Tetrahedron Letters, Vol.32, No.9, pp 1171-1174, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

CHIRAL AMINAL TEMPLATES 6[1]. DIASTEREOSELECTIVITY OF HYDRAZONE ALKYLATION. ASYMMETRIC SYNTHESIS OF α-AMINOALDEHYDES

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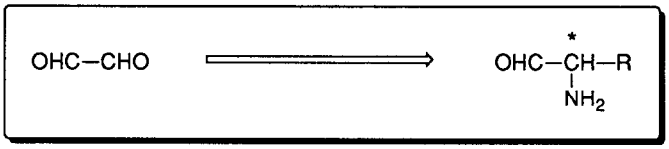
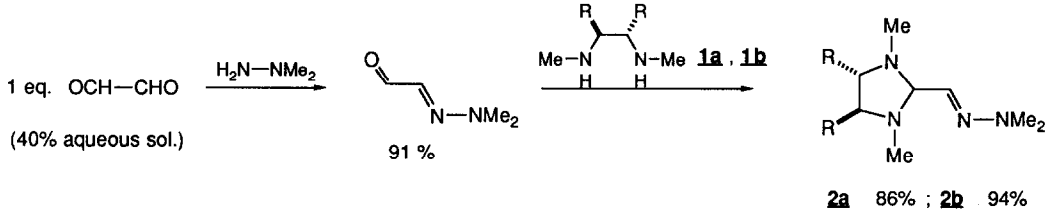
*Abstract : Glyoxal is efficiently transformed into the chiral aminals bearing the hydrazone functionality **2a** and **2b**. These compounds react under complete diastereocontrol with various organolithium reagents, affording chiral hydrazines **3**-**9**. Reduction with Raney nickel leads to aminal protected α-aminoaldehydes, which , in turn, are easily hydrolyzed to the free chiral aldehydes (after tBoc protection of the amine).*

Glyoxal is one of the most fascinating and useful two carbon synthons[2]. Among the various synthetic possibilities, the temporary protection of only one of the two aldehyde functionalities allows the transformation of the other one, the overall result being the formation of an α-heterosubstituted aldehyde. The asymmetric version of this concept uses a chiral acetal as a protective group, and the free aldehyde is attacked by various organometallic reagents[3]. Alternatively, a recent paper describes the transformation of this free aldehyde into a hydrazone and the overall result is the synthesis of chiral α-aminoacids[4]. We report herein our results using chiral aminals as auxiliaries and protective reagents of the aldehyde functionality which allow the obtention of a variety of optically pure α-amino aldehydes.



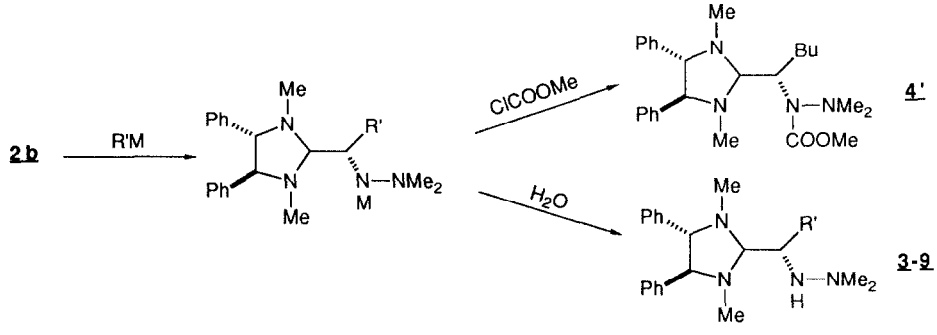
The desymmetrization of glyoxal by formation of the monohydrazone is a straighforward process[5] and the aminalization of the remaining aldehyde functionality is easily and smoothly done with our chiral diamines having a *C2* axis of symmetry[6], such as **1a** and **1b**. Thus, the preparation of the starting materials, **2a** and **2b**, is simple and very efficient since no creation of a new stereogenic center occurs during the aminalization process :



2a 86% ; **2b** 94%

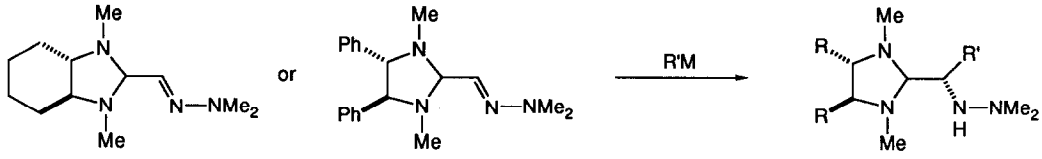
1a and **2a** : R,R = -$(CH_2)_4$- **1b** and **2b** : R,R = Ph,Ph

The most successful organometallic reagents in the nucleophilic attack of a hydrazone are usually organolithium[7] and organocerium[8] derivatives. Grignard reagents are less frequently used for that purpose[9]. We have also tried various reagents (see Table, entries 3, 4, 5 and 9) and, indeed, as far as yield is concerned, RLi are the reagents of choice. The alkylated hydrazines **3-9** are easily obtained upon addition of the required organolithium reagent to hydrazones **2a** or **2b**, at -78° C, by letting the reaction warm up to room temperature for 1-5 h. Generally, the reactions are faster in Et_2O than in THF and we also noticed that aminal **2a** was more reactive than aminal **2b**. Although the crude yield is quantitative, the purified hydrazine is obtained in moderate yield. Indeed, it is known that such hydrazines are prone to air oxidation and unstable upon storage or handling on silica-gel[8]. In one case (entry 12) we quenched the lithium hydrazide with methyl chloroformate to obtain, in higher yield, the corresponding carbamate **4'**. However, the NMR spectra were plagued by the problem of conformers (duplication and widening of all signals) and we preferred to determine more precisely the diastereomeric excess on the crude hydrazines **3-9**. Indeed, the determination of the d.e. is cleanly performed by ^1H and/or ^{13}C NMR, as is usually possible when a chiral aminal is present[10]. In the case of **3a** (entry 1 and 2) a GC determination was also done.



As far as diastereoselectivity is concerned, the most closely related work is that of Thiam and Chastrette with acetals as chiral auxiliaries. They obtained high d.e. (>90%) only with diols lacking the C2 axis of symmetry. In our case we detect only one diastereomer when the reactions are performed in THF. In Et_2O however, some reactions (entries 6, 16, 18 and 20) afforded both diastereomers ; the major diastereomer is the same as the single one detected in THF. However, in the case of PhLi (entry 18) a reversal of selectivity is observed. With sBuLi, the product obtained has two stereogenic centers and four isomers are possible ; we only detect two of them in 64:36 ratio. We believe that the condensation is as stereoselective as usual and that it is the stereogenic center on the sBu group which cannot be controlled. Finally we should emphasize the generality of this diastereoselective reaction since a very large array of organolithium reagents (primary, secondary, tertiary alkyls, aryl and alkenyl) may be used with equal success.

Hydrazines such as **3-9** are known to be easily cleaved into free amines by Raney nickel[7,8]. Under the conditions described (H_2/Raney Ni, 40 bar, 40°C), compound **3b** was smoothly tranformed into the primary amine and the aminal protecting group remained intact in this process. The free amine was easily protected as the *tBoc* derivative **10**, and purified at this stage (overall yield 73%). The determination of the absolute configuration of the newly created stereogenic center was accomplished by mild hydrolysis of the aminal protective group which afforded the known α-amino aldehyde **11**[11] (yield 74%). Reformation of the chiral aminal shows that no

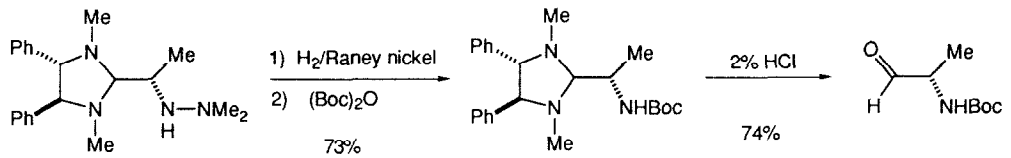


2a 2b 3-9

Entry	Aminal	Organometallic reagent	Solvent	Yield[a] %	Product	D.e.[b] %
1	2a	MeLi.LiBr	Et_2O	>90	3a	20
2	"	"	THF	>90 (62)	"	40
3	2b	MeMgBr	THF	0	3b	-
4	"	Me_2CuLi	Et_2O	0	"	-
5	"	MeLi.$CeCl_3$	THF	0	"	-
6	"	MeLi.LiBr	Et_2O	>95 (72)	"	95
7	"	"	THF	>90 (54)	"	96
8	"	"	THF + TMEDA	>90 (60)	"	>99
9	"	nBuMgBr	THF	0	4	-
10	"	nBuLi	Et_2O	>95 (60)	"	>99
11	"	"	THF	>90 (50)	"	>99
12	"	"	THF then ClCOOMe	>90 (74)	4'	>99
13	"	sBuLi	Et_2O	>95 (75)	5	>99 or 28[c]
14	"	"	THF	0	"	-
15	"	tBuLi	Et_2O	>95 (60)	6	>99
16	"	iBuLi.LiBr	"	>95 (70)	7	74
17	"	"	THF	>95 (52)	"	>99
18	"	PhLi.LiBr	Et_2O	>95 (50)	8	-53[d]
19	"	"	THF	>90	"	>99
20	"	Me_2C=CHLi.LiBr	Et_2O	>95	9	60
21	"		THF	>85 (60)	"	>99

a) Yield of the crude product according to the NMR spectra.In parentheses yield of isolated pure material
b) Determined by ^1H and ^{13}C NMR on the crude product.
c) See text
d) The major isomer is not the same as in THF.

racemization occured either during the hydrolysis or during the reaminalization. As a confirmation of these results we prepared aldehyde **11** starting from L-alanine, through known techniques[11], and, then, aminal **10** again.



3b **10** **11**

tBoc-aminals such as **10** are stable direct precursors to the less stable α-amino aldehydes and therefore to α-amino acids as well as α-amino alcohols. Thus, the present method may be viewed also as a preparation of these useful classes of compounds. Again chiral aminals show their high efficiency as auxiliaries in asymmetric syntheses, especially as the inductor diamines ar easily and quantitatively recovered.

Aknowledgements : *The authors thank Prof. J.F. Normant for fruitful discussions.*

References and notes.

1. For part 5 see : Gosmini, R.; Mangeney, P.; Alexakis, A.; Commerçon, M.; Normant, J.F. : *Synlett* **1990**, 0000
   For part 4 see : Commerçon, M.; Mangeney, P.; Tejero, T.; Alexakis, A. : *Tetrahedron Asymmetry* **1990**, *1*, 283 and 287
2. Mattioda, G.; Métivier, B.; Guetté, J.-P. : *Actualité Chimique* **1982** (5) 23 and (6-7) 33
3. Heitz, M.P.; Gellibert, F.; Mioskowski, C. : *Tetrahedron Lett.* **1986**, *27*, 3859
4. Thiam, M.; Chastrette, F.: *Tetrahedron Lett.* **1990**, *31*, 1429
5. Severin, T.; Poelhmann, H.: *Chem. Ber.* **1977**, *110*, 491
6. Mangeney, P.; Grojean, F.; Alexakis, A.; Normant, J.F. : *Tetrahedron Lett.* **1988**, *29*, 2675
7. Enders, D.; Schubert, H. : *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1109
8. Denmark, S.E.; Weber, T.; Piotrowski, D.W.: *J. Am. Chem. Soc.* **1987**, *109*, 2224
9. Takahashi, H.; Tomita, K.; Otamasu, H. : *J. Chem. Soc. Chem. Comm.* **1979**, 668
10. a) Mangeney, P.; Alexakis, A.; Normant, J.F. : *Tetrahedron Lett.* **1988**, 29, 2677
    b) Cuvinot, D.; Mangeney, P.; Grojean, F.; Alexakis, A.; Normant, J.F. : *J. Org. Chem.* **1988**, *29*, 2677
11. Fehrentz, J.-A.; Castro, B. : *Synthesis* **1983**, 676

(Received in France 4 December 1990)