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# Isoleucine-Catalyzed Direct Asymmetric Aldol Addition of Enolizable Aldehydes

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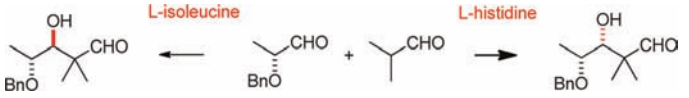
## ABSTRACT

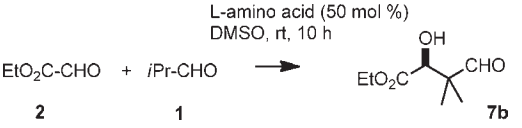



**Isoleucine-catalyzed direct enantioselective aldol additions between enolizable aldehydes are reported. Intermediate acetal structures dictate the configurative outcome and were supported by a hydrogen bond. This direct isoleucine-catalyzed aldol addition represents a welcome complement to both proline- and histidine-catalyzed aldol additions of enolizable aldehydes.**

A vast number of publications over the past decade have demonstrated the successful application of amino acids as organocatalysts in aldol reactions of ketones with enolizable aldehydes. Particularly, proline-catalyzed direct aldol additions of enolizable aldehydes and ketones have been investigated extensively.[1] Targeted investigations on catalytic activities of other amino acids are rare.[2] In contrast, the search for general, efficient methods of direct aldol reactions between two different, enolizable aldehydes remains an illusive challenge and intensively investigated topic. Although amino acids have been utilized as organocatalysts, systematic studies on the catalytic deployment of amino acids in direct aldol additions of enolizable aldehydes do not exist.[3] For cross-aldol additions between enolizable aldehydes with other organocatalysts, see ref 4.

Recently, we demonstrated the suitability of histidine as a catalyst in direct, asymmetric aldol additions between enolizable aldehydes.[5] During these ongoing studies we systematically tested all proteinogenic amino acids in the aldol addition of isobutyraldehyde **1** to ethyl glyoxylate **2**. The results of these investigations are summarized in Table 1. Our results only include reactions, where aldol adduct **7b** was detected in a clear reaction in more than 50% yield.[6]

**Table 1.** L-Amino Acid-Catalyzed Aldol Additions




| entry | amino acid | yield, % | ee, % |
|---|---|---|---|
| 1 | leucine | 76 | 64 |
| 2 | isoleucine | 81 | 77 |
| 3 | alanine | 65 | 60 |
| 4 | valine | 78 | 74 |
| 5 | lysine | 90 | 16 |
| 6 | asparagine | 75 | 76 |
| 7 | arginine | 71 | 17 |
| 8 | phenylalanine | 79 | 72 |

(1) For overviews in this field, see: (a) Guillena, G.; Najera, C.; Ramon, D. J. *Enantioselective Organocatalyzed Reactions*; Mahrwald, R., Ed.; Springer: 2011; Vol. II, p 245. (b) Panday, S. K. *Tetrahedron: Asymmetry* **2011**, *22*, 1817. (c) Pihko, P. M.; Majander, I. E. *Top. Curr. Chem.* **2010**, *291*, 29. (d) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (f) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (g) Tanaka, F.; Barbas, C. F., III. In *Enantioselective Organocatalysis*; Dalko, P., Ed.; WILEY-VCH: Weinheim, 2007; pp 19−55. (h) Berkessel, A.; Gröger, H. *Asymmetric Organocatalyis*; WILEY-VCH: Weinheim, 2005. (i) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (j) List, B. *Tetrahedron* **2002**, *58*, 5573.

(2) (a) Jiang, Z.; Yang, H.; Han, X.; Luo, J.; Wong, M. W.; Lu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1368. (b) Deng, D.; Liu, P.; Ji, B.; Fu, W.; Li, L. *Catal. Lett.* **2010**, *137*, 163. (c) Hayashi, Y.; Itoh, T.; Nagae, N.; Ohkubo, M.; Ishikawa, H. *Synlett* **2008**, 1565. (d) Deng, D.-S.; Cai, J. *Helv. Chim. Acta* **2007**, *90*, 114. (e) Nagamine, T.; Inomata, K.; Endo, Y.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 123. (f) Amedjkouh, M. *Tetrahedron: Asymmetry* **2007**, *18*, 390. (g) Cordova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem.—Eur. J.* **2006**, *12*, 5383. (h) Cordova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586.

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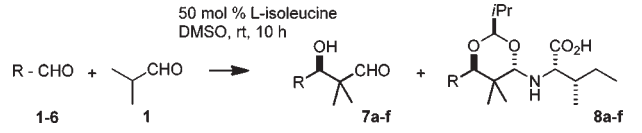
In general, the best results with regard to both yields and stereoselectivities were obtained with neutral, aliphatic amino acids (entries 1, 2, 3, 4, and 8, Table 1). Also, there is a marked stereochemical dependence on the amino acids deployed (compare entries 1 and 2, Table 1). The highest enantioselectivities were obtained using $\beta$-branched amino acids (with the exception of phenylalanine and asparagine, entries 6 and 8, Table 1). Consequently, we selected isoleucine to test this amino acid in cross-aldol additions of isobutyraldehyde with enolizable and nonenolizable aldehydes.

The results of this investigation are depicted in Table 2. Differences to proline catalysis and similarities and differences to histidine catalysis were noticed. First of all, aldol adducts **7a**–**f** are not accessible by proline catalysis for chemoselectivity reasons.[7] Like histidine catalysis, a high chemoselectivity was observed. Isoleucine strictly differentiates between electron-rich and electron-deficient aldehydes. Isobutyraldehyde **1**, an electron-rich aldehyde, reacts exclusively as an enamine component whereas electron-deficient aldehydes **3**, **4**, **5**, and **6** act as carbonyl components in isoleucine-catalyzed aldol additions.

In contrast to L-proline and L-histidine catalysis, opposite configured aldol adducts **7b**–**f** were detected with L-isoleucine. The aldol adducts **7b**–**d** were also isolated with good enantioselectivities. Complete enantioselectivity was observed when using with oxygen-containing aldehydes **5** and **6**. An exception was the self-aldol addition of isobutyraldehyde **1**. No enantioselectivity was observed; aldol adduct **7a** was isolated in racemic form. Moreover, substantial amounts of the corresponding aminoacetal **8a** were detected (65%, Table 2). This compound was isolated in enantiopure form.[8]

**Table 2.** Isoleucine-Catalyzed Cross Aldol Addition between Enolizable Aldehydes




| entry | compound | **7a**–**f** yield, % (ee, %) | **8a**–**f** yield, % |
|---|---|---|---|
| 1 | **7a**: R = *i*Pr | 23[a] (0) | 65[b] |
| 2 | **7b**: R = $EtO_2C$ | 81 (77) | – |
| 3 | **7c**: R = $ClCH_2$ | 62 (85) | – |
| 4 | **7d**: R = 4-$NO_2$-$C_6H_4$ | 76 (63) | – |
| 5 | **7e**: R = $(MeO)_2CH$ | 83 (>98) | – |
| 6 | **7f**: R = $BnOCH_2$ | 45 (>98) | 21[b] |

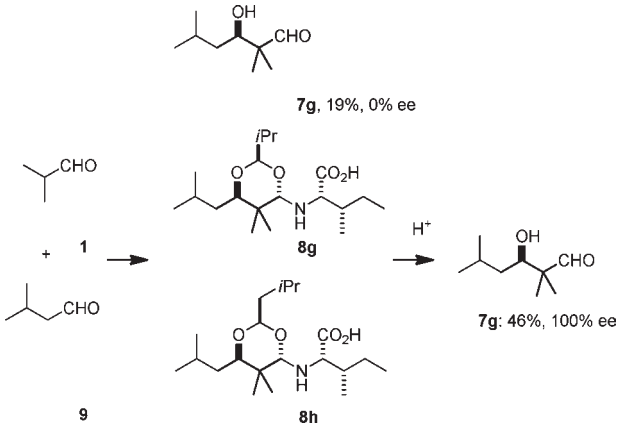
[a] Yield related to isobutyraldehyde. [b] Yield related to isoleucine.

Aminoacetals were also encountered as side products when benzyloxyacetaldehyde **6** was employed (entry 6, Table 2). In addition to aldol adduct **7f** (ee >98%) enantiopure isobutyracetal **8f** was isolated with 21% yield.

These results prompted us to look more closely at the stereochemical events of this reaction. To this end, isobutyraldehyde **1** was reacted with isovaleraldehyde **9** in the presence of L-isoleucine. A mixture of aldol adduct **7g** and corresponding acetals **8g** and **8h** was detected. The aldol adduct **7g** was obtained in racemic form (19% yield). The aminoacetals **8g** and **8h** differ in the aldehyde component, as can be seen in Scheme 1.

After straightforward separation of the acetals and acidic treatment, the aldol adduct **7g** was isolated in enantiopure form (46% yield). Isoleucine strictly differentiates between isobutyraldehyde **1** ($\alpha$-branched aldehyde) as an enamine component and isovaleraldehyde **9** as a carbonyl component. Self-aldol adducts or reversed aldol adducts (in this case isovaleraldehyde **9** acts as the enol component) were not observed under these reaction conditions. In addition, formation of the corresponding aminoacetals **8a**–**f** of isolated aldol adducts **7a**–**f** was not accomplished under the described reaction conditions. These results indicate two reaction modes, which may operate with different rates under these conditions. One mode proceeds without stereocontrol. The other one, the stereocontrolled mode, runs through acetalization, which yields indeed enantiopure aldol adducts. These considerations are supported by the experiments depicted in Scheme 1.

**Scheme 1.** Isoleucine-Catalyzed Aldol Addition of Isobutyraldehyde and Isovaleraldehyde[a]




[a] Reaction conditions: 50 mol % L-isoleucine, DMSO, rt, 10 h.

(3) For an overview of organocatalyzed cross-aldol additions of enolizable aldehydes, see: Scheffler, U.; Mahrwald, R. *Synlett* **2011**, 1660.

(4) (a) Chiral sulfonamides: Kano, T.; Sugimoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 18130. (b) Diarylprolinols: Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082. (c) Diarylprolinos: Hayashi, Y.; Yasui, Y.; Kawamura, T.; Kojima, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2804.

(5) Markert, M.; Scheffler, U.; Mahrwald, R. *J. Am. Chem. Soc.* **2009**, *131*, 16642.

(6) Same results were obtained when used with 25 mol% isoleucine. In these reactiones longer reaction times are required (up to 6–8 days at rt).

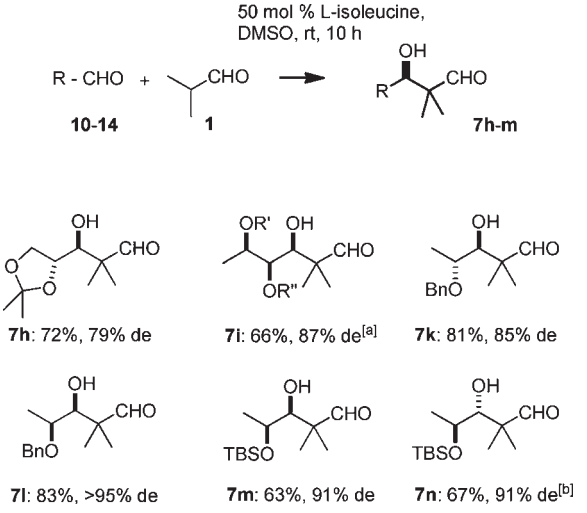
(7) With the exceptions of cross-aldol additions of isobutyraldehyde **1** as the ene component and 4-nitrobenzaldehyde **4** as the carbonyl component: (a) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. (b) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077. (c) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734.

(8) Thus, for the first time by cleavage of acetal **8a** an access to optically pure aldehyde **7a** is given. See Supporting Information.

In order to gain a deeper insight into the stereochemical course of this reaction, oxygen-containing chiral aldehydes **10-14** were reacted with isobutyraldehyde **1**. Aldol adducts **7h**–**n** were isolated with high degrees of diastereoselectivity, in some cases even in diastereopure form. The corresponding aminoacetals were not detected in these transformations. Racemization of starting aldehydes **10**–**14** was not detected. Matched/mismatched cases were not observed by isoleucine catalysis.

In reactions of protected *R*- or *S*-configured lactaldehyde **12** and **13**, similar values of diastereoselectivities and yields were detected (compare aldol adduct **7k** and **7l**, Scheme 2). Also, when D- or L-isoleucine were used, *syn*- and *anti*-configured aldol adducts **7m** and **7n** were isolated with the same high degrees of diastereoselectivity (Scheme 2). These results contrast with those obtained through histidine catalysis. TBS-protected lactaldehyde **14** does not react at all in histidine catalysis.

**Scheme 2.** Isoleucine-Catalyzed Cross-Aldol Addition with Chiral Oxygen-Containing Aldehydes




[a] R′ = R″ = $CMe_2$. [b] D-isoleucine was used.

Based on these results the following considerations can be made. The configuration of amino acid deployed clearly dictates installation of the absolute configuration of the newly created stereogenic center during the aldol step. The reaction proceeds via an enamine mechanism and the direction of the incoming aldehyde is determined by hydrogen bonds. The enamine is formed by the primary amine of the amino acid permitting the deployment of α-branched aldehydes. Structure **A** is favored over **B** (steric interactions of the incoming aldehyde with *sec*-butyl group of isoleucine; Figure 1). In addition, formation of preferred conformations by further hydrogen bonds as known from histidine catalysis[9] is not observed in isoleucine catalysis when used with oxygen-containing aldehydes. Thus, isoleucine determines the chirality of the new stereogenic center, without being influenced by the chirality of oxygen-containing aldehydes **10**–**14**.

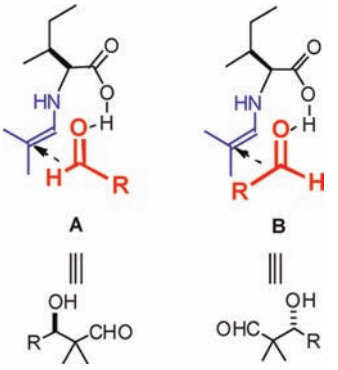
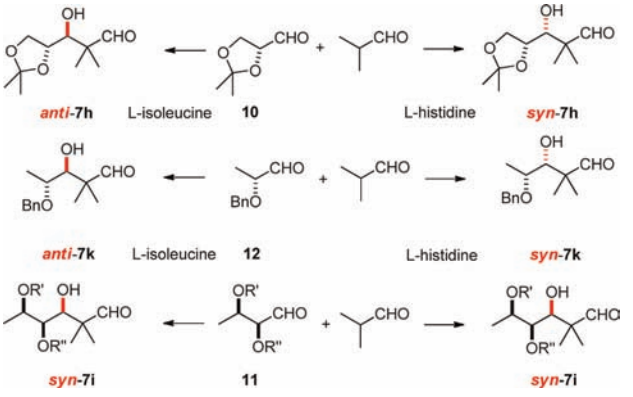



**Figure 1.** Proposed stereochemical models.

To emphasize these considerations, comparable results for the histidine and isoleucine catalysis are depicted in Scheme 3. *Anti*-configured aldol adducts **7h** and **7k** were obtained via isoleucine catalysis, whereas the corresponding *syn*-configured products were accessible by histidine catalysis. In contrast to that, identical *syn*-aldol adducts **7i** were obtained in both the histidine- and isoleucine-catalyzed aldol additions of isobutyraldehyde.

**Scheme 3.** Comparison between Histidine and Isoleucine Catalysis[a]




[a] R′ = R″ = $CMe_2$.

With the advent of isoleucine a further amino acid is now on hand to catalyze the direct asymmetric aldol addition of two potentially enolizable aldehydes of different electronic character. These new transformations are characterized by operationally simple and very mild conditions as well as high stereoselectivities and yields. The direct isoleucine-catalyzed aldol addition represents a welcome alternative to both proline and histidine catalysis of direct aldol additions of enolizable

(9) (a) Scheffler, U.; Mahrwald, R. *J. Org. Chem.* **2012**, *77*, 2310. (b) Lam, Y.-h.; Houk, K. N.; Scheffler, U., Mahrwald, R. *J. Am. Chem. Soc.* **2012**, *134*, 6286.

aldehydes. Further investigations and extensions of these findings are underway.

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**Supporting Information Available.** Experimental procedures, details on method development, and product characterization including spectroscopic data can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.