrahedron Lett.*, **1991**, *32*, 3981.

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