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Asymmetric Synthesis of Homochiral 1,2-Diols via *N*-Boc Oxazolidines

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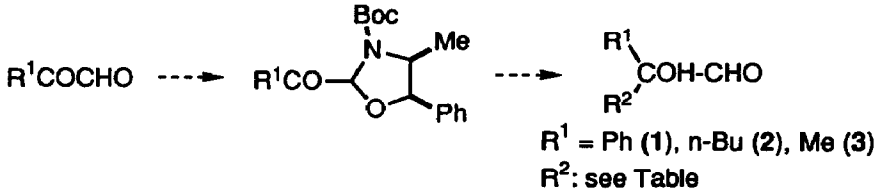
Abstract: Diastereoisomerically pure *N*-Boc 2-acyloxazolidines were synthesized from phenylglyoxal and ethyl glyoxylate. Reaction of these heterocycles with Grignard reagents is highly stereoselective. Homochiral 1,2-diols were ultimately obtained after *N*-deprotection, hydrolysis and reduction of the intermediate α-hydroxy aldehyde. The asymmetric induction can be explained by a chelated model.

β-Amino alcohols belonging to the ephedrine family are excellent precursors to oxazolidines. These heterocycles are among the most widely used chiral auxiliaries for asymmetric transformations of aldehydes; therefore, cyclopropanations,[1a] conjugate additions[1b] and dihydroxylations[1c] of unsaturated aldehydes, alkylations of γ-oxo esters,[1d] syntheses of chiral enamines[1e] and Diels-Alder reactions,[1f] have been achieved in this way.[2]

Most interesting are oxazolidines derived from ephedrine and its analogs since these starting materials are cheap and available under both enantiomeric forms.[3] Clearly this explains their renown. It should be noted however that the *N,O*-acetal moiety is very sensitive to hydrolysis and this problem was addressed by Scolastico[4] and Hoppe[5] who developed the use of *N*-tosyl oxazolidines. The electron-withdrawing substituent prevents the heterocycle from hydrolysis but deprotection of the aldehyde function now requires a treatment with 1,2-ethanedithiol and BF_3-Et_2O followed by the removal of the dithiolane moiety.

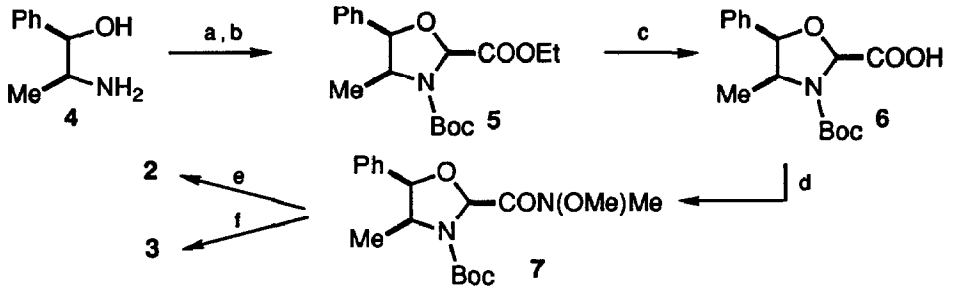
In order to create an hydroxyl-bearing stereogenic center adjacent to an aldehyde function (Scheme 1),



Scheme 1

we first considered the stereochemical course of nucleophilic addition on *N*-Boc 2-phenacyloxazolidine **1**. This heterocycle was obtained (overall yield: 76%) via two consecutive reactions: 1*R*,2*S*-norephedrine was condensed with phenylglyoxal (equimolar ratio, CH_2Cl_2, 4Å molecular sieves, rt, 0.5 h) and the resulting oxazolidine was treated with di-*tert*-butyldicarbonate $(Boc)_2O$ (equimolar ratio, AcOEt, reflux, 1.5 h). Other oxazolidines (i.e. substrates **2** and **3**) were synthesized, via the Weinreb amide method,[6] as shown on Scheme 2. ^1H and ^{13}C NMR spectra show that all oxazolidines were obtained as single diastereomers, and a *cis* relative geometry was assigned to the ring substituents in agreement with well-established results.[7]

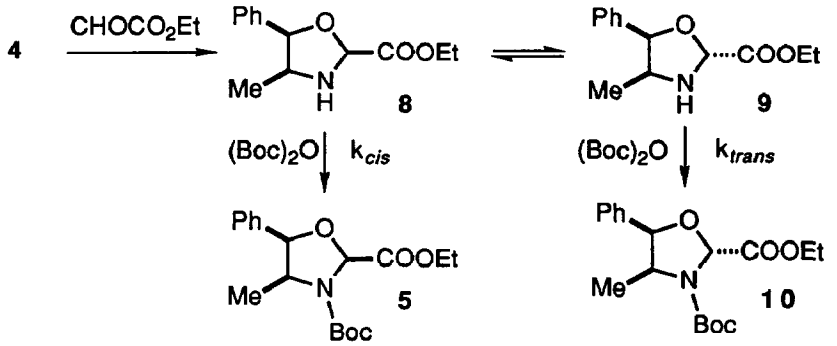
The above procedure provides access to various oxazolidines which could not be synthesized by direct condensation of an α-keto aldehyde with a β-amino alcohol, as in the case of phenylglyoxal: enolizable dicarbonyl compounds are inappropriate to react cleanly in this way.[3]



Reagents and conditions: (a) CHOCOOEt, toluene, Dean-Stark; (b) $(Boc)_2O$, AcOEt, 50 °C, 98% from **4**; (c) LiOH, 90%; (d) DCC, $Me(OMe)NH_2^+ Cl^-$, pyridine, 70%; (e) *n*-BuLi, THF, 55%; (f) MeMgI, Et_2O, 93%.

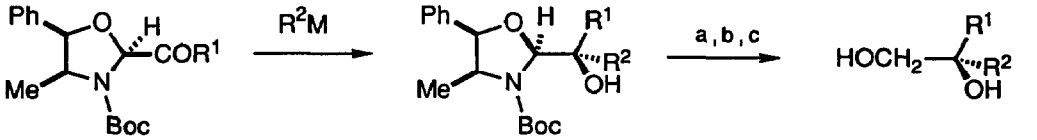
Scheme 2

A slow rate of addition of $(Boc)_2O$ was crucial to the totally stereoselective production of ester **5**. Actually both epimeric oxazolidines **8** and **9** (*ca.* 1:1 ratio) resulted from the condensation of amino alcohol **4** with ethyl glyoxylate and a mixture of the *N*-Boc derivatives **5** and **10** was obtained when $(Boc)_2O$ was added too rapidly. On the other hand, a very slow introduction[8] of this reagent afforded oxazolidine **5** as the sole product. Since it was verified that there is no equilibrium, under these experimental conditions, between *N*-Boc oxazolidines **5** and **10**, the above observation is likely to be due to a higher reactivity ($k_{cis} > k_{trans}$) of oxazolidine **8** whose nitrogen electron pair is less crowded by the ring substituents (Scheme 3).



Scheme 3

NMR spectra of the products showed that highly stereoselective reactions occurred when various Grignard reagents and allyltrimethylsilane-$TiCl_4$ reacted with acyloxazolidines **1-3** (Scheme 4) Except for the allylmagnesium bromide reagent[9] which afforded both diastereomers in a 1:1 ratio (cf. table), in every other case only one stereoisomer was observed and a diastereoisomeric excess higher than 95% can thus be estimated.[10]



Reagents and conditions: (a) CF_3COOH, CH_2Cl_2, 0 °C, 1h; (b) H_2O, THF, rt, 1 h; (c) $NaBH_4$, EtOH, 0 °C (overall yield: 70-80%).

Scheme 4

The produced hydroxy oxazolidines **11-15** furnished the corresponding 1,2-diols **17-21** by a three-step procedure: i) acid-mediated *N*-Boc deprotection, ii) hydrolysis of the oxazolidine ring, iii) reduction of the resulting aldehyde function (Scheme 4).[11]

Table. Addition of Organometallic Reagents on 2-Acyloxazolidines **1-3**.

Substrate	Organometallics (R^2M)[a]	Conditions	Product (yield)[b]
1	CH_2=CH-MgCl	THF, 0 °C	**11** (69%)
1	CH_3CH_2MgBr	THF, 0 °C	**12** (53%)
1	CH_3MgI	Et_2O, 0 °C	**13** (70%)
1	CH_2=CH-CH_2MgBr	Et_2O, 0 °C	**14** (54%)[c]
1	CH_2=CH-CH_2SiMe_3	$TiCl_4$, CH_2Cl_2 -78 °C	**14** (96%)
2	CH_3MgI	Et_2O, 0 °C	**15** (91%)
3	PhMgBr	Et_2O, 0 °C	**16** (53%)

a) 3 equiv RMgX; 1.1 equiv Me_3Si-CH_2CH=CH_2. *b)*Isolated products. *c)* In this case, **14** was obtained as an epimeric 1:1 mixture (see text).

Absolute configuration of all these 1,2-diols was determined to be *R* on the basis of published optical rotation values.[12] Enantiomeric excesses higher than 95% were ascertained by NMR analysis of the Mosher derivatives of the primary alcohols.[14] The totally stereoselective synthesis of the new stereogenic center can be rationalized by assuming that the nucleophilic attack onto the *Si* diastereoface of the carbonyl group is directed by a chelated transition state (see figure below).[15,16] Inspection of molecular models shows that, under these coordinating conditions, there is a severe steric crowding of the *Re* face by the phenyl and methyl substituents.

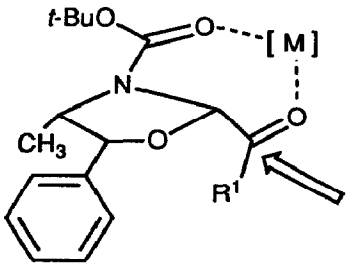


Figure. *Si* Diastereoface attack onto the acyl group.

In conclusion, it appears that using the *N*-Boc group is beneficial: it can be easily introduced and removed, and moreover it allows a high level of stereoselectivity owing to its coordinating property towards Lewis acids.

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8. A solution of $(Boc)_2O$ (7 g) in AcOEt (100 ml) was added dropwise during 6 h into a solution of oxazolidine (3 g) in AcOEt (100 ml).
9. The absence of stereoselectivity displayed in this case can be ascribed to a reversibility of the addition by the organometallic reagent; see: Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542-1544.
10. In each case, ^1H NMR spectrum of the methine proton at C-2 (sharp singlet at 5.1-5.3 ppm) allowed a clear analysis of the reaction product. Furthermore, compounds **11-14** (R^1 = Ph, R^2: see Table) showed a remarkable shielding effect by the phenyl substituent (R^1) on the methyl group at C-4 which thus resonated at *ca.* -0.20 ppm. The corresponding signal of product **16** (R^1 = Me, R^2 = Ph) appeared at 0.80 ppm. In the case of the products resulting from the addition of the allyl Grignard reagent, two doublets were present at -0.24 and 0.82 ppm.
11. Oxazolidines **13** and **16** are respectively the precursors of 1,2-diols **19** and *ent*-**19**.
12. Observed $[\alpha]_D^{20}$ values: (a) **17** (R_1 = Ph, R_2 = CH_2=CH): +47 (*c* 1.2, EtOH), lit.[13a]: -40 (*c* 1, EtOH) for *ent*-**17**; (b) **18** (R_1 = Ph, R_2 = Et): +7 (*c* 0.5, EtOH), lit.[13a]: -11 (*c* 3.7, EtOH) for *ent*-**18**; (c) **19** (R_1 = Ph, R_2 = Me): -8 (*c* 3.7, Et_2O), lit.[13b]: +9 (*c* 6.8, Et_2O) for *ent*-**19**; (d) **20** (R_1 = Ph, R_2 = CH_2=$CHCH_2$): +43 (*c* 1.2, $CHCl_3$), lit.[13c]: -47 (*c* 1, $CHCl_3$) for *ent*-**20**; (e) **21** (R_1 = *n*-Bu, R_2 = Me): +2 (*c* 0.8, $CHCl_3$), lit.[13d]: +4 (*c* 1, $CHCl_3$).
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14. The ^1H NMR spectra (200 MHz, $CDCl_3$ solution) of the Mosher derivatives (prepared from *S*-MTPA chloride) can be analyzed by observing the signals of the methoxy groups. This signal appeared, for instance, at 3.40 and at 3.41 respectively for the derivatives of **19** and *ent*-**19**.
15. For examples of chelation-controlled reactions of organometallic compounds with oxazolidines derived from hydroxy aldehydes, see: a) Garner, P.; Park, J.M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395-4398. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 41439-1446. (c) Coleman, R.S.; Carpenter, A.J. *Tetrahedron Lett.* **1992**, *33*, 1697-1700.
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