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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7745–7748

Stereoselective synthesis of functionalized 1,3 diols through the tandem isomerization–aldolization reaction mediated by nickel catalysts

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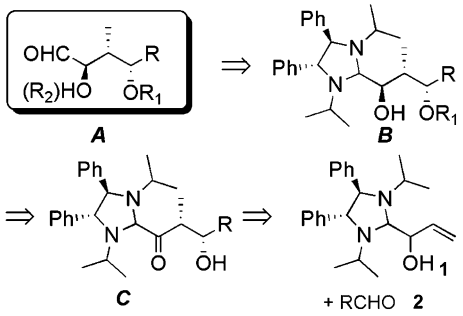
Received 19 July 2006; revised 22 August 2006; accepted 25 August 2006
Available online 18 September 2006

Abstract—A new approach to functionalized 1,3 diols, such as **15**, is described using as the key step the tandem isomerization–aldolization reaction of allylic alcohols **1**. The chiral imidazolidine group is shown to play a key role for the stereocontrol during aldolization and reduction steps.

The 1,3 diol structure is a basic subunit for many bioactive compounds such as, for instance, the polypropionate natural products.[1] Therefore, the preparation of this type of fragment is of much interest, especially if functional groups are present in the appropriate positions in order to complete the total synthesis of the target molecules. Although, various elegant alternative approaches have also been reported, the aldol reaction still remains the most versatile strategy toward such 1,3 diol structures.[2] Our group has discovered a new tandem isomerization–aldolization reaction starting from allylic alcohols and mediated by various types of transition metal catalysts (Fe, Rh, Ru, Ni).[3] Furthermore, detailed computational and experimental studies have established the key role of the free enol in the mechanism of this reaction.[4] In parallel to these mechanistic studies, we were interested in developing the synthetic uses of this reaction. As a first step toward this goal we have selected as targets, the protected 1,3 diol subunits with the type **A** basic structure, since the aldehyde group is a versatile precursor for many synthetic transformations.

Our retrosynthetic analysis is given in Scheme 1 indicating that a masked and chiral equivalent of the formyl group, based on the imidazolidine rings, was considered as a precursor for the aldehyde.[5] Therefore, the type **B** monoprotected diols could be used as key intermediates and they should be accessible by stereoselective reduction of aldols **C** followed by a protection step. Finally, the latter derivatives should be obtained from the allylic alcohol **1** and aldehyde **2** by the tandem isomerization–aldolization process.



Scheme 1. Retrosynthetic approach to the key intermediates **A**.

This approach should open to a large molecular diversity by changing the nature of the R group, as well as by using all the potentialities of the formyl group. The main challenges in this new strategy are the following:

- Is this transition metal mediated isomerization–aldolization process compatible with such a bulky and

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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.125

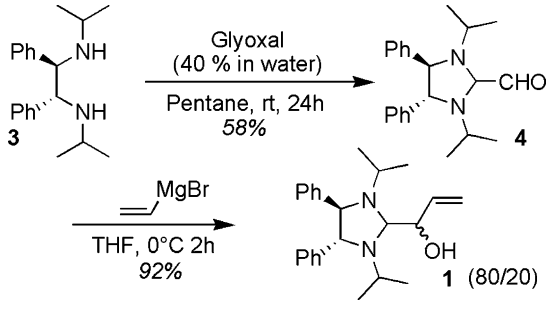
basic imidazolidine group on the allylic alcohol component?
- What is the effect of this chiral imidazolidine on the diastereoselectivity of the aldol reaction, as well as on the reduction of aldols such as **C**?

The purpose of this letter is to report our preliminary results in this area establishing: (i) the feasibility of this strategy through the preparation, with a good stereoselectivity, of a type **A** intermediate (with R = Ph) and (ii) the versatility of this compound, which can be used in many reactions such as reduction, reductive amination, and Wittig or Petasis type reactions.

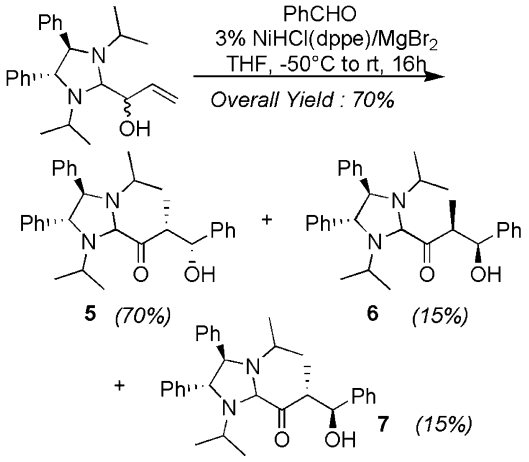
The allylic alcohols **1** were prepared following the literature procedures.[5a] The known formyl imidazolidine **4** was obtained in 58% yield by condensation of aqueous glyoxal with the chiral diamine **3**. For the latter derivative, the isopropyl substituents on the nitrogen atoms were selected since the corresponding imidazolidines are more stable than the *N*-methyl analogues. Furthermore, they are known to induce higher diastereoselectivities in the reactions on a vicinal carbonyl group.[5a] Addition of a vinyl Grignard on **4** afforded in 92% yield the allylic alcohols **1** as a 4:1 mixture of stereoisomers which could be separated by chromatography on SiO_2 (Scheme 2).

The tandem isomerization–aldolization, with benzaldehyde selected as a model aldehyde, was performed starting from **1** (as the 4:1 mixture of stereoisomers) and using the most efficient catalytic system previously discovered: NiHCl(dppe) + $MgBr_2$.[3d,4b] It afforded, in 70% overall yield, a mixture of three stereoisomeric aldol products **5**–**7**, which could be separated by chromatography on SiO_2 (Scheme 3). Exactly the same results (both in terms of yield and stereoselectivity) were obtained when the reactions were performed starting from each pure stereoisomer of **1**. This is in agreement with the results obtained previously in another series of allylic alcohols and using an iron-carbonyl derived catalyst.[6] The ratios of the three stereoisomers were the following: major *syn* aldol **5** (70%), minor *syn* aldol **6** (15%), and *anti* aldol **7** (15%). The structures of these adducts were unambiguously established by X-ray analysis (Fig. 1 for major aldol **5**, and for **6** and **7** see data deposited at CCDC).[7,8]

In the next step we have studied the reduction of these aldols. The major adduct **5** was reduced by $LiAlH_4$ in



Scheme 2. Synthesis of the chiral allylic alcohols **1**.



Scheme 3. Tandem isomerization–aldolization.

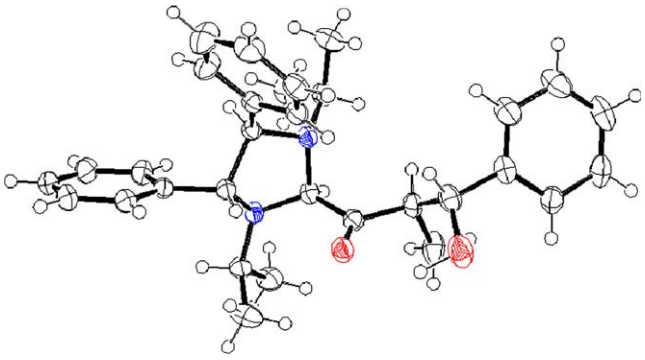
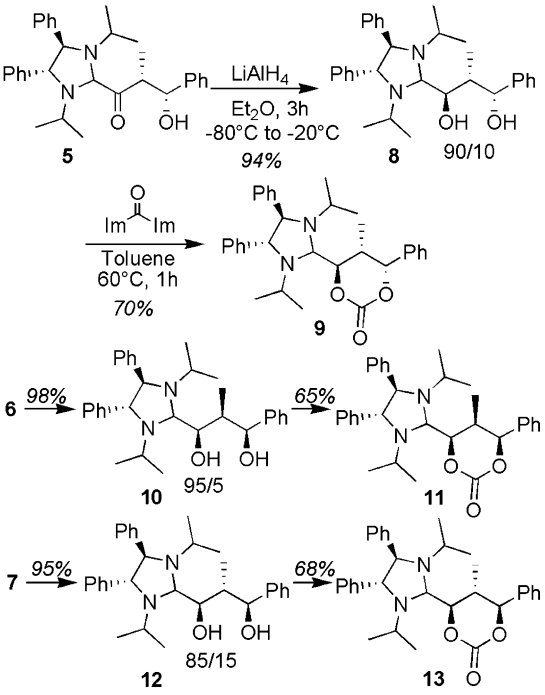


Figure 1. ORTEP representation of major aldol **5**.

a highly stereoselective manner, affording the corresponding diols in a 9:1 ratio. The major compound **8** was isolated by crystallization and it was easily transformed in good yield into the cyclic carbonate **9**. In the same way, the other aldols **6** and **7** were reduced, with high stereoselectivities (95:5 for **6** and 85:15 in the case of **7**) and in excellent yields, to the corresponding diols **10** and **12** and these derivatives could also be transformed into the corresponding carbonates **11** and **13** (Scheme 4). The stereochemistry of these diols was first established by extensive NMR studies of their carbonates **9**, **11**, and **13**. It was confirmed by X-ray analysis of **8** (Fig. 2) and **10** (see data deposited at CCDC). It is worth mentioning that during these three reductions, the same configuration was obtained at the newly created carbinol center for the major diastereoisomer. This indicates that the reduction step is essentially controlled by the bulky *N*-isopropyl group on the imidazolidine and is almost completely independent from the substituents at the other stereocenters. This is in agreement with previous literature data for 1,2 additions on formyl imidazolidine **4**.[5]

The monoprotection of the benzylic alcohol of **8** was easily performed, affording the first key intermediate **14** in 53% yield (Scheme 5). The protection of the second hydroxyl group is under active study, but it appeared of much interest to develop first the chemistry of the α-hy-



Scheme 4. Stereoselective reduction of aldols **5**–**7**.

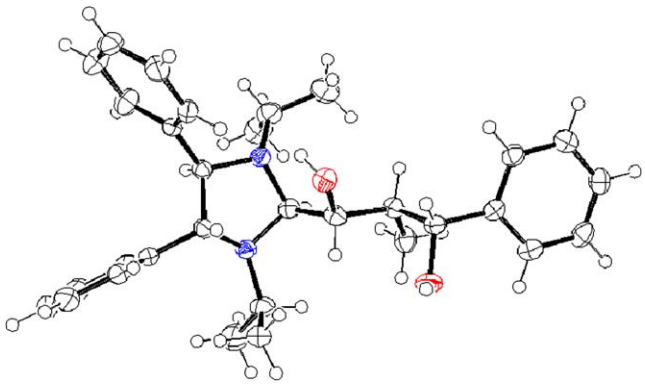
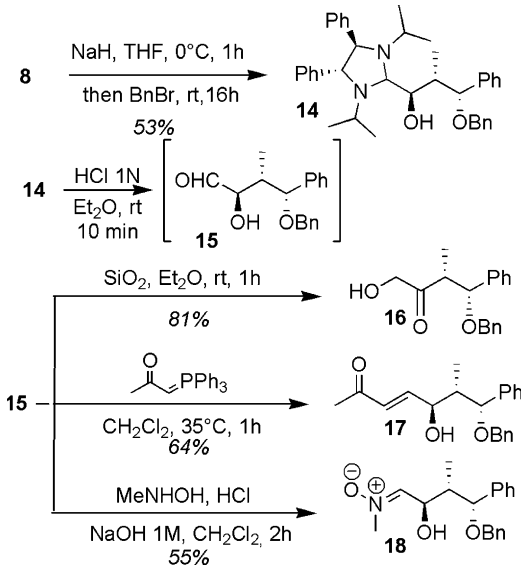


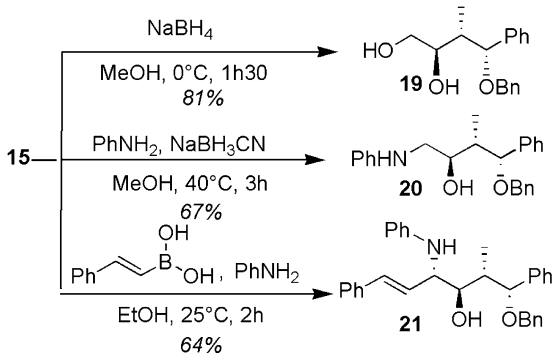
Figure 2. ORTEP representation of major diol **8**.

droxy aldehyde derivative. In fact, under biphasic conditions, the hydrolysis of **14** was rapid, affording the labile aldehyde **15** easily characterized by NMR. On standing, or more efficiently by stirring on humid silica gel, it was transformed into the hydroxy ketone **16** by a classical transformation of α-hydroxy aldehydes.[9] On the other hand, the crude aldehyde **15** reacted with the ketophosphorane to afford, in 64% yield, the *E*-enone **17**. In the same way, by reaction with *N*-Me hydroxylamine, the chiral functionalized nitrone **18** was isolated in 55% yield.

Several other basic transformations were performed starting from the chiral functionalized intermediate **15** (Scheme 6). The reduction gave the monoprotected triol **19** in 81% yield, while the reductive amination afforded the monoprotected aminodiol **20** in 67% yield. Finally, the Petasis reaction[10] was also possible starting from **15**. With cinnamylboronic acid and aniline, selected as



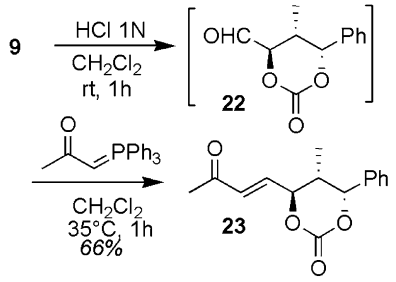
Scheme 5. Synthesis and reactions of the key intermediate **15**.



Scheme 6. Further reactions of the key intermediate **15**.

model reagents, it afforded the protected amino diol **21**, in a completely stereoselective manner. The *anti* aminoalcohol structure was attributed by analogy with the literature data on this reaction and the NMR data of **21**, with a low ^{3}J value (3.2 Hz) at the aminoalcohol unit, were also in agreement with this structure.[10]

The cyclic carbonates can also be used in synthesis. Under the same conditions as before, starting from **9**, the hydrolysis of the imidazolidine afforded the labile intermediate aldehyde **22** which could also be used in a Wittig type reaction to afford the *E*-enone **23** in 66% overall yield from **9** (Scheme 7).



Scheme 7. Wittig reaction of intermediate **22**.

In conclusion, we have demonstrated that the tandem isomerization–aldolization reaction can be extended to allylic alcohols bearing a chiral imidazolidine group.[11] This reaction affords useful intermediates with a 1,3 functionalized diol structure. Extension of this approach to asymmetric synthesis and use of such intermediates in total synthesis are currently under active study in our laboratory.

Acknowledgments

We thank the French Ministry for Education and Research for a fellowship to J.P. and the CNRS for financial support. We thank Ms. S. M. Nazarin for preliminary experiments. We thank Professor A. Alexakis for very fruitful discussions.

References and notes

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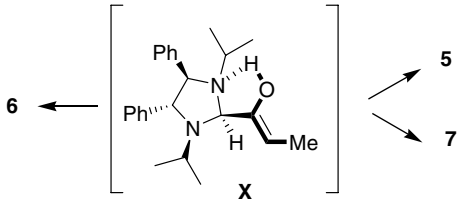
7. The scope and limitations of the reaction, starting from **1**, appear similar to those previously described for allylic alcohols bearing a bulky substituent in allylic position (Ref. 4b). Preliminary data (with non-optimized yields) indicate that the reaction can be performed with (i) substituted aromatic aldehydes such as *p*-fluorobenzaldehyde (59%) or *p*-methoxybenzaldehyde (35%), (ii) aliphatic aldehydes such as propionaldehyde (70%) or isobutyraldehyde (47%), or (iii) heterocyclic derivatives such as the challenging pyridine-2-carboxaldehyde (51%). The stereoselectivities are close to those observed with benzaldehyde and the corresponding results will be discussed in the full paper on this research.
8. The stereoselectivity of the isomerization–aldolization reaction, strongly in favor of the *syn* isomers, is in agreement with previous results in these series. A tentative explanation for the facial selectivity could be the following: as previously observed with bulky substituents at the carbinol center (see Ref. 4b) the isomerization could lead first to a *Z* enol, such as **X**, possibly stabilized by hydrogen bonding with the next imidazolidine nitrogen. Then reaction of the aldehyde from the less hindered side could afford aldols **5** and **7**, while reaction on the other face of the enol would give aldol **6**. Of course, other transition states are possible for these reactions and further studies will be necessary in order to fully rationalize this facial selectivity.



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11. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 615450, CCDC 615451, CCDC 615452, CCDC 615453, CCDC 615454. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].