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Chiral aminals: Powerful auxiliaries in asymmetric synthesis

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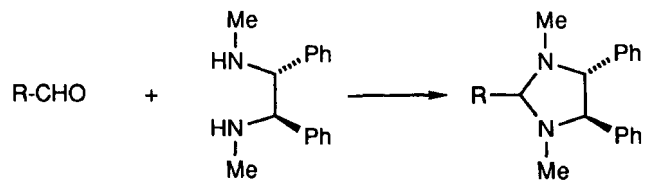
Abstract - Chiral aminals are prepared from chiral C2 symmetrical diamines and aldehydes. The chiral imidazolidine ring exerts its stereocontrol either through steric or chelation effects. Reaction of aqueous glyoxal with diamine **1** results in a new chiral synthon **6** ; this "chiron" is a useful precursor for α-hydroxy aldehydes and for α-amino aldehydes. An aminal of nicotinaldehyde **7** reacts stereoselectively with organocopper reagents to afford a chiral dihydropyridine, which is a starting point for several short asymmetric syntheses of indolo- and benzo-quinolizine alkaloids.

Aminals are the nitrogen equivalents of acetals (1). Cyclic aminals are more stable than their acyclic counterparts. In particular, the five membered rings, imidazolidines, are easily prepared from an aldehyde and a diamine. We choose to indroduce chirality by using a C2 symmetrical chiral diamine. The most efficient diamine for this purpose is N,N'-dimethyl-1,2-diphenylethylene diamine **1** (2) :

Scheme I



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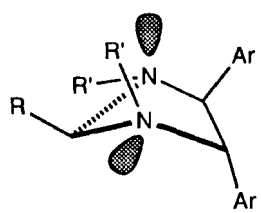
As compared to acetals, aminals disclose the following advantages :
- Their formation is very easy, requiring no catalyst. Aminals may even be prepared in aqueous media !
- Aminals of ketones are formed in only exceptional cases and, therefore, the selectivity for aldehydes is total in compounds having both the ketone and the aldehyde functionality.
- Aminals are stable to bases and their hydrolysis back to the aldehydes is done under very mild conditions, without any racemization.

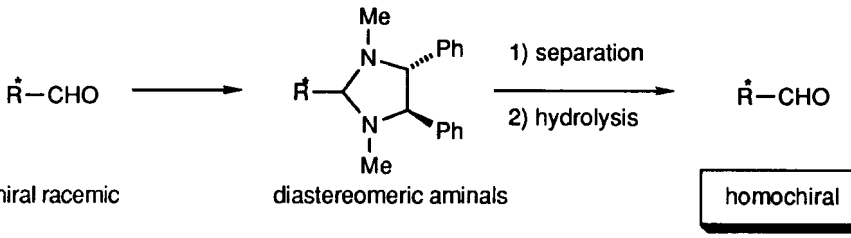
The use of a C2 symmetrical diamine in the formation of aminals avoids the creation of a new stereogenic center and the diastereoselective reactions are controlled by the specific conformation of such imidazolidine rings. Thus, according to the X-ray structures known for such aminals (3), each substituent on the nitrogen atoms is located trans to the substituent of the adjacent carbon, one being pseudoequatorial and the other pseudoaxial. The new stereogenic centers are in fact the nitrogen atoms which may exert a dual control :
- Steric control by the size of of the N-substituent R'
- Chelation control by the lone pair of one of the two nitrogen atoms

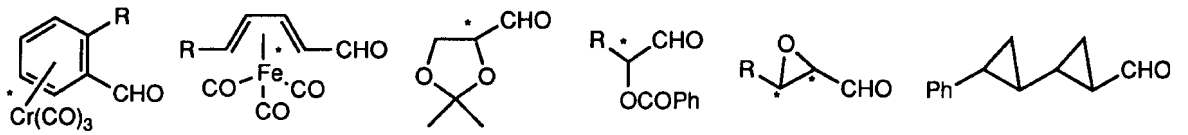
Scheme II



One of the first uses of chiral aminals lies in the determination of the enantiomeric composition of chiral aldehydes by NMR or chromatographic (HPLC or GC) techniques (3b, 4). On the other hand, the diastereomeric aminals may be separated by column chromatography (4) or by recrystallization (3c).

Scheme III

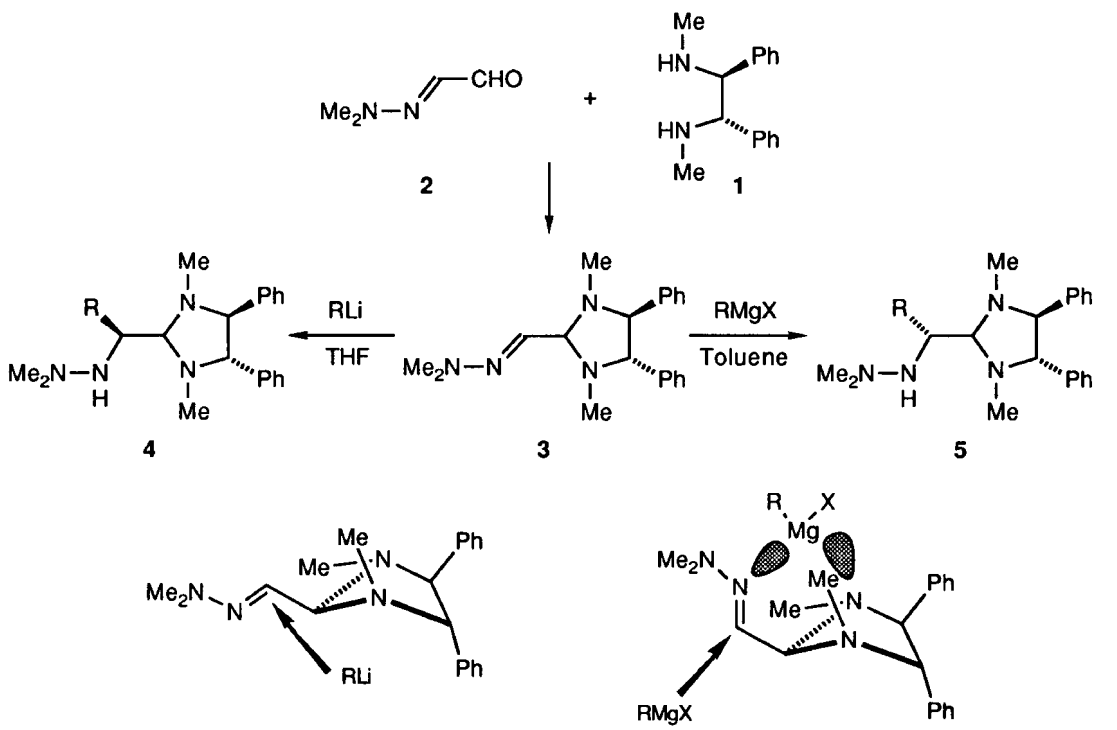




The present lecture will focus on two aspects of chiral aminals in asymmetric synthesis. The first one concern the synthesis of chiral α-amino and α-hydroxy aldehydes and the second one the synthetic applications of chiral dihydropyridines.

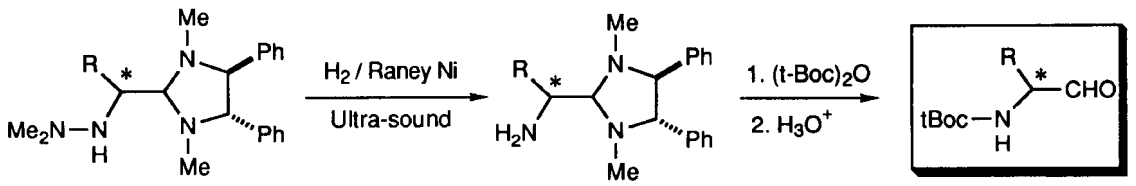
The easily prepared monohydrazone of glyoxal **2** (5) was a starting point of a general methodology directed towards the synthesis of α-amino aldehydes. Such aldehydes are ideal precursors of α-amino acids or α-amino alcohols (6). Thus, compound **2** was treated with diamine **1** to afford the crystalline aminal **3**. This aminal gave a single diastereomer upon reaction with an organolithium reagent in THF, through a steric control (7). By contrast, with Grignard reagents, in toluene as solvent, **3** gave the adduct of opposite stereochemistry, through a chelation controlled reaction (de 88-99%) (8) :

Scheme IV



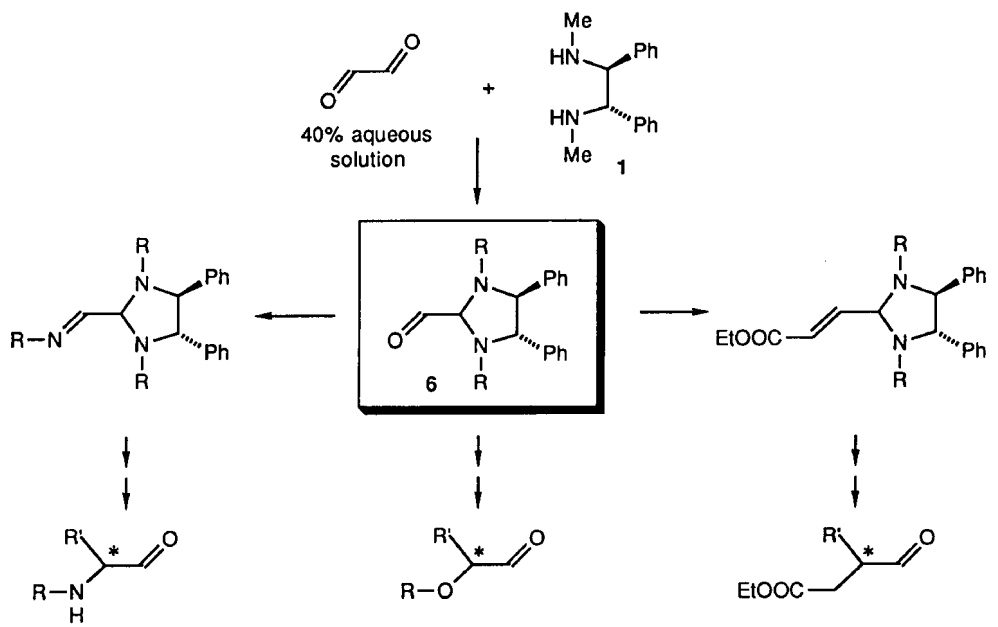
The cleavage of the hydrazine N-N bond was best achieved with Raney nickel under ultrasonic conditions (9). Protection of the primary amine functionality, as *t*-Boc, followed by sligthly acidic hydrolysis of the aminal protecting group, gave the desired enantiomerically pure α-amino aldehyde :

Scheme V



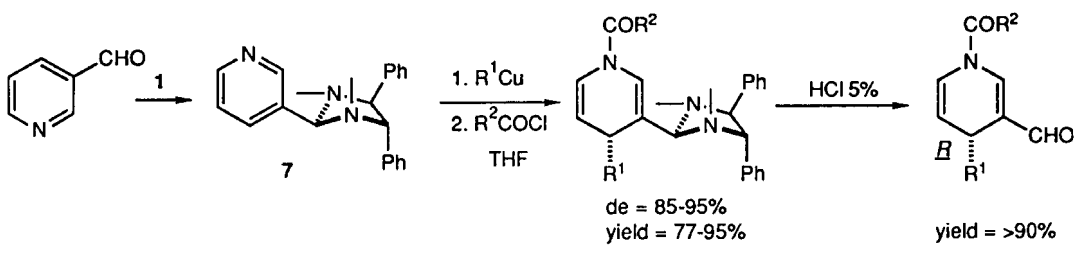
An alternative chiral synthon was prepared by the direct reaction of diamine **1** with aqueous glyoxal. The resulting monoaminal of glyoxal **6** (10) is the starting point for several further transformations. Direct reaction with an organolithium reagent gave ultimately chiral α-hydroxy aldehydes as a single enantiomer. Formation of an imine with tritylamine, followed by reaction with organolithium or Grignard reagents gave α-amino aldehydes. Wittig-Horner olefination on synthon **6** gave an enoate on which conjugate addition could be performed to give a single adduct. In all these examples the deprotection of the aldehyde functionality occured without noticeable epimerization.

Scheme VI



The second topic concern the synthetic uses of chiral dihydropyridines. The general approach to such synthons starts with the chiral aminal of nicotinaldehyde **7**. This easily prepared compound (now commercialy available) reacts with organocopper reagents in the presence of a chloroformate or an acyl chloride as activator.(11) The reaction is regioselective (exclusive attack in position 4 of the pyridine ring) and very stereoselective (de 95->95%). A wide variety of organocopper moieties are allowed (even functionalized ones) and several acid chlorides may be used (12).

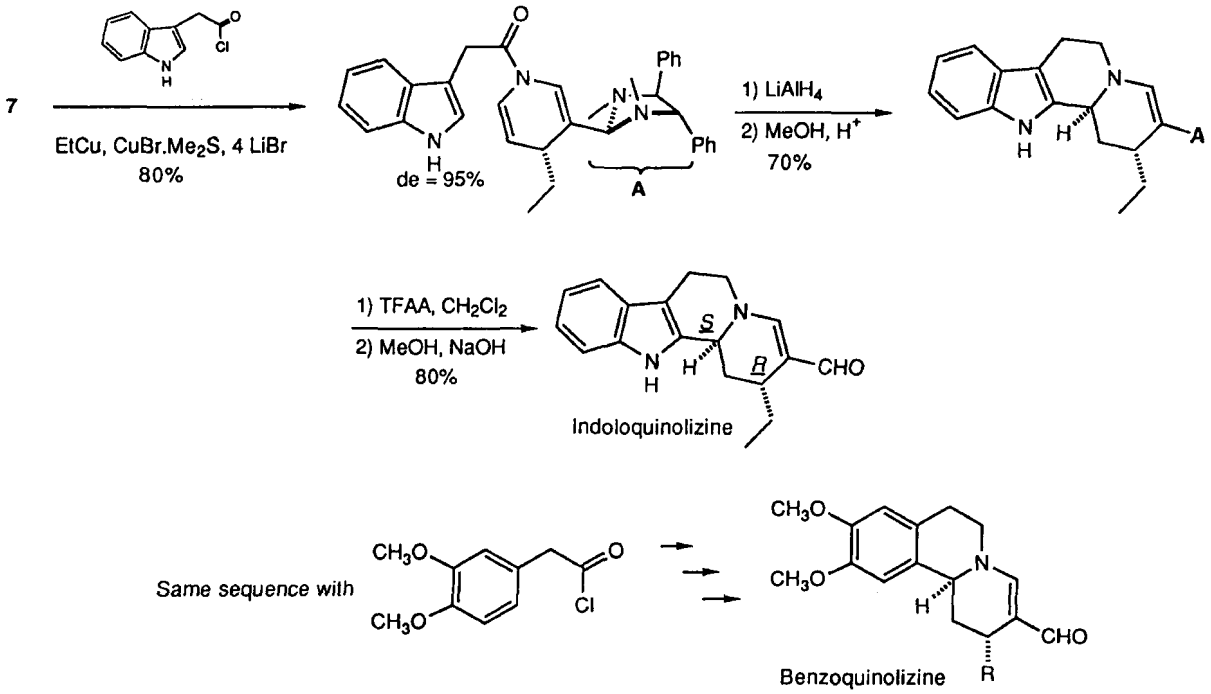
Scheme VII



R^1 = Me, Et, Bu, vinyl, Ph, iPr, $MeO_2C(CH_2)_3$, indolyl R^2 = CH_3O or CH_3

These chiral dihydropyridines were the starting point for the synthesis of several classes of alkaloids. Thus, the possibility of using functionalized acyl chlorides was exploited in the enantioselective syntheses of indoloquinolizine (12, 13) and benzoquinolizine frameworks (12). This approach allows an exceedingly short asymmetric construction of such skeleta.

Scheme VIII



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