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STEREOSELECTIVE SYNTHESIS OF β-HYDROXYAMINO ACIDS BY ALDOL REACTION OF α-ISOCYANOCARBOXYLATE WITH ARENE-CHROMIUM-TRICARBONYL COMPLEXES.

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Abstract: *High diastereoselectivity is obtained during the addition of ethyl isocyanoacetate 1 to chiral complexes 2 and 3. The 2-oxazoline-4-carboxylic esters are intermediates for the synthesis of β-substituted serines in a stereoconservative process.*

π-Arene-chromium complexes play a major role in stereoselective reactions and allow the preparation of a variety of useful organic molecules via modification of the complexed substrate and subsequent removal of the chromium moiety[1].

We previously showed[2] that more than 98% of asymmetric induction is obtained during the addition of tosyl methyl isocyanide to complexed aldehydes, to give trans oxazolines, which, after decomplexation and reduction, lead to optically pure R aminoalcohols.

Here we report our preliminary results concerning the diastereoselectivity of the addition of ethyl isocyanoacetate 1 on complexed aldehydes 2, 3 and, for comparison, on uncomplexed aldehydes 6, 7, Figure 1.

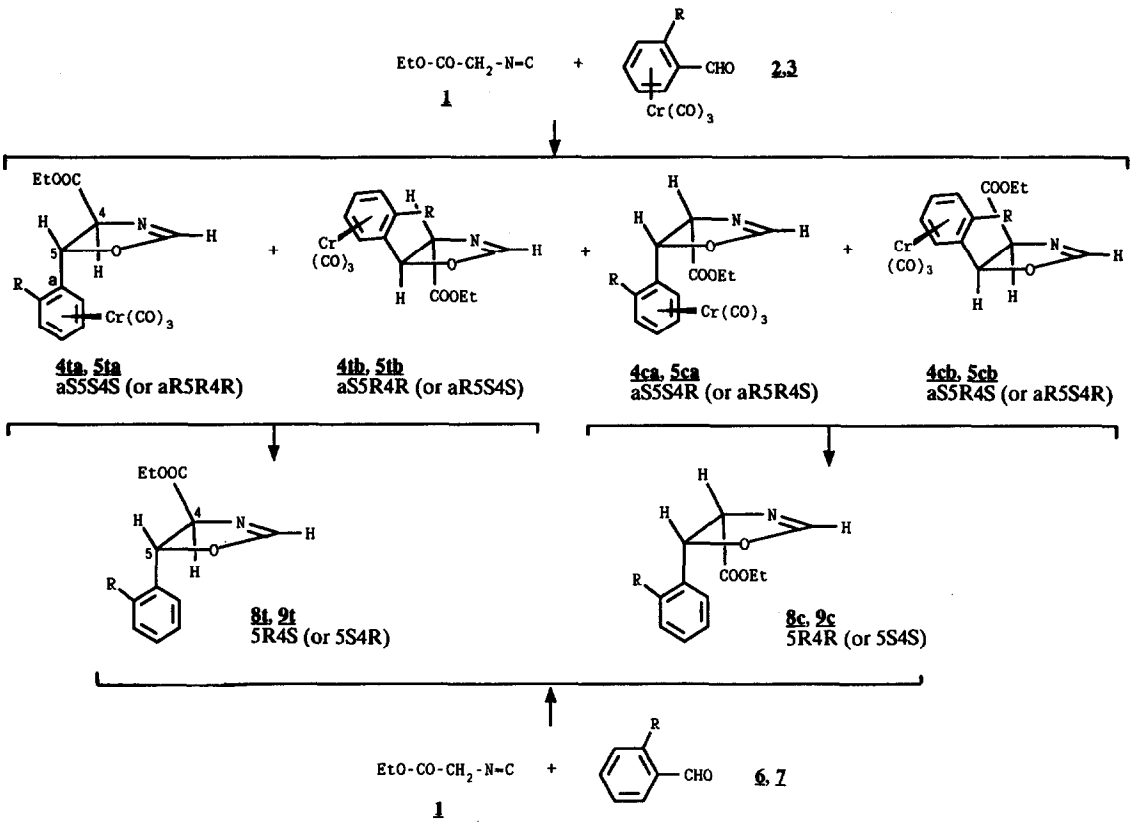
Oxazolines 4, 5, 8 and 9[3] are obtained in high yield in ethanol at room temperature with KCN as base according to Schöllkopf's method[4] or in tetrahydrofuran at -78°C and with LDA as base. The results are given in the Table . Of the four diastereomers expected from the complexes (2 and 3) two to three are obtained (Table, entries 1-4). The configuration of the complexed oxazolines 4ta, 4tb, 5ta and 5tb has been assigned on the following chemical and spectroscopical evidences:

- chromium complexed oxazolines 4ta, 4tb and 5ta, 5tb lead, after decomplexation, to trans oxazolines 8t and 9t respectively.

- the coupling constants between protons H4 and H5 are smaller in compounds 4ta, 4tb, 5ta, 5tb, 8t, 9t compare to compounds 4ca or 4cb, 5ca or 5cb, 8c, 9c which is respectively consistent with a trans and a cis geometrical relationship between those protons[5].

One notices that, when the reaction is performed at -78°C and with LDA as base, the asymmetric

Figure 1:



induction is higher: **trans a/trans b** = 9/1 versus 6/4 (entries 1 and 2) or = 10/0 versus 9/1 (entries 3 and 4) and that the diastereoselectivity is also better: **trans/cis** = 10/0 versus 8/2 (entries 6 and 7).

The prefered conformation of the carbonyl, predicted on the basis of known effects (H-bond, steric hindrance, dipolar interactions, etc) accounts for the preferential diastereoisomer[6]. Therefore, one can postulate that both aS complexes **2** and **3** will give preferentially the aS,5S,4S trans oxazoline. The higher diastereoselectivity found when starting from complexed aldehyde **3** can be explained by the increased steric and electronic demands of the methoxy group with respect to the methyl one. Such demand should shift the equilibrium towards the most stable conformer in the case of the methoxy substituent.

The purified 2-oxazoline-4-carboxylic esters **4ta** and **5ta** obtained from LDA method (Table, entries 2 and 4) can be transformed without epimerization into optically pure α-amino-β-hydroxy esters with conc. HCl in methanol[7], Figure 2.

This asymmetric aldol reaction thus constitutes an easy route to β-substituted serines.

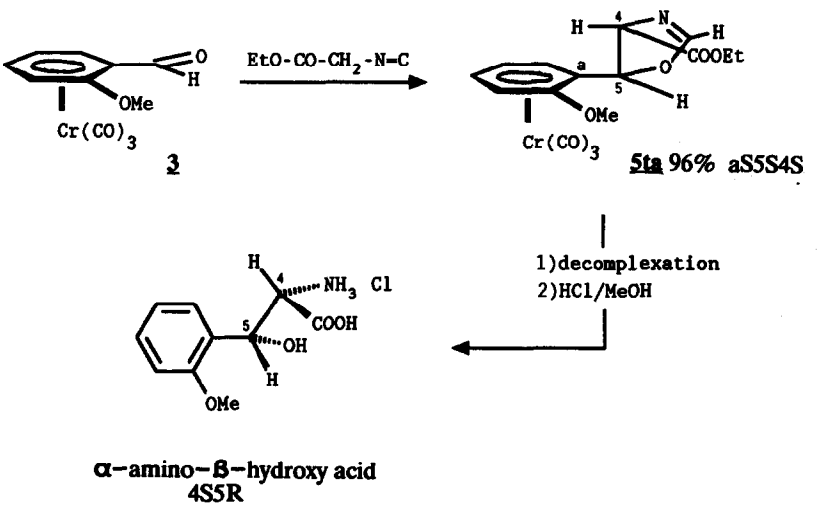
High enantio- and diastereoselectivities have also been reported by Hayashi and co-workers[7] in the same asymmetric aldol reaction; however these authors used catalytic amounts of a chiral ferrocenyl-phosphine-gold(I) complex which is less readily available than arene-chromium-tricarbonyl complexes.

Table:

Entry	Starting compound	R	:B	T (°C)	Complexed* oxazolines ta/tb//ca/cb	Uncomplexed oxazolines trans:cis	Yield‡ (%)
1	2	Me	CN^-	20	54/34//12/0		100
2	2	Me	LDA	-78	90/10// 0/0		95
3	3	OMe	CN^-	20	84/5//11/0		100
4	3	OMe	LDA	-78	96/0//4/0		98
5	6	Me	CN^-	20		84 : 16	100
6	7	OMe	CN^-	20		82 : 18	100
7	7	OMe	LDA	-78		100 : 0	80

* **ta** = **trans a** = major isomer = aS,5S,4S when the starting complex is aS ; **tb** = **trans b** = minor = aS,5R,4R when the starting complex is aS ; **ca, cb** = the two cis isomers, not assigned.
‡ In weight of crude compound corrected from remaining starting material, using 200 MHz NMR.

Figure 2 :



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References.

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2) Solladié-Cavallo A., Quazzotti S., Colonna S., Manfredi A. *Tetrahedron Lett.*, 1989, *30*, 2933.

3) ^{1}H NMR ($CDCl_3$/TMS), Bruker WP 200 SY: δ ppm

Oxazolines **4**: **4ta** (major): 1.33 (t, 3H, Me); 2.21 (s, 3H, Me); 4.26 (q, 2H, CH_2); 4.5 (dd, 1H, H4, J_{45}=7Hz, J_{42}=1.5Hz); 5.15 (d, 1H, Harom); 5.25 (t, 1H, Harom); 5.3 (d, 1H, Harom); 5.4 (t, 1H, Harom); 5.75 (d, 1H, H5); 7.1 (d, 1H, H2). **4tb**: 1.35 (t, 3H, Me); 2.28 (s, 3H, Me); 4.25 (q, 2H, CH_2); 4.75 (dd, 1H, H4, J_{45}=7.5Hz, J_{42}=1.5Hz); 5.05 (d, 1H, Harom); 5.2 (t, 1H, Harom); 5.43 (d, 1H, Harom); 5.5 (t, 1H, Harom); 5.75 (d, 1H, H5); 6.95 (d, 1H, H2). **4c**: 1.34 (t, 3H, Me); 2.26 (s, 3H, Me); 4.33 (q, 2H, CH_2); 5.0 (dd, 1H, H4, J_{45}=10.5Hz, J_{42}=1Hz); 5.56 (d, 1H, H5); 7.2 (d, 1H, H2); 5-5.5 (4Harom overlaped with the signals of **4ta** and **4tb**).

Oxazolines **5**: **5ta** (major): 1.25 (t, 3H, Me); 3.69 (s, 3H, Me); 4.2 (q, 2H, CH_2); 4.5 (d, 1H, H4, J_{45}=7.5Hz, J_{42}=1.5Hz); 4.81 (t, 1H, Harom); 5 (d, 1H, Harom); 5.45 (t, 1H, Harom); 5.55 (d, 1H, Harom); 5.59 (d, 1H, H5); 7 (d, 1H, H2). **5tb**: overlaped with **5ta** but: 3.7 (s, 3H, Me); 4.65 (dd, 1H, H4, J_{45}=7Hz, J_{42}=1Hz); 6.85 (d, 1H, H2). **5c**: overlaped with **5ta** and **5tb** but: 3.75 (s, 3H, Me); 7.13 (d, 1H, H2).

Oxazolines **8**: **8t** (major): 1.3 (t, 3H, Me); 2.32 (s, 3H, Me); 4.28 (q, 2H, CH_2); 4.53 (dd, 1H, H4, J_{45}=7.5Hz, J_{42}=1.5Hz); 6.91 (d, 1H, H5); 7.1 (d, 1H, H2). **8c**: overlaped with **8t** but: 5.05 (dd, 1H, H4, J_{45}=11Hz, J_{42}=1.5Hz); 5.87 (d, 1H, H5).

Oxazolines **9**: **9t** (major): 1.3 (s, 3H, Me); 3.8 (s, 3H, Me); 4.3 (q, 2H, CH_2); 4.56 (dd, 1H, H4, J_{45}=7.9Hz, J_{42}=1.5Hz); 5.85 (d, 1H, H5); 6.85 (d, 1H, Harom); 6.9 (t, 1H, Harom); 7.1 (d, 1H, H2); 7.3 (m, 2H, Harom). **9c**: overlaped with **9t** but: 5.05 (dd, 1H, H4, J_{45}=10.7Hz, J_{42}=1Hz); 5.95 (d, 1H, H5); 6.81 (d, 1H, Harom).

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5) See ref. 3): J (**4ta**,**4tb**,**5ta**,**5tb**,**8t**,**9t**)=7-7.9Hz and J (**4c**,**5c**,**8c**,**9c**)=10-11Hz.

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