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Stereoselective Direct Amine-Catalyzed Decarboxylative Aldol Addition

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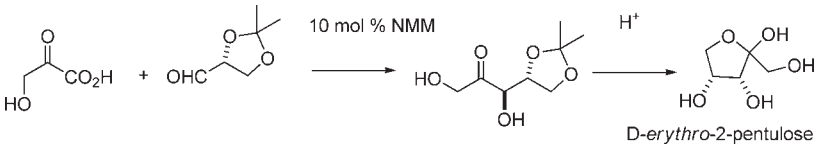
ABSTRACT



A stereoselective decarboxylative aldol addition of β- and α-keto acids in the presence of catalytic amounts of amines is described. By the optional deployment of chiral enolizable aldehydes an access to enantiopure configurative defined ketopentoses, ketohexoses, or ketoheptoses is given.

Only a few reports in the metal-catalyzed series so far have tried to demonstrate the synthetic usefulness of deployment of direct decarboxylative aldol additions in asymmetric C−C bond formation processes.[1] This mild and operationally simple transformation plays a very important role in aldol processes of polyketide[2] or carbohydrate[3] biochemical pathways. Also, organocatalytic solutions of this transformation have been tackled. β-Keto carboxylic acids, typically malonic monoesters, were reacted with aldehydes in the presence of stoichiometric or catalytic amounts of tertiary amines at room temperature.[4] Only a very limited number of manuscripts have been published that report the deployment of α-keto carboxylic acids in direct decarboxylative aldol additions.[5] Accounts on the synthesis of enantiopure aldol adducts by direct and amine-catalyzed decarboxylative aldol addition have not been reported so far.

During our ongoing studies in the field of amine-catalyzed direct aldol additions[6] we have been able to develop a direct amine-catalyzed decarboxylative aldol addition of β- as well as α-keto carboxylic acids with enolizable aldehydes. Thus, by deployment of chiral enolizable aldehydes, an access to defined configured optically pure aldol products is given. Herein, we want to discuss the results of these investigations. Preliminary experiments indicate that tertiary amines

(1) (a) Mukaiyama, T.; Sato, T.; Suzuki, S.; Inoue, T.; Naka mura, H. *Chem. Lett.* **1976**, 95. (b) Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126. (c) Nokami, J.; Konishi, H.; Matsuura, H. *Chem. Lett.* **1991**, 2023. (d) Baskaran, S.; Nagy, E.; Braun, M. *Lieb. Ann.* **1997**, 311. (e) Luo, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440. (f) Orlandi, S.; Benaglia, M.; Cozzi, F. *Tetrahedron Lett.* **2004**, *45*, 1747. (g) Fortner, K. C.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 1032. (h) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284. (i) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852.

(2) (a) Staunton, J.; Wilkinson, B. *Chem. Rev.* **1997**, *97*, 2611. (b) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380. (c) Piel, J. *Nat. Prod. Rep.* **2010**, *27*, 996.

(3) For recent reviews, see: (a) Hailes, H. C.; Dalby, P. A.; Lye, G. J.; Baganz, F.; Micheletti, M.; Szita, N.; Ward, J. M. *Curr. Org. Chem.* **2010**, *14*, 1883. (b) Wohlgemuth, R. *J. Mol. Catal. B: Enzym.* **2009**, *61*, 23.

(4) (a) Binder, D.; Noe, C. R.; Baumann, K.; Wildburger, J. M. F. *Arch. Pharm.* **1985**, *318*, 243. (b) Grayson, D. H.; Tuite, M. R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2137. (c) Tanaka, M.; Ooota, O.; Hiramatsu, H.; Fujiwara, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2473. (d) Thalji, N. K.; Crowe, W. E.; Waldrop, G. L. *J. Org. Chem.* **2009**, *74*, 144. (e) Blaquiere, N.; Shore, D. G.; Rousseaux, S.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 6190. (f) Khodakovskiy, P. V.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2009**, 1099. (g) For an unselective lipase-catalyzed decarboxylative aldol process, see: Feng, X.-W.; Li, C.; Wang, N.; Li, K.; Zhang, W.-W.; Wang, Z.; Yu, X.-Q. *Green Chem.* **2009**, *11*, 1933. (h) Baudoux, J.; Lefebvre, P.; Legay, R.; Lasne, M.-C.; Rouden, J. *Green Chem.* **2010**, *12*, 252. (i) Ramachary, D. B.; Ramakumar, K.; Bharanishashank, A.; Narayana, V. V. *J. Comb. Chem.* **2010**, *12*, 855.

(5) (a) Smith, M. E. B.; Smithies, K.; Senussi, T.; Dalby, P. A.; Hailes, H. C. *Eur. J. Org. Chem.* **2006**, 1121. Three examples were described in the presence of morpholinopropane-sulfonic acid. The aldol adducts were isolated with yields betweeen 35 and 25%, with the exception of hydroxyacetaldehyde (63%).(b) Cazares, A.; Galmann, J. L.; Crago, L. G.; Smith, M. E. B.; Strafford, J.; Rios- Solis, L.; Lye, G. J.; Dalby, P. A.; Hailes, H. C. *Org. Biomol. Chem.* **2010**, *8*, 1301. Eight examples in the racemic series were described in this report. The aldol adducts were isolated with yields between 35% and 2%.

(6) Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* **2007**, *129*, 7258.

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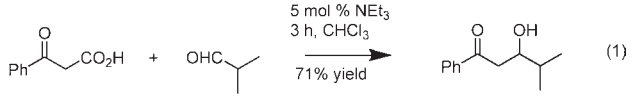
catalyze a direct decarboxylative aldol addition of β-keto carboxylic acids with enolizable aldehydes, producing the corresponding aldol adducts in high yield. To this end, we reacted isobutyraldehyde with benzoylacetic acid in the presence of catalytic amounts of triethylamine (eq 1).



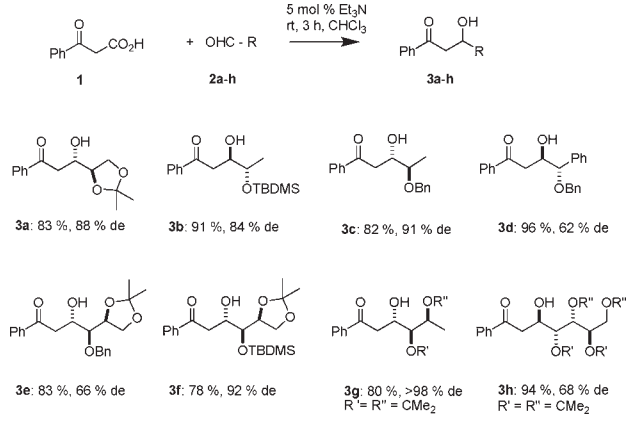
(1)

The reactions were complete after 2−3 h at room temperature. Longer reaction times caused side reactions and thus diminished yields (among others aldol condensation). Yields do not depend on the amines employed. The same yields and reaction times were observed with secondary, primary, or tertiary amines.[7] In a very clean reaction, the corresponding aldol adduct was isolated in 71% yield. Products derived from a competitive self-aldol addition of isobutyraldehyde were not detected.

In further investigations we were able to extend this transformation. By deployment of several chiral enolizable aldehydes **2a**−**h**, aldol adducts **3a**−**h** were isolated in good to excellent yields.

Racemization or epimerization was not detected during these processes. The aldol adducts were obtained in enantiopure form (Scheme 1).

Scheme 1. Direct Decarboxylative Amine-Catalyzed Aldol Addition of Benzoylacetic Acid



The configurational outcome of this reaction was not influenced by the deployment of different tertiary amines. As a rule, high *anti*-selectivities were observed under these reaction conditions. In some cases practically only one diastereoisomer could be detected. The high *anti*-selectivity observed for aldol adduct **3c** can be explained by transition state model **A**. An equatorial attack on the benzyl-protected *R*-configured lactaldehyde **2c** would give rise to the *anti*-configured product **3c** (91% de). The *syn*-configured aldol product **3c** could be expected by assumption of an unfavored axial attack on the *R*-configured aldehyde **2c** (transition state model **B**, Figure 1).

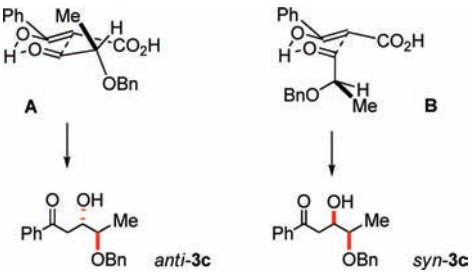
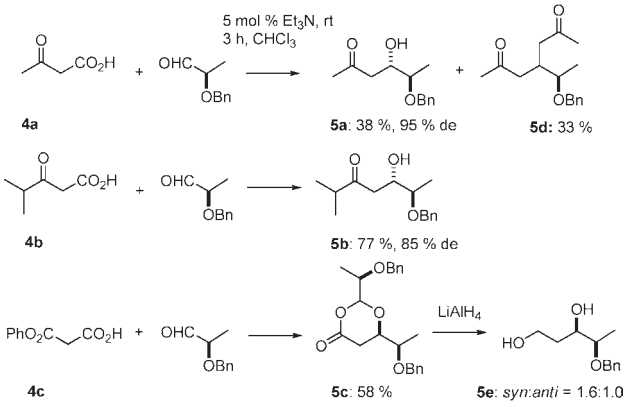


Figure 1. Proposed transition states.

In a next series of experiments several different β-ketoacids were tested in these reactions (Scheme 2). Again high *anti*-selectivities were detected under these reaction conditions. The formation of chiral 1.5-diketone **5d** can be explained by an aldol condensation/Michael addition. With malonic ester a different behavior is observed. By reacting the monophenyl malonate **4c** with protected lactaldehyde **1c** the formation of lactone **5c** was observed. In order to determine the configuration, lactone **5c** was reduced with $LiAlH_4$ to afford the *syn*-configured diol **5e** (Scheme 2).

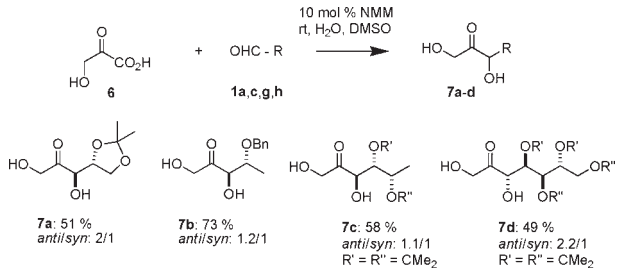
Scheme 2. Decarboxylative Amine-Catalyzed Aldol Additions of Different β-Keto Acetic Acids



Further investigations revealed that even α-keto acids engage in the decarboxylative C−C bond forming process under these reaction conditions. This transformation is very sensitive to the amines and aldehydes deployed. When pyruvate, phenylpyruvate, or bromopyruvate was treated with protected lactaldehyde **1c**, no reaction was observed. However, a clear decarboxylative addition of hydroxypyruvate **6** with protected lactaldehyde **1c** was observed in the presence of catalytic amounts of triethylamine.

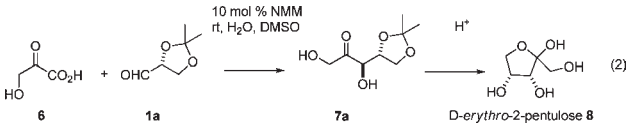
(7) See Supporting Information

Scheme 3. Amine-Catalyzed Decarboxylative Addition of Aldehydes to α-Keto Acids



On the other hand, no reactions took place when hydroxypyruvate **6** was reacted with protected aldehyde **1a**, **1g**, or **1h** in the presence of triethylamine. Optimization indicated that *N*-methylmorpholine (NMM) as the optimal catalyst for these substrates. When catalytic amounts of *N*-methylmorpholine were used, the corresponding aldol adducts **7a**−**7d** were isolated in good yields and with a slight *anti*-diastereoselectivity (Scheme 3).[8]

In order to demonstrate the utility of this transformation in the total synthesis of carbohydrate derivatives, *anti*-configured aldol adduct **7a** was converted into D-*erythro*-2-pentulose **8** (eq 2). This was easily accomplished by deprotection of the acetal of hydroxyketone **7a** followed by spontaneous cyclization. The spectral data of pentulose **8** matched in full those described in the literature.[9]



In conclusion, we have described an amine-catalyzed decarboxylative addition of chiral aldehydes to β-keto as well as α-keto acids. This operationally simple protocol gives a very easy access to polyhydroxylated defined configured carbohydrate derivatives. Especially chiral aldol adducts of the β-keto acetic acid series are of particular interest, since asymmetric synthesis of these so-called "acetate"-aldol adducts cannot be as easily accomplished by other aldol methodologies[10] as it is demonstrated by this procedure. Further investigations of the mechanism and an asymmetric and catalytic version of this transformation are underway.

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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.

(8) Reaction times strongly depend on the amount of amines deployed: by application of 10 mol% NMM a complete reaction was observed after 24−36 h, whereas when used with equimolar amounts of NMM the end of the reaction was detected after 2−3 h.

(9) Vuorinen, T.; Serianni, A. S. *Carbohydr. Res.* **1990**, *209*, 13. 100 mg of D-*erythro*-2-pentulose **8** = $435.

(10) Carreira, E. M.; Fettes, A.; Marti, C. *Org. React.* **2006**, *67*, 1.