Communications to the Editor

Catalytic Asymmetric Synthesis of *anti*-1,2-Diols

Wolfgang Notz and Benjamin List*

The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

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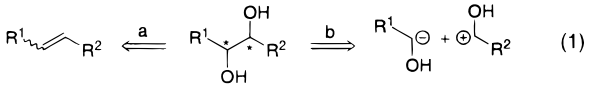
The 1,2-diol unit occurs frequently in natural products, such as carbohydrates, polyketides, and alkaloids, and the development of enantioselective methodologies for its preparation has been at the forefront of modern catalytic asymmetric synthesis. While the *syn*-1,2-diol unit may be considered a "clearable"[1] stereochemical element due to the Sharpless asymmetric dihydroxylation (AD) of (*E*)-olefins,[2] the diastereomeric *anti*-1,2-diols are far less accessible, mainly because the corresponding (*Z*)-olefins are more difficult to obtain and show reduced enantioselectivity in the AD. In this paper we disclose a novel, highly diastereo-, and enantioselective catalytic synthesis of *anti*-1,2-diols that is based on the proline-catalyzed direct asymmetric aldol reaction.

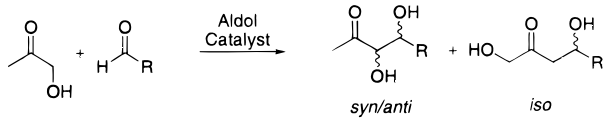
The enantioselective synthesis of 1,2-diols may, in principle, be achieved either via carbon−oxygen bond-formation (path a, eq 1, e.g., Sharpless AD) or via carbon−carbon bond-formation (path b).[3] Despite the exceptional usefulness of the catalytic asymmetric dihydroxylation process, path b provides a potentially superior strategy because the two adjacent stereocenters are created simultaneously upon carbon−carbon bond-formation.



(1)

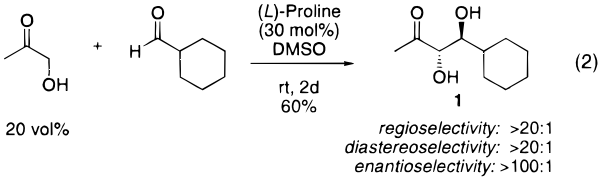
In a manner analogous to path b, the catalytic asymmetric Mukaiyama reaction of glyoxalate esters with aldehydes has been used.[4] However, this method requires two additional steps to introduce and remove a hydroxyl protecting group and one additional step to preform the enolate equivalent. As an alternative, the direct catalytic asymmetric aldol reaction of α-hydroxylated ketones with aldehydes has so far only been used with protein-catalysts such as aldolases and catalytic antibodies.[5,6] In particular the development of aldolase antibody 38C2 has taught us the power and mildness of catalysis involving enamines. While aldolases are typically limited to dihydroxyacetone phosphate as the donor, which usually necessitates an additional enzymatic dephosphorylation step, aldolase antibody 38C2 is capable of using α-hydroxylated ketones such as hydroxyacetone as the donor.[6a] These reactions are highly regio- and enantioselective with both 38C2 and the natural fructose-1,6-bisphosphate-aldolase but selectively provide the *syn*-diastereomer. Herein we demonstrate that proline catalyzes the highly regio- and diastereoselective aldol reaction between hydroxyacetone and various aldehydes to provide *anti*-1,2-diols with excellent enantioselectivities.

Scheme 1. Aldol Reaction between Hydroxyacetone and an Aldehyde



We have recently shown that proline is a remarkably effective catalyst for the direct asymmetric aldol reaction of acetone to various aldehydes with ee's of the aldol products ranging from 60 to 96%.[7] We became interested to determine whether proline is capable of using unprotected hydroxyacetone as the aldol donor. This is a challenging task since three different regio- and diastereomeric products and their enantiomers may be expected (Scheme 1).

We found that L-proline catalyzes the aldol reaction between cyclohexanecarboxaldehyde and hydroxyacetone to furnish *anti*-diol **1** in 60% yield, with a dr >20:1 and an ee >99% (eq 2).



(2)

Next, a series of *anti*-diols was prepared in moderate to good yield, by application of this new methodology (Table 1).[8] Regioisomeric products were only found in reactions with an aromatic aldehyde (~4%, entry 4) and 3,3-dimethyl butyraldehyde (14%, entry 5). Diastereoselectivities are very high with α-substituted aldehydes (>20:1, entries 1−3), whereas low diastereoselectivities are obtained in reactions with 2-chlorobenzaldehyde (entry 4),[9] the α-unsubstituted aldehyde (entry 5) and with α-oxygenated D-isopropylidene-glyceraldehyde (entry 6). The reaction with *rac*-2-phenylpropionaldehyde (entry 3) provided two readily separable diastereomers (**3a** and **3b**) that both had the *anti*-configuration regarding the 1,2-diol subunit while differing at the benzylic stereocenter. Excellent ee's were obtained in all

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons: New York, 1989.

(2) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1995**, *34*, 1059. (b) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 3−2547.

(3) For alternative, indirect, and noncatalytic methods, see for example: (a) Enzymatic desymmetrization of 2,3-protected *meso*-butane-1,2,3,4-tetrol derivatives: Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769. (b) Enantioselective hydroxyallylation of aldehydes: Roush, W. R.; Grover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563−7566. (c) Asymmetric epoxidation/Payne-rearrangement/epoxide-opening: i. Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245−264. (d) Enantioselective enzymatic hydrolysis of a racemic *trans*-epoxide: Weijers, C. A. G. M. *Tetrahedron: Asymmetry* **1997**, *8*, 639−647.

(4) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708−1716.

(5) For excellent reviews on aldolases and the catalytic asymmetric aldol reaction in general, see: (a) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443−473. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374.

(6) (a) List, B.; Shabat, D. Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **1998**, 881−885. (b) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768−2779.

(7) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

(8) Diastereoselectivities and enantioselectivities were determined by comparison with the *syn*-enantiomers obtained from the aldehydes via Horner−Wadsworth−Emmons-reaction followed by Sharpless asymmetric dihydroxylations using either AD-mix-α or AD-mix-*β* (Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605−606). The proline catalyzed reactions were performed with both D- and L-proline so that all four stereoisomers were available. Finally, conditions for the separation of all four stereoisomers were established by using chiral-phase HPLC techniques.

(9) Benzaldehyde gave similar results (dr = 1.3:1, ee = 80%).

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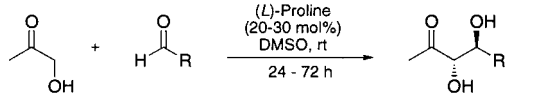
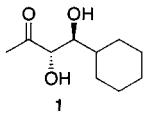
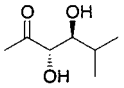
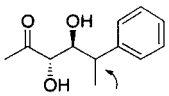
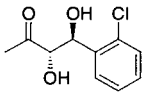
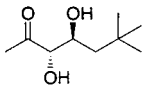
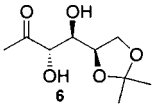
Table 1. *anti*-Diols Synthesized Using the Proline-Catalyzed Aldol Reaction with Hydroxyacetone and Various Aldehydes



Entry	Product	Yield	dr[a]	ee[b]
(1)	 **1**	60%	>20 : 1	>99%
(2)	 **2**	62%	>20 : 1	>99%
(3)	 **3a + 3b** (2 : 1)	51%[c]	>20 : 1[d]	>95%[d]
(4)	 **4**	95%[c]	1.5 : 1[e]	67%
(5)	 **5**	38%[c]	1.7 : 1	>97%
(6)	 **6**	40%[c]	2 : 1	>97%[f]

[a] The s*yn:anti*-ratio was determined by weighing the separated isomers and/or ^{1}H NMR-spectroscopy, respectively. [b] ee of the *anti*-isomer; determined by chiral HPLC analysis. [c] Combined yield of separated diastereomers. [d] Identical ee and dr values for **3a** and **3b**. [e] Diastereomers could not be separated. [f] From optical rotation. In a typical experiment, cyclohexanecarboxaldehyde (60 μL, 0.5 mmol), hydroxyacetone (1 mL), DMSO (4 mL), and L-proline (14 mg, 25 mol %) were stirred at room temperature for 60 h. Aqueous work up and purification by flash chromatography (50% ethyl acetate/hexanes) afforded pure diol *anti*-**1** (56 mg, 60%) as a solid.

cases except in the reaction with 2-chlorobenzaldehyde (entry 4). In the reaction with 3,3-dimethyl-butyraldehyde, the diastereomeric *syn* side-product was obtained in 84% ee but with the opposite absolute configuration at the β-position (Sharpless AD-β-product). Similarly, the reaction with the protected glyceraldehyde gave known D-tagatose derivative **6**[10] ($[\alpha]_D = +69°$, lit.[10] $[\alpha]_D = +71°$) together with the *syn* byproduct 1-deoxy-5,6-*O*-isopropylidene-D-*fructose* having the opposite configuration at the β-position.[11] These hexoses are readily converted into the natural sugars 1-deoxy-D-tagatose and 1-deoxy-D-fructose.[10,11] Absolute configurations of diols **2-5** have been assigned based on the crystal structure of diol **1** (Figure 1) and on the absolute configuration of the known products of the reaction with the enantiomerically pure glyceraldehyde-substrate (entry 6, Table 1). The enantiofacial selectivity (*re*) of the aldehyde in these reactions is identical to that obtained using acetone as the aldol donor. Accordingly, the *si*-face of the hydroxyacetone enamine attacks the *re*-face of the aldehyde (*unlike*-topicity) to give the *anti*-product. This selectivity is consistent with chairlike transition state **A** and our originally proposed mechanism (Figure 2).[7,12] Transition state **B** leading to the *syn*-product (*like*-topicity) possesses a boat conformation and may become increasingly important with sterically less hindered (reduced eclipsed interactions) or α-oxygenated aldehydes (hydrogen-bonding). Interestingly, transition state **B** resembles **C**, which has been proposed for the Corey−Bakshi−Shibata (CBS) reduction.[13]

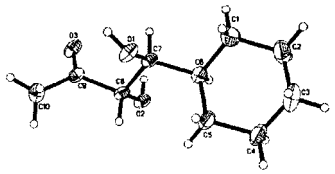


Figure 1. X-ray structure of diol **1**.

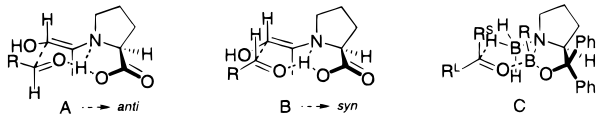


Figure 2. Potential transition states of the proline-catalyzed aldol reaction between hydroxyacetone and aldehydes.

In summary we have shown that proline catalyzes the direct aldol reaction between hydroxyacetone and various aldehydes to give *anti*-diols **1**−**6** in excellent diastereo- and enantioselectivities. Important features of this reaction are the following: (1) This method is the first small-molecule catalyzed asymmetric synthesis of *anti*-diols and complements the Sharpless-AD. (2) For the first time, unprotected hydroxyacetone has been used as a donor in nonenzymatic aldol reactions. (3) The reactions are typically highly regioselective, diastereoselective, and enantioselective, and (4) do not require protecting groups, metals, preformed enolate equivalents, inert atmosphere, or temperature manipulations.

Future studies will focus on mechanistic aspects and on further applications of proline and other chiral amines in important carbon−carbon bond-forming reactions. The results of which will be reported in due course.

Acknowledgment. Generous financial support, encouragement, and critical manuscript reading by Richard A. Lerner and Carlos F. Barbas, III, is most gratefully acknowledged. W.N. is a research associate in the laboratories of CFB. We kindly thank Raj K. Chadha, The Scripps Research Institute, for the X-ray-structural analysis of diol **1**.

Supporting Information Available: (1) General experimental procedure and characterizations of *anti*-diols **1**−**6** and their *syn*-isomers, (2) X-ray data for diol **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001460V

(10) Izquierdo Cubero, I.; Garcia Poza, D. *Carbohydr. Res.* **1985**, *138*, 139−42.

(11) Lopez Aparicio, F. J.; Gomez Guillen, M.; Izquierdo Cubero, I. *Ann. Quim.* **1976**, *72*, 938−945.

(12) Regio- and presumed (*E*)-stereoselectivity of the enamine formation may result from (a) conjugation (Lin, J.-F.; Wu, C.-C.; Lien, M.-H. *J. Phys. Chem.* **1995**, *99*, 16903−16908) and (b) minimization of 1,3-allylic strain (Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860). However, the enamine geometry may not necessarily be reflected in product diastereoselectivity, as in the case of kinetically controlled aldol reactions of preformed enolates; related transition states involving a (*Z*)-enamine can be constructed.

(13) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.