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Amine-Catalyzed Direct Aldol Addition

Morris Markert, Michael Mulzer, Bernd Schetter, and Rainer Mahrwald*

Institut für Chemie der Humboldt-Universität zu Berlin, Brook-Taylor Strasse 2, 12 489 Berlin, Germany

Received March 29, 2007; E-mail: rainer.mahrwald@rz.hu-berlin.de

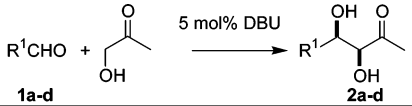
At present there exists a broad spectrum of methods to synthesize β-hydroxy carbonyl compounds−aldol adducts.[1] The amine-catalyzed aldol addition represents one of these methods and belongs to the organo-catalyzed aldol additions.[2] The deployment of catalytic amounts of amines in aldol additions has been known for a long time.[3] Several different applications of amines exist in this important C−C bond-formation process. The catalysts deployed are primary or secondary amines, amines in combination with an acid or simply aminoacids. These methods are not the subject of the present work. It is assumed that these transformations run through an imine−enamine mechanism, similar to the reaction mode of class I aldolases,[4] which are well documented in several reviews.[5]

On the other hand, there are only a few examples over the last years reporting intermolecular aldol additions of aldehyde−acceptors with ketone-donors catalyzed only by tertiary amines;[6] mostly aldol condensations were observed.[7] Recently, an aldol addition of phenylglyoxylate to cyclopent-2-enone mediated by 1.8-diazabicyclo-[5.4.0]undec-7-ene (DBU) was published by Shi and Zhang.[8] Gutsche et al. reported a pyridine-catalyzed conversion of D-glyceraldehyde to hexoses via partial isomerization to dihydroxyacetone during the reaction and subsequent aldol addition in aqueous medium.[9] The authors did not observe an internal stereocontrol under these reaction conditions. Both, D-fructose and D-sorbose were isolated in a ratio of nearly 1:1. In addition the authors pointed out that, in contrast to the results under aqueous reaction conditions, in anhydrous pyridine only isomerization of D-glyceraldehyde to dihydroxyacetone was detected. No aldol additions were observed in anhydrous reaction media. To summarize these findings, a general and tertiary amine-catalyzed intermolecular aldol addition of aldehydes to ketones is still unknown.

Also, catalytic amounts of amines were used in combination with metal salts in aldol reactions. For the use of zinc salts in the presence of tertiary amines see ref 10. Recently, we were able to demonstrate the application of catalytic amounts of tertiary amines in the presence of $LiClO_4$ in aldol condensations.[11] Under these reaction conditions the application of 0.5 mol % of Et_3N proved sufficient to achieve quantitative yields in cross-aldol reactions of ketones even with enolizable aldehydes.

By optimizing reaction conditions as well as substrates used we were able to realize a more general amine-catalyzed aldol addition. Preliminary results of these investigations will be discussed here. As we have previously reported, attempts to perform aldol condensations of aldehydes with hydroxylated acetone derivatives have failed.[11b] No condensation products of hydroxyacetone, methoxyacetone, or dihydroxyacetone with aldehydes were observed by using $LiClO_4$ in combination with catalytic amounts of triethylamine. But investigations of these reaction conditions revealed that aldol additions can be performed by using tertiary amines in the absence of $LiClO_4$. Under these reaction conditions aldol adducts of hydroxacetone could be isolated. Moreover, the reactions proceeded even when we used enolizable aldehydes and hydroxyacetone. In contrast to that, we did not observed aldol

Scheme 1. Aldol Addition of Hydroxyacetone Catalyzed by DBU

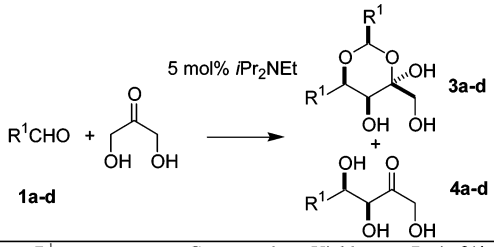


1a-d 2a-d

Entry	R^1	Compound	Yield (%) [a]	Ratio *syn*/*anti* (%) [b]
1	*i*Pr	**2a**	83	91: 9
2	$PhCH_2CH_2$	**2b**	87	77:23
3	Cy	**2c**	92	90:10
4	Ph	**2d**	89	68:32

[a] Isolated yields. [b] Diastereomer ratios was determined by ^{1}H NMR.[13]

Scheme 2. *i*Pr_2NEt-Catalyzed Direct Aldol Additions of Dihydroxyacetone



1a-d

Entry	R^1	Compound	Yield (%)	Ratio **3/4** (%) [a,b]
1	*i*Pr	**3a**	92	> 99: 1
2	$PhCH_2CH_2$	**3b / 4b**	68	95: 5
3	Cy	**3c**	94	> 99: 1
4	Ph	**4d**	46	> 1:99

[a] Aldol adducts **4a**, **4c**, and ketal **3d** could not be detected. [b] Confirmation of the assigned configuration of hemiketals **3a**−**c** and aldol adducts **4b** and **4d** was achieved by analysis of the corresponding ^{1}H and ^{13}C NMR spectra. The coupling constants of protons of hemiketals clearly indicate the syn-configuration. An X-ray structure analysis of **3c** is provided.[13]

adducts of ketones and aldehydes when using diethylketone or acetone as the ene-components. The role of tertiary amines in these reactions is crucial and depends on the substrates. Best results in the hydroxyacetone-series with regards to catalyst loading, yields, reaction times, and stereoselectivities were obtained by the application of 5 mol % DBU (Scheme 1).

Aldol adducts **2a**−**d** were isolated with an extremely high degree of regioselectivity (Scheme 1). The attack of aldehydes was observed only at the hydroxylated α-carbon-atom. Moreover, the aldol adducts **2a**−**d** were isolated with moderate to high degrees of syn-diastereoselectivity in all of our reactions. With these results in hand we examined aldol additions of enolizable aldehydes with dihydroxyacetone. In these reactions diisopropylethylamine (*i*Pr_2-NEt) proved to be the amine of choice. When used with 5 mol % of *i*Pr_2NEt a smooth aldol addition of dihydroxyacetone and aldehydes was observed. Results of these investigations are demonstrated in Scheme 2.

The reactions were carried out at room temperature and without any solvent. Depending on the nature of aldehydes used the reactions have been finished after 6−48 h. In contrast to the reaction with hydroxyacetone (Scheme 1), hemiketals **3a**−**c** of aldol adducts or the corresponding aldol adducts **4b** and **4d** (entry 2 and 4,

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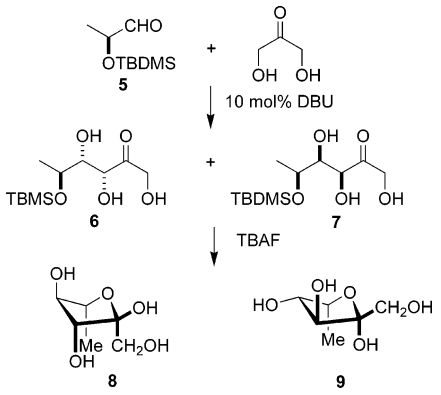
Scheme 3. Synthesis of L-rhamnulofuranose **8** and 6-Deoxy-L-sorbose **9**



Scheme 4. Cinchonine-Catalyzed Aldol Addition of Isopropylidene-(*R*)-glyceraldehyde **10** with DHA

Scheme 2) were isolated.[12] The hemiketals **3a**−**c** and aldol adducts **4b** and **4d** were observed to have an extremely high degree of syn-diastereoselectivity. Anti-configured hemiketals or aldol adducts could not be detected under the reaction conditions described. Hydrogen bonds are supposed to be responsible for this extremely high syn-selectivity.[13]

Scheme 3 and 4 very instructively demonstrate the power of this transformation. The DBU-catalyzed aldol addition of TBDMS-protected (*S*)-lactaldehyde **5** with DHA provided an access to both L-rhamnulofuranose **8** as well as 6-deoxy-L-sorbose **9**. The products were isolated with an extremely high degree of relative syn-diastereoselectivity. Anti-configured products could not be detected. In contrast to that, an internal diastereoselectivity derived from the chiral lactaldehyde **5** could not be detected (1,2-asymmetric induction). As a consequence of that, L-rhamnulofuranose **8** and 6-deoxy-L-sorbose **9** were isolated in a ratio of nearly 1:1 (overall yields of **8** and **9** = 51% yields) (Scheme 3).

Similar results with regards to stereoselectivities were obtained in DBU-catalyzed aldol additions of isopropylidene-(*R*)-glyceraldehyde **10** and DHA. D-Fructose and D-sorbose were detected in a ratio of 1:1. On the other hand, an extremely high stereoselective aldol addition was observed when used with 30 mol % cinchonine as the tertiary amine instead of DBU. This reaction furnished D-fructose **11** with a high degree of syn-stereoselectivity. In addition the internal anti-stereoselectivity derived from the starting chiral isopropylidene-(*R*)-glyceraldehyde **10** was extremely high under these reaction conditions (91:9).[14] Thus, this amine-catalyzed aldol addition represents a very easy and elegant approach to D-fructopyranose **11** with high yields (71%) and with a high degree of stereoselectivity. Since racemization of aldehydes **5** and **10** does not occur under these reactions conditions, enantiomerically pure aldol adducts can be obtained (>98% ee).[15]

In summary, we have uncovered a remarkable catalytic effect of tertiary amines in aldol processes. This discovery resulted in the development of an amine-catalyzed direct aldol addition. The extremely high syn-stereoselectivity that we have observed in aldol additions with unprotected dihydroxyacetone represents a valuable addition to the anti-selectivities that have been described for proline-catalyzed aldol reactions of protected dihydroxyacetone.[16] In addition, this reaction cannot be compared with aldol additions catalyzed by primary or secondary amines or aminoacids with regards to the reaction mechanism.[17] Further investigations are currently conducted and will be published in a separate, forthcoming paper.

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

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(13) See Supporting Information.
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