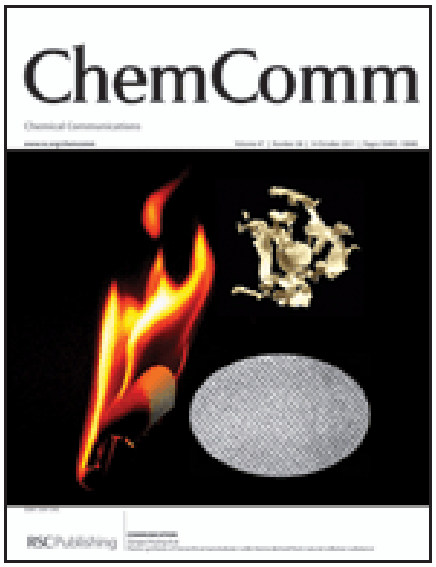


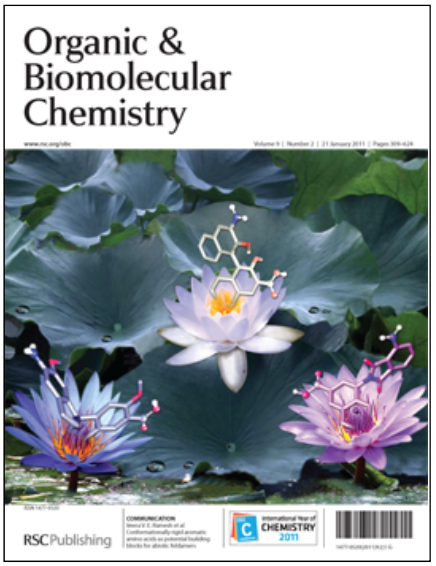


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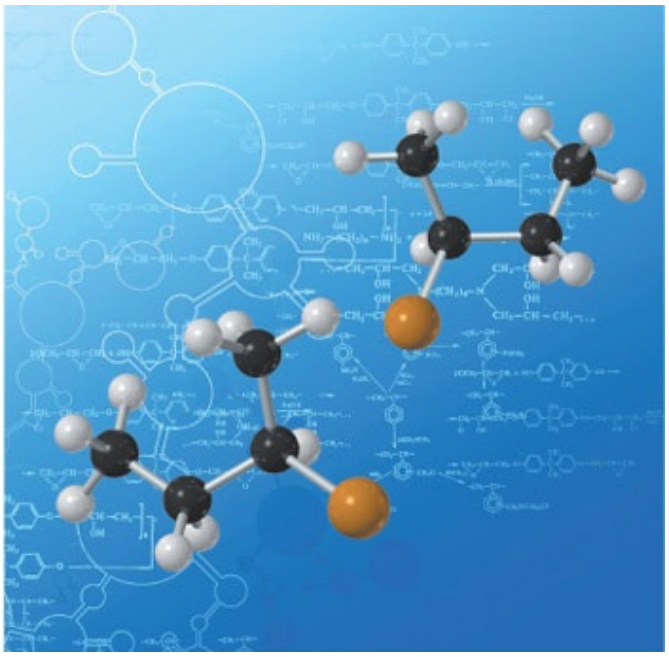

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COMMUNICATION



# Stereoselective amine-catalyzed carbohydrate chain elongation†‡

**Benjamin Voigt, Ulf Scheffler and Rainer Mahrwald***

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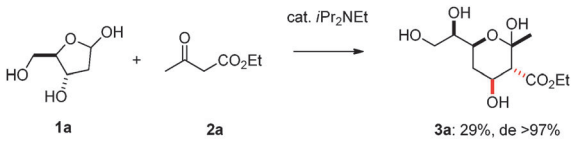
**Aldol additions of unprotected carbohydrates to 1.3-dicarbonyl compounds have been described. This transformation is based on a dual activation by tertiary amines and 2-hydroxypyridine.**

Chain elongated carbohydrates—higher carbon sugars—are important compounds with biologically fundamental properties. Nature realizes these important transformations, apparently effortless, through a deployment of distinctly working aldolases and ketolases with extremely high degrees of stereoselectivity (Scheme 1).[1] However this high specificity is limited to a small number of substrates. Also, not all possible stereoisomers can be accessed by enzymatic transformations.

Today a multitude of methods exists to accomplish these transformations. These synthetic maneuvers are associated with extensive handling of protecting groups and additional activation of the anomeric carbon atom.[2] Recent results of organocatalyzed aldol reactions in this field however promise to overcome these problems.[3]

Recently we have tested several organocatalyzed transformations for their utility in the synthesis of carbohydrates. We demonstrated the value of amines as catalysts in direct aldol additions of dihydroxyacetone[4] and in decarboxylative aldol additions.[5] Based on these results we proceeded to test also unprotected carbohydrates as carbonyl compounds in direct aldol additions. Thus we have reacted these substrates with 1.3-dicarbonyl compounds. In preliminary experiments we have tested deoxyribose **1a**[6] in reactions with acetoacetic ester **2a** as the enol component. The reactions were performed in the presence of catalytic amounts of amines at room temperature in neat. As a result we were able to isolate hemiketal **3a** with 29% yield as a single diastereoisomer in a rapid and clear reaction (eqn (1)).

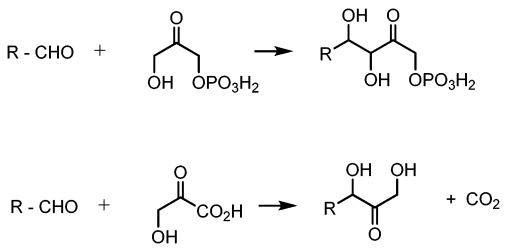



(1)

The C–C bond formation process occurs *via* an aldol addition step. Aldol condensation products were not detected under these reaction conditions. Successful aldol additions of aldehydes to 1.3-dicarbonyl compounds are rare and difficult to realize. Mostly, a competitive condensation process cannot be prevented. For a successful execution of this reaction in the absence of amines see ref. 7. Next, the C–C bond formation process proceeds with an extremely high degree of *syn*-diastereoselectivity. One single stereoisomer was detected by NMR-techniques. In addition high chemoselectivity is observed. An aldol addition at the methyl group was not detected. Comparable reactions have not been described in the literature so far.[8]

Several attempts were made to react unprotected and unactivated carbohydrates with 1.3-dicarbonyl compounds. These studies describe condensation processes that are connected with the loss of stereogenic centers (Knoevenagel-reaction[9]). Furan-derivatives or C-glycosides[10] were obtained depending on reaction conditions. Recently this methodology was extended to synthesize fused pyridine/pyrrole derivatives of carbohydrates.[11]

Inspired by the results we obtained, several carbohydrates of the pentose set were tested as carbonyl compounds in an initial series. To this end D-ribose **1b**, D-arabinose **1c**, D-xylose **1d** and D-lyxose **1e** were reacted with acetoacetic ester **2a** at rt in the presence of catalytic amounts of diisopropylethylamine. In preliminary experiments the expected products **3a–e** were isolated with different and low yields. A pronounced correlation of yields in this reaction to deployed carbohydrates was observed. Highest yields were obtained with deoxyribose **1a** and ribose **1b** and other carbohydrates resulted in decreasing yields. Finally, the lowest yields were obtained by the deployment of arabinose **1c** and lyxose **1e**. Yields and reaction rates correlate with the tendency of the corresponding carbohydrates to exist in acyclic structure.[12] Comparable results were obtained by glycosidation of unprotected and unactivated carbohydrates.[13] To overcome the problems of long reaction times and low yields we have tested 2-pyridone as an additive in these reactions. 2-Pyridone is known




**Scheme 1** Examples of aldolase- and transketolase-catalyzed reactions.

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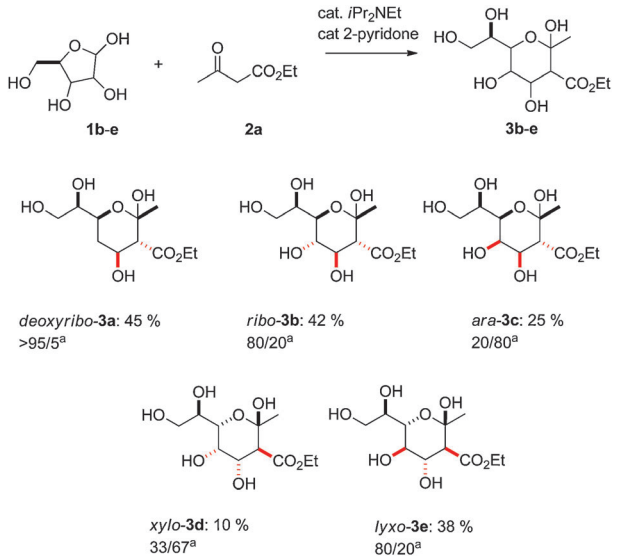
‡ This article is part of the joint *ChemComm–Organic & Biomolecular Chemistry* 'Organocatalysis' web themed issue.




**Scheme 2** Aldol additions of ribose **1b**, arabinose **1c**, xylose **1d** or lyxose **1e** to acetoacetic ester **2a**. Reaction conditions: 1.0 mmol carbohydrate, 1.5 mmol acetoacetic ester **2a**, 20 mol% $i$Pr$_2$NEt, 25 mol% 2-pyridone, 0.5 ml DMSO, rt, 60–96 h. [a]Internal *syn*/*anti* ratio.

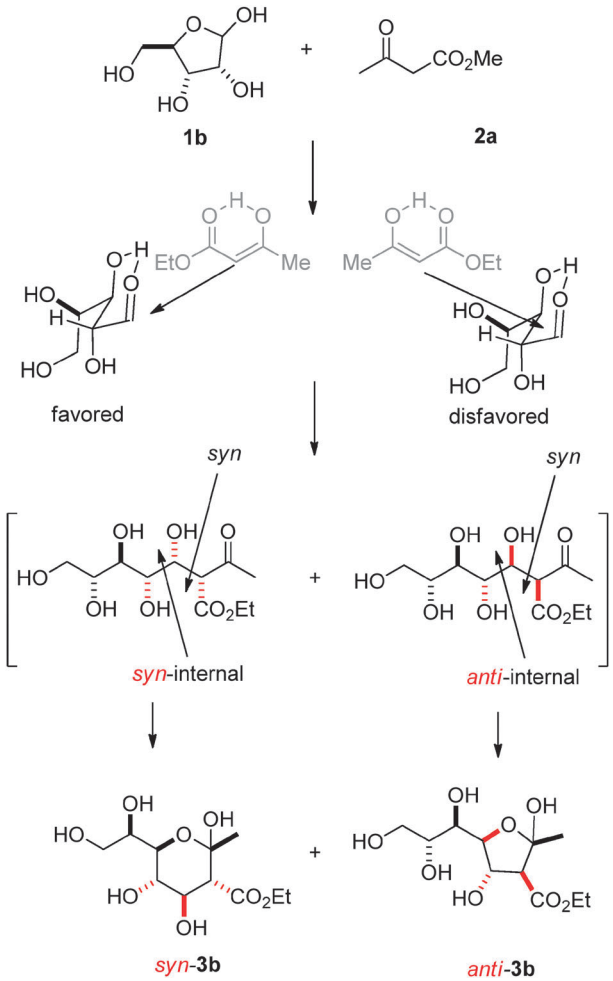
to potentially catalyze the mutarotation of carbohydrates by forming hydrogen bonds.[14] As expected, yields increase under comparable conditions when catalytic amounts of 2-hydroxypyridine are used. The results of these investigations are depicted in Scheme 2.

Extremely high *syn*-diastereoselectivities were observed during the C–C bond formation process. *Anti*-configured products were not detected under these reaction conditions. These results are consistent with those obtained in aldol additions with dihydroxyacetone.[4] In addition, an asymmetric induction is observed. The internal *syn*- and *anti*-configured products were detected in a ratio of about 3/1. Scheme 3 illustrates an example for the reaction of ribose **1b** with acetoacetic ester **2a** as a substitutional explanation for all other carbohydrates. The *syn*-configured aldol product **3b** is obtained in its pyranoid structure. In contrast, the internal *anti*-configured aldol product develops a furanoid structure to avoid unfavored 1.3-diaxial interactions (*anti*-**3b**, Scheme 3). The anomeric hydroxyl group was installed at the axial position in every reaction (see ESI†).

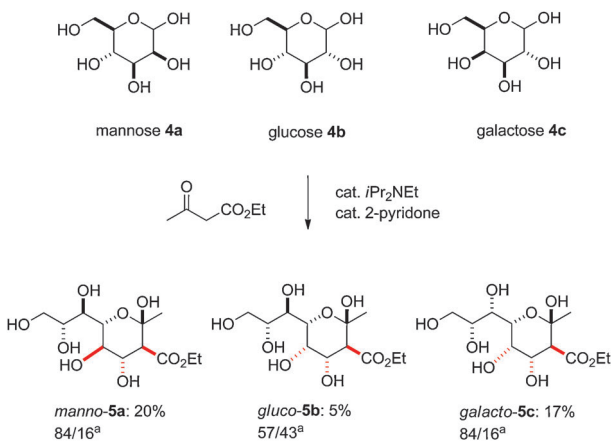
In the next series we have tested several different hexoses in reactions with acetoacetic ester **2a**. Comparable results with those of the pentose-series were obtained (Scheme 4). Again, extremely high *syn*-diastereoselectivity is observed during the C–C bond formation.

The structure of carbohydrates determines both yields and internal diastereoselectivity (Schemes 2 and 4). 2.3-*anti*-Configured carbohydrates give mainly internal *syn*-configured products in good yields (**3b**, **3e** and **5a**). In contrast, when 2.3-*syn*-configured carbohydrates are used internal *anti*-configured products are mainly obtained with lower yields (**3c**, **3d**, **5b** and **5c**). In this context deoxyribose represents an exception, because of the absence of a hydroxy group at the 2-position (**3a**, Scheme 2).

Subsequent formation of pyranoid or furanoid structures depends on steric interactions and is also determined by the configuration of the deployed carbohydrates.

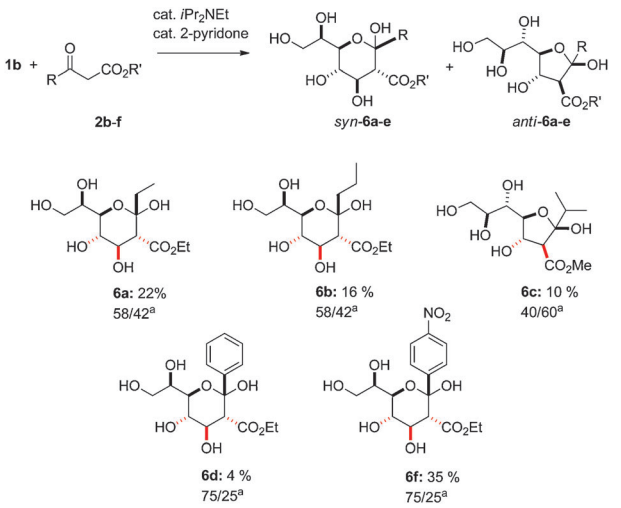



**Scheme 3** Stereochemical course of aldol reaction of ribose with methyl acetoacetate **2a**.




**Scheme 4** Aldol additions of mannose **4a**, glucose **4b** or galactose **4c** to acetoacetic ester **2a**. Reaction conditions: 1 mmol carbohydrate, 1.5 mmol acetoacetic ester **2a**, 20 mol% $i$Pr$_2$NEt, 25 mol% 2-pyridone, 0.5 ml DMSO, rt, 60–96 h. [a]Internal *syn*/*anti* ratio.

In the final series we have tested several different 1.3-dicarbonyl compounds in this amine-catalyzed reaction with ribose **1b**. Results of this investigation are depicted in Scheme 5.




**Scheme 5** Aldol reactions of ribose to different acetoacetic esters **2b–f**. Reaction conditions: 1 mmol carbohydrate, 1.5 mmol ethyl acetoacetate **2a**, 20 mol% $i$Pr$_2$NEt, 25 mol% 2-pyridone, 0.5 ml DMSO, rt, 60–96 h. [a]Internal *syn*/*anti* ratio.

These findings indicate that the internal diastereoselectivity is influenced by substituents of the acetoacetic esters deployed. Moreover these results demonstrate that this new transformation can further be extended to 1.3-dicarbonyl compounds.

In summary, we have developed an organocatalyzed aldol addition of unprotected carbohydrates to 1.3-dicarbonyl compounds without using the classical tedious protecting and deprotecting procedure. These investigations show great advantages in terms of time and atom economy. The successful execution of this process is based on a dual activation by tertiary amines and 2-hydroxypyridine. Also, this operationally simple transformation mimics aldolase-catalyzed transformations, which were identified in many biochemical processes. Further optimization and enlargement of this methodology to more general C–C bond formation processes of unprotected carbohydrates are underway.

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## Notes and references

1 For recent reviews in this field see: (*a*) A. K. Samland, M. Rale, G. A. Sprenger and W.-D. Fessner, *ChemBioChem*, 2011, **12**, 1454–1474; (*b*) P. Clapes and W.-D. Fessner, *Stereoselective Synthesis*, Science of Synthesis, Thieme, 2011, vol. 2, pp. 677–734; (*c*) W.-D. Fessner, in *Asymmetric Organic Synthesis with Enzymes*, ed. W.-D. Fessner and T. Anthonsen, Wiley, 2008, pp. 275–318.
2 For recent reviews in this field see: (*a*) R. N. Monrad and R. Madsen, *Tetrahedron*, 2011, **67**, 8825–8850; (*b*) P. Vogel and I. Robina, in *Comprehensive Glycoscience*, ed. J. P. Kamerling, Elsevier, 2007, vol. 1, pp. 261–310.
3 For an overview in this field see: (*a*) R. Mahrwald, *Aldol Reactions*, Springer, 2009; (*b*) M. Markert and R. Mahrwald, *Chem.–Eur. J.*, 2008, **14**, 40–48.
4 M. Markert, M. Mulzer, B. Schetter and R. Mahrwald, *J. Am. Chem. Soc.*, 2007, **129**, 7258–7259.
5 K. Rohr and R. Mahrwald, *Org. Lett.*, 2011, **13**, 1878–1880.
6 Ribose consists in solution at rt of a mixture of furanoid and pyranoid structures of appr. 2/8.
7 K. Rohr and R. Mahrwald, *Adv. Synth. Catal.*, 2008, **350**, 2877–2880.
8 With the sole exception of reaction of 2-acetamido-glyceraldehyde with *tert*-butyloxalacetate: M. Miljkovic and P. Hagel, *Carbohydr. Res.*, 1985, **141**, 213–220.
9 M.-C. Scherrmann, *Top. Curr. Chem.*, 2010, **295**, 1–18.
10 (*a*) P. M. Foley, A. Phimphachanh, E. S. Beach, J. B. Zimmerman and P. T. Anastas, *Green Chem.*, 2011, **13**, 321–332; (*b*) A. Cavezza, C. Boulle, A. Gueguiniat, P. Pichaud, S. Trouille, L. Ricard and M. Dalko-Csiba, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 845–849; (*c*) S. Norsikian, J. Zeitouni, S. Rat, S. Gerard and A. Lubineau, *Carbohydr. Res.*, 2007, **342**, 2716–2728; (*d*) J. Zeitouni, S. Norsikian and A. Lubineau, *Tetrahedron Lett.*, 2004, **45**, 7761–7763; (*e*) Y. Hersant, R. Abou-Jneid, Y. Canac, A. Lubineau, M. Philippe, D. Semeria, X. Radisson and M.-C. Scherrmann, *Carbohydr. Res.*, 2004, **339**, 741–745; (*f*) I. Riemann, M. A. Papadopoulos, M. Knorst and W.-D. Fessner, *Aust. J. Chem.*, 2002, **55**, 147–154; (*g*) F. Rodrigues, Y. Canac and A. Lubineau, *Chem. Commun.*, 2000, 2049–2050.
11 (*a*) B. V. S. Reddy, C. D. Vani, Z. Begum, J. S. Yadav and T. P. Rao, *Synthesis*, 2011, 168–172; (*b*) L. Nagarapu, V. N. Cheemalapati, S. Karnakanti and R. Bantu, *Synthesis*, 2010, 3374–3378.
12 B. Capon, *Chem. Rev.*, 1969, **69**, 407–498.
13 M. Pfaffe and R. Mahrwald, *Org. Lett.*, 2012, **14**, 792–795.
14 (*a*) W. T. Smith and T. L. Hearn, *Bioorg. Chem.*, 1972, **2**, 39–43; (*b*) P. R. Rony, *J. Am. Chem. Soc.*, 1968, **90**, 2824; (*c*) C. G. Swain and J. F. Brown, *J. Am. Chem. Soc.*, 1952, **74**, 2534–2537; (*d*) C. G. Swain and J. F. Brown, *J. Am. Chem. Soc.*, 1952, **74**, 2538–2543.



 