

A Novel Chiral Synthetic Equivalent of Glyoxal and its Application to the Asymmetric Synthesis of *O*-Protected α -Hydroxy Aldehydes.

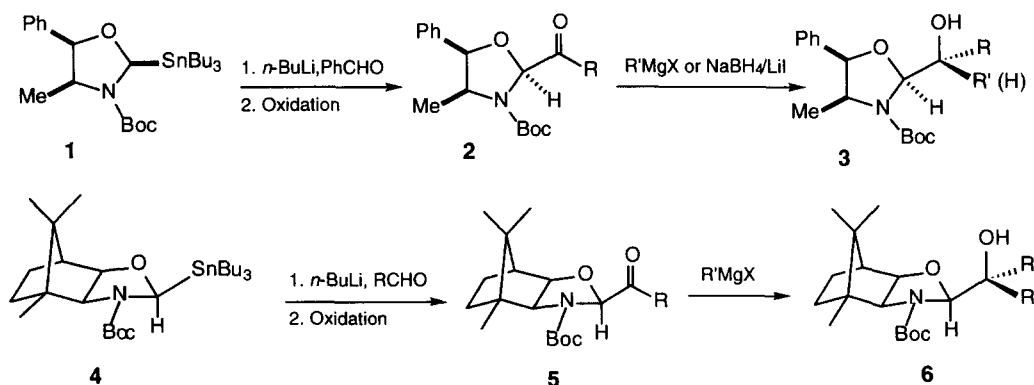
Lino Colombo, Marcello Di Giacomo

Dipartimento di Chimica Farmaceutica, Università di Pavia, V.le Taramelli 12, I-27100 Pavia, Italy

Received 5 October 1998; revised 21 December 1998; accepted 7 January 1999

Abstract : Diastereomerically pure 2-formyl-*N*-Boc-1,3-oxazolidine **7** was prepared in 83% yield from stannyloxazolidine **4**. Grignard additions to the formyl group of compound **7** in the presence of Lewis acids afforded diastereomerically pure secondary carbinols **8**. Protection of the hydroxyl group and unmasking of the oxazolidine ring gave *O*-protected α -hydroxy aldehydes **11**, which were immediately reduced to the corresponding 1,2-diols **12**. © 1999 Elsevier Science Ltd. All rights reserved.

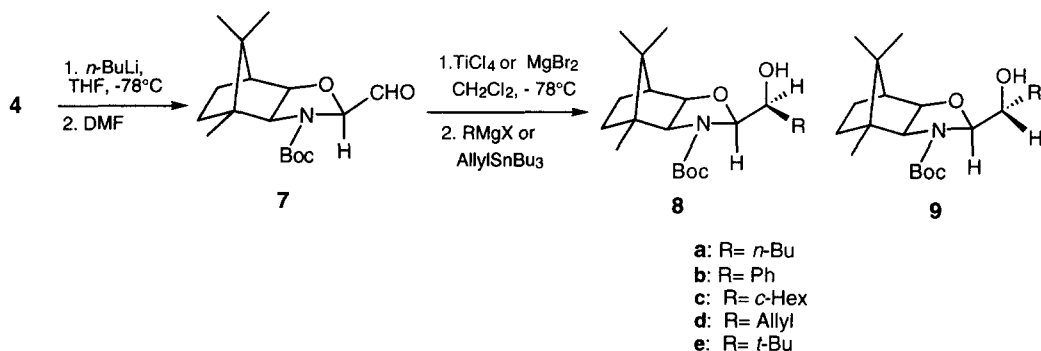
We recently introduced norephedrine- and camphor-derived 2-acyl-*N*-Boc-oxazolidines **2** and **5** as efficient chiral templates for the enantioselective synthesis of α -hydroxy aldehydes and their corresponding 1,2-diols.^{1,2} These compounds could be easily obtained diastereomerically pure by a two step sequence starting from 2-stannyloxazolidines **1** and **4**, as depicted in Scheme 1. High levels of stereocontrol in nucleophilic additions to the acyl group of these systems was realized. Reduction of the benzoyl derivative **2** (R=Ph) with NaBH₄/LiI and Grignard additions to various acyl derivatives **5** produced the corresponding carbinols **3** in a highly diastereoselective fashion. Similar results were also obtained by Agami³ in Grignard reactions with norephedrine derivatives **2**. The usefulness of this synthetic sequence was shown by conversion of alcohols **3** and **6** into the corresponding 1,2-diols with very high enantiomeric excess (>96%).



Scheme 1

In order to demonstrate the versatility and the efficiency of camphor-derived 1,3-oxazolidines as chiral auxiliaries in asymmetric synthesis, we considered the possibility of preparing in an easy and highly diastereoselective way the 2-formyloxazolidine **7**. This would constitute a new chiral synthetic equivalent of a glyoxal synthon. Other chiral versions of monoderivatized glyoxal reported in the literature have used acetals,^{4a,b} amins,⁵ and thioacetals⁶ as protecting groups. Stereoselective addition of nucleophiles to either 2-formyloxazolidine **7** or its hydrazone derivatives⁷ should provide access to enantiomerically enriched α -hydroxy and α -amino aldehydes respectively.

In this preliminary communication we report on the preparation of formyloxazolidine **7** and the results of its reactions with Grignard reagents, lithium alkyls and allyltributylstannane (Scheme 2 and Table 1).



Scheme 2

Treatment of a THF solution of stannyloxazolidine **4** with *n*-butyllithium at -78°C , followed by rapid addition of excess freshly distilled DMF (20 eq.), afforded 2-formyloxazolidine **7**. ^1H and ^{13}C NMR spectra of the crude reaction mixture showed that the product aldehyde **7** was diastereoisomerically pure. The absolute configuration at C2 of the oxazolidine ring was assigned as *S* on the basis of n.O.e. correlations between all three protons on the oxazolidine nucleus. After chromatographic purification on silica gel (*n*-Hex/EtOAc 9:1), aldehyde **7** was obtained in as high as 83% yield, as a pure colorless oil that crystallized on standing (m.p. $45\text{--}46^\circ\text{C}$; $[\alpha]_D +7.7$, *c* 1 in CHCl_3). The results of organometal reagent additions to formyloxazolidine **7** are reported in Table 1.

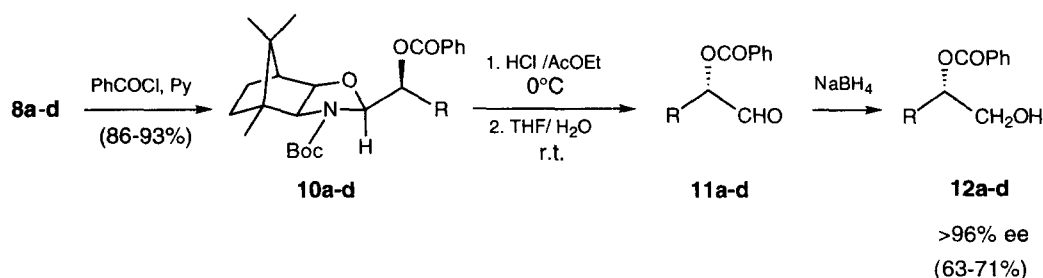
Initial experiments involving addition of Grignard and organolithium reagents to aldehyde **7** under the conditions previously used for ketones **5** (THF as solvent) resulted in the formation of both epimeric alcohols with marginal selectivity (entry 1 and 6). When using less coordinating solvents, only a modest improvement of the diastereomeric ratio was observed (entry 2 and 3). A modification of the reaction conditions, aimed to further improve the stereoselectivity by favoring the formation of a cyclic bis-chelate intermediate, involved precomplexation of the formyloxazolidine with a strong Lewis acids, such as MgBr_2 or TiCl_4 in CH_2Cl_2 solution.⁸ Addition of Grignard reagents to the aldehyde **7** under these conditions proved to be highly stereoselective, affording diastereomerically pure secondary alcohols **8** in good yield. Also, the addition of allyltributylstannane afforded a single adduct **8d** in high yield (entry 10).

Table 1: RM additions to formyloxazolidine **7**.

Entry	RM	Exp. conditions	Yield (%)	Diast. ratio (8 : 9)
1	<i>n</i> -C ₄ H ₉ MgCl	THF, -78°C	87	60:40
2		Et ₂ O, -78°C	85	65:34
3		CH ₂ Cl ₂ , -78°C	90	70:30
4		MgBr ₂ , CH ₂ Cl ₂ , -78°C	63	>98:2
5		TiCl ₄ , CH ₂ Cl ₂ , -78°C	84	>98:2
6	<i>n</i> -C ₄ H ₉ Li	THF, -78°C	82	50:50
7	<i>c</i> -C ₆ H ₁₁ MgBr	TiCl ₄ , CH ₂ Cl ₂ , -78°C	78	>98:2
8		MgBr ₂ , CH ₂ Cl ₂ , -78°C	54	>98:2
9	C ₆ H ₅ MgBr	TiCl ₄ , CH ₂ Cl ₂ , -78°C	80	>98:2
10	CH ₂ =CHCH ₂ SnBu ₃	TiCl ₄ , CH ₂ Cl ₂ , -78°C	90	>98:2
11	<i>t</i> -C ₄ H ₉ MgBr	TiCl ₄ , CH ₂ Cl ₂ , -78°C	75	>98:2

¹H and ¹³C NMR analysis of the crude reaction mixture showed the presence of only one diastereoisomer: no signals attributable to the other diastereoisomer were detected.⁹ Moreover, we observed that all major stereoisomers had a similar coupling constant of the C2 oxazolidine proton ranging from 6.2 to 6.7 Hz. Indeed, the same coupling constant in all the minor isomers showed values from 1.2 to 1.8 Hz. Molecular mechanics calculations¹⁰ gave calculated constants in excellent agreement with the experimental values (6.2-6.6 Hz and 2.6-2.8 Hz respectively), allowing for the configuration of the carbinolic center in the major isomers **8a-e** to be determined as *S*.

Confirmation of the configurational assignment came from comparison of optical rotation values with compounds of known configuration (see below).

**Scheme 3**

The unmasking procedure (Scheme 3) involved benzylation of alcohols **8a-d** to afford benzoyl derivatives **10a-d**,¹¹ which in turn were subjected to hydrolysis by treatment with 4M HCl in AcOEt solution at 0°C, followed by evaporation of the solvent and treatment with aqueous THF. The α -benzoyloxyaldehydes **11a-d** thus obtained were isolated and, without purification, submitted to reduction with NaBH₄ to afford the monoprotected diols **12a-d**. The enantiomeric excess of **12a-d** was shown to be >96% in all cases by NMR analysis of the Mosher esters.¹² Configurational assignment was confirmed by comparison of the optical rotation values of deprotected diols, derived from **12a-d** by LiAlH₄ reduction, with compounds of known configuration.^{2e,c}

It is worth noting that the optical rotation value of the diol derived from **12c** was found to be +7.1, notably higher than that (+5.1) previously reported for the same optically pure compound measured under the same conditions.^{2c}

In conclusion, it has been shown that the addition of Grignard reagents and allyltributylstannane to the 2-formyl oxazolidine **7** under chelation control conditions (complexation with MgBr_2 or TiCl_4 in CH_2Cl_2 solution) is highly stereoselective and synthetically useful for the synthesis of highly enantiomerically enriched *O*-protected α -hydroxy aldehydes. Future work will focus on nucleophile additions to hydrazone derivatives of 2-formyloxazolidine **7** as a new approach toward the asymmetric synthesis of α -amino aldehydes.

Acknowledgements: Financial support from University of Pavia and MURST (Rome) is acknowledged.

References and notes

- Colombo, L.; Di Giacomo, M.; Brusotti, G.; Delogu, G. *Tetrahedron Lett.* **1994**, *35*, 2063-2066; Colombo, L.; Di Giacomo, M.; Brusotti, G.; Milano, E. *Tetrahedron Lett.* **1995**, *36*, 2863-2866.
- For reference on this topic see: a) Eliel, E. L. In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press, New York, **1983**, Vol 2, p 125. b) Lynch, J.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2937-2942. c) Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333-1343. d) Asami, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 569-572. e) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843-2846.
- Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron Lett.* **1994**, *35*, 3309-3312; Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron* **1995**, *51*, 4043-4056.
- a) Heitz, MP; Gellibert, F.; Mioskowski, C. *Tetrahedron Lett.* **1986**, *27*, 3859-3680. b) Chastrette, F.; Chastrette, M.; Bracoud, C. *Bull. Soc. Chim. Fr.* **1992**, 161-167.
- Alexakis, A.; Tranchier, J.-F.; Mangeney, P. *J. Am. Chem. Soc.* **1995**, *117*, 10767-10768.
- Matsubara, S.; Ukita, H.; Kodama, T.; Utimoto, K. *Chem. Lett.* **1994**, 831-834.
- For additions of nucleophiles to hydrazones see: a) Thiam, M.; Chastrette, F. *Tetrahedron Lett.* **1990**, *31*, 1429-1432. b) Alexakis, A.; Lensen, N.; Mangeney, P. *Tetrahedron Lett.* **1991**, *32*, 1171-1174. c) Alexakis, A.; Lensen, N.; Tranchier, J.-F.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 4563-4567. d) Enders, D.; Funk, R.; Klatt, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 418-421. e) Denmark, E.S.; Nicaise, O. *Synlett* **1993**, 359-361.
- For Lewis acid-mediated nucleophilic additions to α - or β -alkoxy aldehydes under chelation control see: Reetz, T. M. *Acc. Chem. Res.* **1993**, *26*, 462-468.
- The minor stereoisomeric alcohols **9a-e** were obtained as the predominant compounds in diastereoisomeric mixtures deriving from NaBH_4 reduction of the corresponding ketones **5**.
- Molecular mechanics calculations were performed using MM2* and AMBER* force fields as implemented in MacroModel V5.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440-467.
- Compound **8e** was shown to be unreactive to any attempt at benzoylation under many different conditions.
- Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.