Monoaminals of Glyoxal: Versatile Chirons

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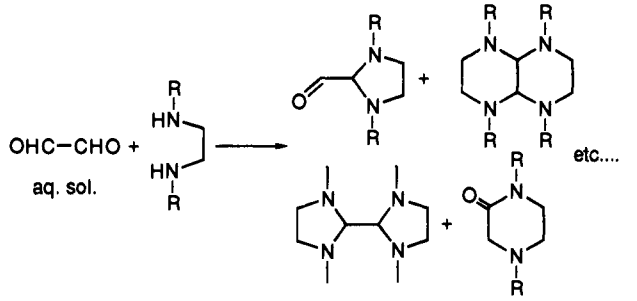
Glyoxal is a small, attractive synthon with great synthetic potential,[1] provided the two aldehyde functionalities could be differentiated. Apart from indirect routes,[2−6] there are few efficient direct monoderivatization methods. Although monoacetalization of aqueous solutions of glyoxal is feasible,[6−8] even on an industrial scale,[9] it affords products of technical grade purity (~70−90%). Nevertheless, these monoacetals have found many uses in synthetic chemistry.[1] Monothioacetals have also been described.[10] On the other hand, the formation of monohydrazone is a high-yielding process and a very selective one.[11] For our part, we were interested in the chiral monoaminals of glyoxal which could be versatile synthons in asymmetric synthesis.[4,12]

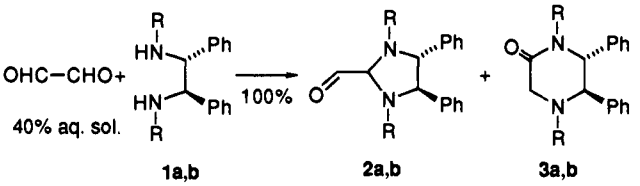
It was reported that aqueous solutions of glyoxal react with N,N′-disubstituted 1,2-diamines to afford a plethora of products (Scheme 1).[13] However, as shown in Scheme 2, with chiral C_2 symmetrical diamines (*R,R*)-**1a** and (*R,R*)-**1b**, which are 1,2-disubstituted on the carbon framework,[14] only two products were observed: the desired monoaminals **2a** and **2b** and the cyclic glycine derivatives **3a** and **3b**. The ratio of these two products varied according to the reaction conditions (solvent, pH, temperature, etc.), and as reported above,[13] compound **3** seemed to be a thermodynamic dead end. We have found that the "kinetic" desired monoaminal **2a** or **2b** can be the major reaction product when a large excess of the cheap glyoxal (as a 40% aqueous solution) is used, in a biphasic system where dichloromethane or pentane is the organic solvent. Under these conditions, **2a** or **2b** is obtained in a *ca.* 90% crude yield. **2a** has to be used as such in a further reaction step; any attempt to purify it resulted in its transformation into **3a**. In contrast, monoaminal **2b** was a stable crystalline compound which could be purified by standard column chromatography on silica gel and obtained in 67% isolated yield.

Besides the synthesis of these monoaminals, we briefly report herein some of their uses in asymmetric synthesis in order to demonstrate the versatility of such chiral synthons (Scheme 3).

Scheme 1



Scheme 2

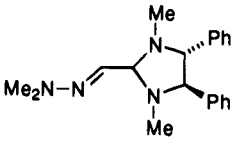


1a,b **2a,b** **3a,b**

a	R = Me	90	10
b	R = i-Pr	90 (67% isolated)	10

Our group has already shown the usefulness of chiral aminals as efficient stereodirecting groups.[15]

Monoaminals **2a** and **2b** may be reacted with various organometallic reagents to afford α-hydroxy aminals.[16] Organolithium reagents in THF solvent proved to be the best choice. Thus, reaction of *n*-PentLi with **2a**, followed by acetylation of the hydroxy group, gave aminal **4a** in 75% yield and 76% de. Knowing the crystal conformation of the analogous hydrazone **2c**,[15d] we ascribe this stereoselectivity to steric control exerted



2c

by the N-substituent. A better steric control could be achieved with the more bulky *N*-*i*Pr group of synthon **2b**; **4b** was obtained in 82% yield as a *single diastereomer*, which was hydrolyzed into chiral (*S*) α-acetoxy aldehyde **5** without any racemization (90% overall).

The aldehyde functionality of monoaminal **2a** could be transformed directly into other functional groups. Thus, crude **2a** reacts in a Wadsworth−Emmons reaction with diethyl carbethoxy phosphonate to afford the pure *E* enoate **6** in 77% isolated and overall yield (based on the starting diamine **1a**). The reaction of lithium dibutyl cuprate reagent, in Et_2O, with **6** results in a *completely diastereoselective* (de > 99%) conjugate adduct **7**. Mild hydrolysis of aminal **7** gave the corresponding aldehyde (*S*)-**8** without any racemization.[17]

* FAX: (+33) (1) 44 27 71 50.

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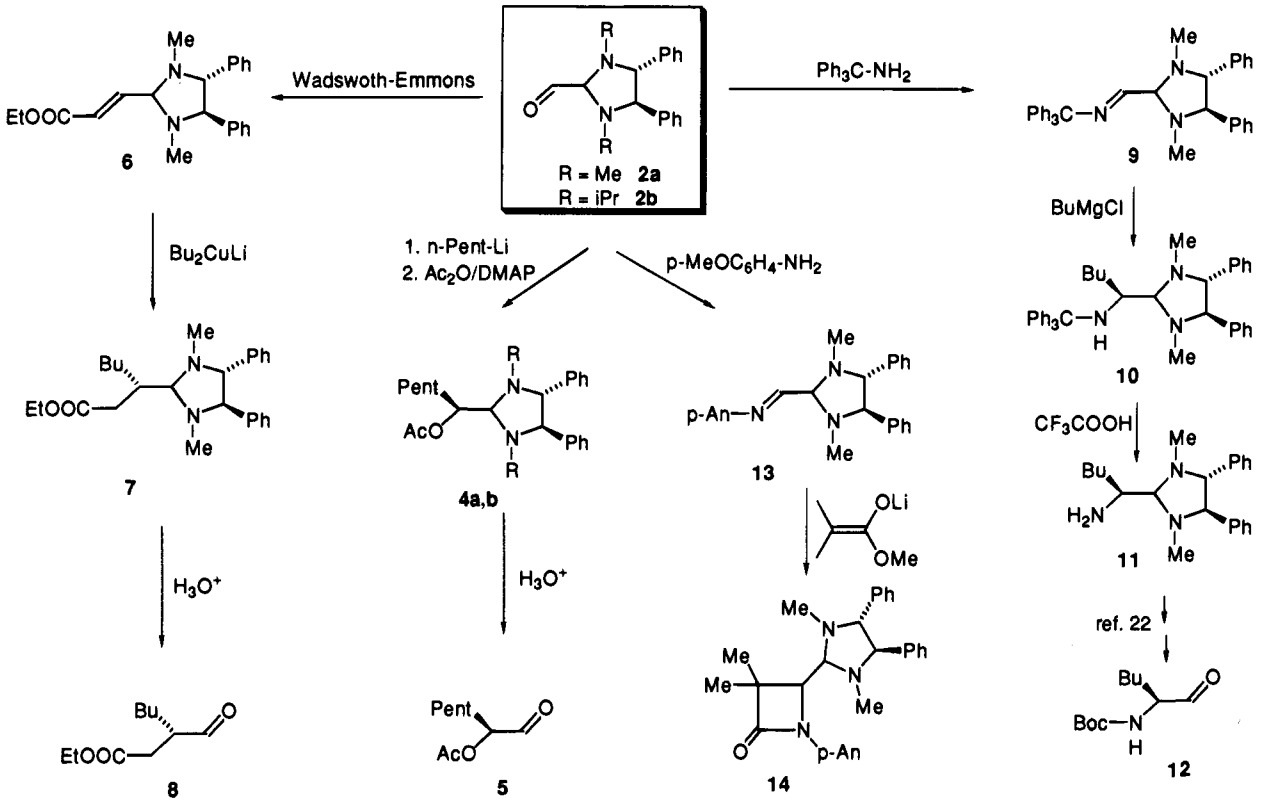
Scheme 3



Crude monoaminal **2a** was also used for imine formation, by reaction with an appropriate primary amine. The choice of this primary amine depends upon the further use of the imine obtained. Thus, reaction with tritylamine (Ph_3CNH_2) gave imine **9** in 92% isolated and overall yield. By analogy to our previous work with hydrazone **2c** bearing an aminal chiral auxiliary,[15d,20-22] we reacted imine **9** with several organometallic reagents. Thus, a Grignard reagent in toluene (*n*-BuMgCl) gave α-tritylamino aminal **10** again as a *single diastereomer* (86% yield), probably through a chelation control.[20] The trityl protecting group was chosen because of its ease of removal without cleavage of the aminal ring. Thus, **10**, treated with trifluoroacetic acid in dry dichloromethane, afforded the free (*S*) α-amino aminal **11** in 79% yield, identified with an authentic sample.[15d, 21] Such aminals have been described as precursors of α-amino aldehydes, such as **12**, without any racemization.[15d,22]

Tritylimine **9** was found inadequate for use as a synthon for β-lactam synthesis. Thus, transformation of the aldehyde functionality of **2a** with *p*-anisidine gave imine **13**, which is more reactive than **9** and could be transformed directly into β-lactam **14** by reaction with the lithium enolate of methyl isobutyrate. However, in this case only moderate diastereocontrol (de 77%) could be achieved.[23]

In summary, we have demonstrated that chiral monoaminals of glyoxal could be easily prepared and were versatile synthons for further synthetic transformations with excellent stereocontrol. Other potentially asymmetric transformations include Stetter reactions, aldol or nitroaldol condensations, and Darzens reactions, which are presently being actively studied.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the joumal, can be ordered from the ACS, and can be downloaded from the Intemet; see any current masthead page for ordering information and Intemet access instructions.

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(23) The absolute stereochemistry is not yet determined.