J|A|C|S COMMUNICATIONS

Published on Web 10/30/2009

Asymmetric Histidine-Catalyzed Cross-Aldol Reactions of Enolizable Aldehydes: Access to Defined Configured Quaternary Stereogenic Centers

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Organocatalysis has emerged within the past decade as the third pillar of asymmetric catalysis in addition to metal and enzyme catalysis.[1] Several long-standing problems of asymmetric aldol addition have been solved via organocatalysis. One important example is the direct catalytic asymmetric cross-aldol addition between enolizable aldehydes, which has been realized through the use of proline,[2] derivatives of proline,[3] and chiral imidazolidinones.[4] However, despite tremendous efforts, several serious problems of this reaction still remain. First, these aldol additions are mostly anti-diastereoselective. Moreover, α-branched aldehydes react only as carbonyl components in proline-catalyzed cross-aldol additions. As a result of that, the construction of quaternary stereogenic carbon centers cannot be accomplished. This selectivity is explained by the steric demands of α-branched aldehydes, which cause thermodynamic instability of the intermediate enamine.[5] On the other hand, α-unbranched aldehydes can react as both the ene component and the carbonyl component. This lack of chemoselectivity renders careful and cumbersome syringe pump techniques necessary to avoid self-aldol addition.[6]

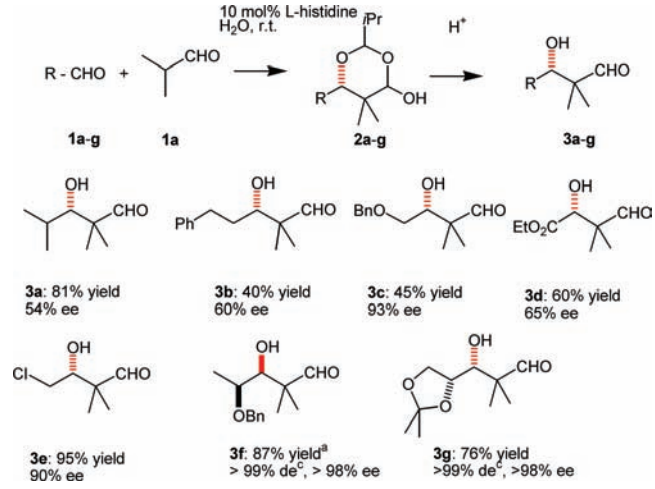
During initial studies of amine-catalyzed direct aldol additions of aldehydes to ketones,[7] we observed that histidine also promotes cross-aldol additions between enolizable aldehydes.[8]

We started our investigations by considering aldol additions of several aldehydes to isobutyraldehyde (**1a**). The histidine-catalyzed aldol addition provides a direct and enantioselective access to variously substituted and functionalized β-hydroxyaldehydes **3a**−**g** (Scheme 1). A varying mixture of aldol adducts **3a**−**c**,**e** and their corresponding hemiacetals **2a**−**c**,**e** was observed (with exception of aldehydes **3d**, **3f**, and **3g**). In order to obtain defined reaction products, the aqueous reaction mixtures were treated with an acidic ion exchanger to yield β-hydroxyaldehydes **3a**−**c**,**e**. The formation of acetals is consistent with observations in chiral imidazolidinone-catalyzed aldol additions[4] and tertiary amine-catalyzed aldol additions.[7]

A stringent chemoselectivity, which is dictated by the electronic nature of the aldehydes, was noticed in all of these reactions. Histidine differentiates strictly as well as efficiently between electron-rich and electron-deficient aldehydes. Electron-rich aldehydes react exclusively as the ene component, whereas electron-deficient aldehydes act as the carbonyl component in histidine-catalyzed aldol additions.[9] Thus, when used with α-branched electron-rich aldehydes, this reaction gives access to aldol adducts with an α-quaternary carbon atom. Hence, syringe pump techniques are no longer necessary. Moreover, when electron-deficient aldehydes are used, a decrease in the formation of the corresponding acetals is observed. When used with α-oxygen-containing aldehydes, higher stereoselectivities were observed.

In order to avoid the formation of intermediate acetals, we analyzed aldol additions of dimethoxyacetaldehyde (**4**) as the carbonyl compound with different α-branched aldehydes as the ene component. During these histidine-catalyzed aldol reactions, the

Scheme 1. Asymmetric L-Histidine-Catalyzed Aldol Addition of Isobutyraldehyde to Enolizable Aldehydes[b,d]



[a] D-Histidine was used as the catalyst. [b] Isolated yields are given, unless otherwise noted. [c] The ratio of diastereomers was determined by ^{1}H NMR spectroscopy. [d] The enantiomeric excess was calculated from the er based on the ^{1}H NMR integration of the corresponding Mosher esters. For determination of the absolute configurations, see the Supporting Information.

β-hydroxyaldehydes **6a**−**d** were accessed directly. In general, intermediate acetals could not be detected (exception in the case of **6e**).

The β-hydroxyaldehydes **6a**−**d** were isolated with yields up to 90%. High chemoselectivies were observed again. Dimethoxyacetaldehyde **4** acted exclusively as the carbonyl component in every case we explored. Syn diastereoselectivities were observed under these reaction conditions (**6b**, **6c**, and **6e**; Scheme 2).[10]

This comfortable situation of histidine in direct aldol additions enabled us to realize several total syntheses of branched-chain natural products (Scheme 3). For example, aldol addition of ethylglyoxylate **1g** to isobutyraldehyde **1a** and subsequent reduction yielded *R*-configured pantolactone (**7**), a vitamin-B_5 precursor. Pantolactone was obtained with 65% ee (see also **3d** in Scheme 1). The enantiomerically pure product could then be obtained by a single recrystallization. Even aldol adducts containing defined-configuration α-tertiary alcohols were accessible with this method. Stereoselective homodimerization of protected (*R*)-glyceraldehyde **1g** in the presence of catalytic amounts of L-histidine gave direct access to 2-hydroxymethyl-D-lyxose (**8**). Histidine-catalyzed dimerization of benzyl-protected lactaldehyde **1f** yielded protected branched-chain 5-deoxy-2-methyl-L-lyxose (**9**) as a single stereoisomer.

Most existing techniques for the synthesis of **7** suffer from being long and complex.[11] The same is true for the synthesis of **9**. For a multistep-synthesis of **9** based on the SAMP-/RAMP-hydrazones method, see ref 12. At this point, there exists no direct aldol addition

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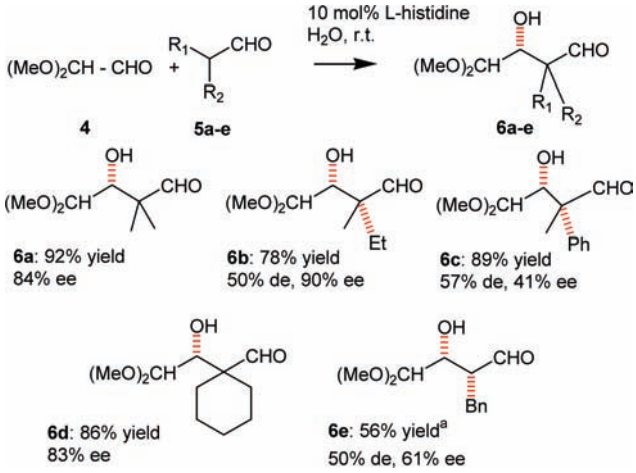
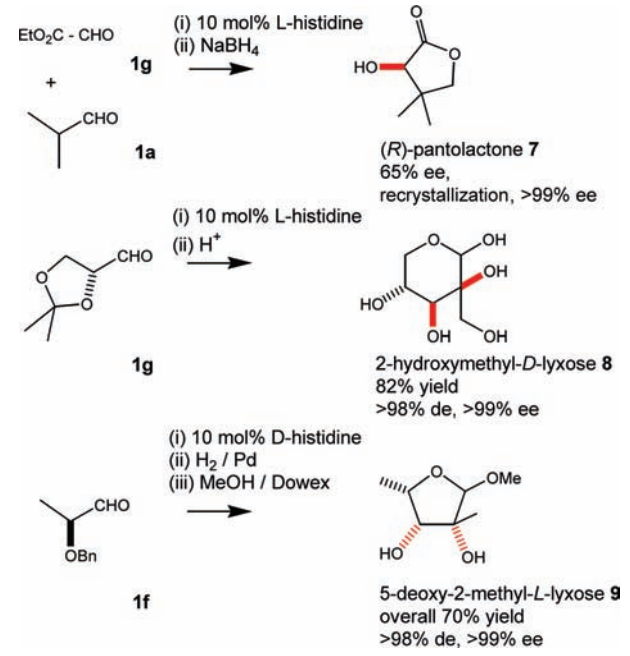
Scheme 2. Asymmetric L-Histidine-Catalyzed Aldol Addition of Dimethoxyacetaldehyde to Enolizable Aldehydes



[a] Using an additional 25% of the corresponding acetal; the corresponding anti-configured aldol adduct **6e** can be accessed by proline catalysis (35% yield, 53% de, 92% ee; see ref 3).

Scheme 3. Utility of Histidine-Catalyzed Aldol Addition in the Total Synthesis of Pantolactone, Hydroxymethyl-D-lyxose, and 5-Deoxy-L-lyxose



for accessing these configurative-complex natural products discussed in Scheme 3.

In summary, we have developed a chemo-, diastereo-, and enantioselective cross-aldol addition between enolizable aldehydes. This transformation is accomplished with catalytic amounts of readily available histidine. The reactions were carried out in water at room temperature. In contrast to proline as the catalyst, histidine is able to differentiate and control the reactivity of various aldehydes. With the use of this protocol, the construction of defined-configuration quaternary stereogenic centers becomes possible. Aldol adducts of such a substitution pattern have not been accessible by organocatalyzed aldol reactions to date. This operationally simple method opens access to polyfunctionalized chiral building blocks and thus provides an approach to branched-chain carbohydrates.

Acknowledgment. The authors thank the Deutsche Forschungsgemeinschaft (Priority Program Organocatalysis), Bayer-Schering Pharma AG, Bayer Services GmbH, BASF AG, and Sasol GmbH for financial support. P. Neubauer and B. Ziemer are gratefully acknowledged for the X-ray structure analyses.

Supporting Information Available: NMR data for all of the synthesized compounds, full characterization of novel compounds, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) This different behavior based on the electronic nature of aldehydes was also observed in proline catalysis (see ref 6a).

(10) The obtained diastereoselectivity as well as the absolute configuration are in accordance with results reported in the literature. For an explanation, see ref 8d.

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JA907054Y