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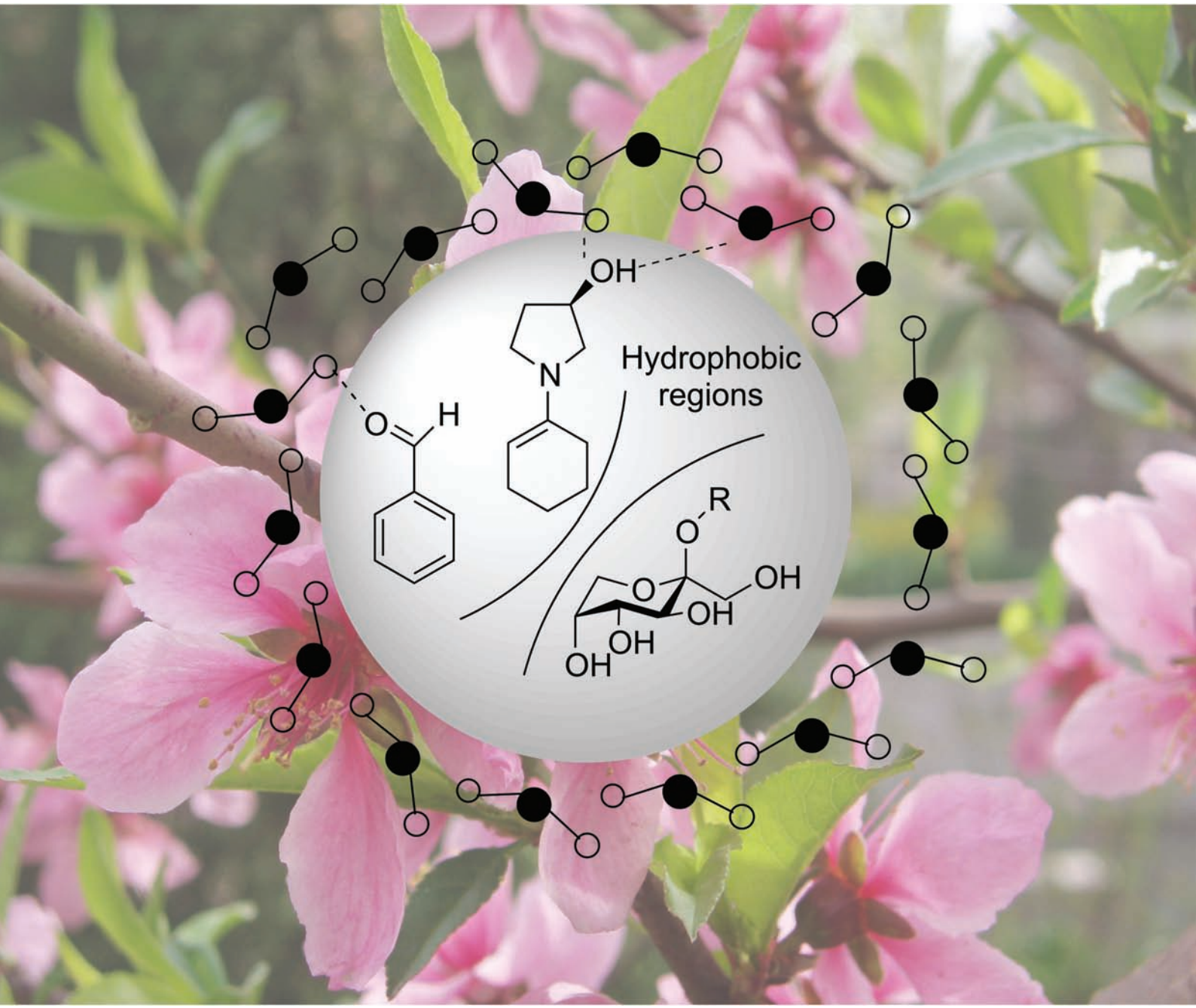

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COMMUNICATION

Aqueous solutions of facial amphiphilic carbohydrates as sustainable media for organocatalyzed direct aldol reactions†

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The organocatalyzed direct aldol reaction was efficiently performed in aqueous solutions of facial amphiphilic carbohydrates with high diastereoselectivity and yield. Such sustainable media in addition with the use of 2% catalyst loading paves the way for the development of original ecofriendly procedures through non-covalent induction.

Introduction

The aldol reaction is one of the most powerful methods of forming carbon–carbon bonds and has tremendous synthetic applications.[1] Biological systems have perfected this stereospecific transformation by using enzymes: type I aldolases function *via* the formation of an enamine intermediate with a lysine residue whereas type II aldolases activate substrates by forming a zinc enolate. Despite their lack of large-scale compatibility and their narrow substrate specificity, aldolases represent a great source of inspiration for the development of catalysts. For example, catalytic antibodies have already been demonstrated to be useful tools in organic chemistry.[2] Seminal works of List, Lerner and Barbas have also proved that small molecules like L-proline are able to act as enamine-based aldol catalysts whose simplicity contrast with the complex machinery of enzymes.[3] However, even if these asymmetric reactions are efficiently performed using both metal- and organocatalysts in organic solvents, similar transformations in water generally require the use of additives or co-solvents, or are just impossible to perform.[4]

As an alternative to the *de novo* design of water-compatible catalysts,[5] we wish to develop environmentally friendly, efficient and stereoselective protocols based on aqueous solutions of sustainable natural products. Especially, inexpensive carbohydrates like sucrose **1** or alkyl β-D-fructopyranosides **2**[6] exhibiting facial amphiphilic characters, *i.e.* their pyranoside ring displaying both a hydrophilic face and a hydrophobic region (Fig. 1), have already demonstrated their potency in selectively promoting reductions, epoxidations and indium-promoted allylations.[7] Faster reactions as well as better solubility of the organic reactants were also observed. Thus, such original media may constitute alternative solvents for the development of sustainable chemistry.

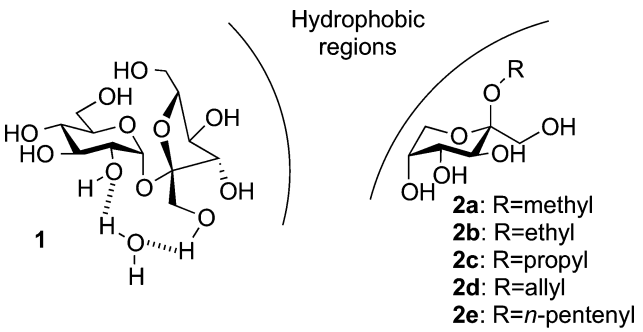

Fig. 1 Structure and hydrophobic areas of facial amphiphilic carbohydrates **1–2**.

Herein we wish to report our findings concerning the mild and stereoselective direct aldol reaction of cyclic ketones in aqueous carbohydrate solutions. Small organic catalysts were selected considering the formation of an enamine intermediate, resembling the mechanistic pathway followed by L-proline and its analogues.[8] It is noteworthy that as previous experiments have shown the low potency of carbohydrates to orientate cyclic ketones in water,[7c] we envisioned that sugars may still be involved in the transition state, diminishing contacts with bulk water[9] and allowing the orientation of the assumed enamine-incoming aldehyde intermediate, thus influencing the stereochemical outcome of the reaction.

Results and discussion

The direct aldol reaction of cyclohexanone (5 equiv.) and *m*-nitrobenzaldehyde (1 equiv.) in 1 M aqueous solution of ethyl β-D-fructopyranoside **2b** was chosen as a model (Table 1). Initial screenings were focused on the catalytic efficiency of commercially available bases and their influence on the diastereoselectivity. Furthermore, fixed catalyst loadings of 2 mol%

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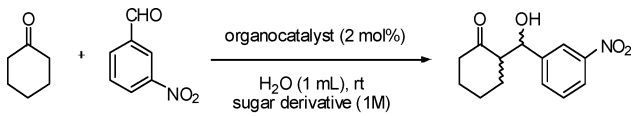
Table 1 Screening of organocatalysts for the direct aldol reaction of cyclohexanone



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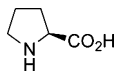
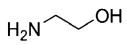
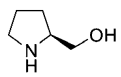
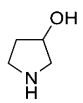
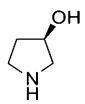
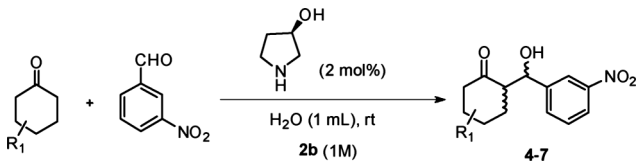
Entry	Organocatalyst	Additive	Time (h)	Yield (%)[a]	*anti*/*syn*	*ee*[b] (%)
1		—	96	No reaction	—	—
2		—	36	90	1.1 : 1	<5
3		**2b**	36	87	1.4 : 1	<5
4		—	1.5	85	1 : 1.3	<5
5		**2b**	1.0	86	1.9 : 1	<5
6		—	72	77	3 : 1	<5
7		**2b**	72	65	2.6 : 1	<5
8		—	2.5	88	3 : 1	<5
9		**2b**	1.5	73	9 : 1	<5
10		—	4	90	3 : 1	<5
11		**2b**	3	91	13.3 : 1	<5
12		**1**	2.5	88	7.3 : 1	<5

[a] Combined yield of isolated diastereoisomers. [b] Determined through ^{1}H NMR experiments in the presence of Eu.

were used. As expected, L-proline was completely inefficient for catalysing aldolisation in water (entry 1).[10] Ethanolamine, a mimic of the lysine side chain, afforded compound **3** in nearly 90% yield (entries 2–3) but with long reaction times and expected poor selectivities. The use of pyrrolidine as catalyst showed better results (entries 4–5), enabling the completion of the reaction in about 1 h. For the first time, **2b** was able to influence significantly the *syn*/*anti* ratio, which increased to 1.9 : 1. L-Prolinol (entries 6–7) exhibited low reactivity and similar 3 : 1 diastereoselectivities whether the sugar additive was present or not. The existence of steric hindrance at position 2 of the pyrrolidine, thus slowing down the formation of the enamine intermediate, easily explained these observations. 3-Hydroxy-pyrrolidine systems showed improved catalytic effects (entries 8–12). *rac*-3-Pyrrolidinol was a good catalyst (entries 8–9) generating the aldol product **3** in around 2 h and good yields. In this case, the presence of **2b** unambiguously influenced the stereochemical outcome of the reaction as the *anti*/*syn* ratio was increased three times (entry 9 compared to 8). The system (*R*)-3-pyrrolidinol/**2b** was the best as compound **3** was obtained in 91% yield, after just 3 h of reaction and with the best 13.3 : 1 observed diastereoselectivity (entry 11), 4.4 times greater than without the sugar additive. Under these conditions, we were able to decrease the amount of cyclohexanone to 1.5 equiv. without compromising the yield and reaction time (87%, 3.5 h). Sucrose, a naturally occurring raw material, rendered **3** in short time and 88% yield but, with an *anti*/*syn* ratio of 7.3 : 1, demonstrating a slightly lower impact on diastereoselectivity (entry 12). Finally, it is also noteworthy that the racemic or enantiopure pyrrolidinol as well as the other organocatalysts tested in this study demonstrated no effect on the enantioselectivity. Still, our results clearly showed that the presence of a polar substituent on the pyrrolidine was crucial i) to generate sufficient facial amphiphilicity in the enamine intermediate, ii) to favour its orientation in the media, and iii) to increase the diastereoselectivity.

The scope of the organocatalytic system was then evaluated with racemic cyclohexanones. As depicted in Table 2, the current method allowed us to obtain aldol products **4–7** *via* the formation of the less substituted or sterically encumbered enamine. Substituted ketone at position 2 (entries 1–2) rendered **4** with low yields and no selectivity, due to its poor reactivity as emphasized by the recovery of 30% of unreacted aldehyde and the long reaction times, even at 65 °C. 3- And 4-methylcyclohexanones were also able to serve as donors (entries 3–6) leading to compounds **5** and **6** in around 90% yields. Moreover, it is of utmost interest that in the presence of **2b**, faster reactions as well as better diastereoselectivities up to 5 : 1 were also observed (entry 4 compared to 3 and 6 to 5). Finally, the 2,2-dimethyl-(*S*)-3-hydroxy-cyclohexanone despite good yields showed no improvement on the ratio of the *anti*/*syn* aldol product **7** (entry 8 compared to 7). However, in these latter cases, a temperature

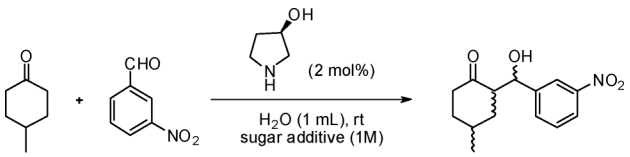
Table 2 Organocatalyzed direct aldol reaction of substituted cyclohexanones in water



Entry	R_1	Product	Additive	Time (h)	Yield (%)[a]	*anti*/*syn*	*ee*[c] (%)
1	2-OMe[b]	**4**	—	72	55	1.1 : 1	<5
2			**2b**	72	30	1 : 1.1	<5
3	3-Me	**5**	—	18	93	1.3 : 1	<5
4			**2b**	12	95	5.7 : 1	<5
5	4-Me	**6**	—	24	82	1.4 : 1	<5
6			**2b**	6	90	4.3 : 1	<5
7	2,2-Me-(*S*)-3-OH[b]	**7**	—	24	75	1 : 1.3	<5
8			**2b**	18	93	1 : 1.3	<5

[a] Combined yield of isolated diastereoisomers. [b] Reactions performed at 65 °C. [c] Determined by ^{1}H NMR experiments in the presence of Eu.

Table 3 Influence of the carbohydrate



Entry	Additive	Time (h)	Yield (%)[a]	*anti*/*syn*	*anti* ratio	*syn* ratio
1	**2a**	20	50	2.6 : 1	4.9 : 1	1 : 2.6
2	**2b**	6	90	4.3 : 1	9 : 1	nd
3	**2c**	10	70	2.7 : 1	7.3 : 1	nd
4	**2d**	18	90	1.9 : 1	4 : 1	1 : 2.7
5	**2e**	8	84	4 : 1	5.7 : 1	1 : 2.1

[a] Combined yield of isolated diastereoisomers.

of 65 °C was needed for the reaction to occur. Once again, these results demonstrated that the reaction is very sensitive to hindered substrates at position 2, which might slow down the formation of the enamine intermediate.

Finally, we turned our attention to the study of the influence of the nature of the sugar additive on the aldolisation using 4-methyl-cyclohexanone (Table 3). Interestingly, all of them were able to induce diastereoselectivity but at different levels. As expected, methyl β-D-fructopyranoside **2a** (entry 1), displaying the lowest facial amphiphilicity, was found to form **6** in only moderate yield as well as long reaction time. The best result was obtained in the presence of **2b** (entry 2) with 90% of yield in 6 h and an *anti*/*syn* ratio of 4.3 : 1. The *n*-pentenyl derivative **2e** (entry 5) showed similar properties with a ratio of 4 : 1 for the *anti* aldol products. The reaction with propyl derivative **2c** and allyl sugar additive **2d** (entries 3 and 4) proceeded with satisfactory yields but with decreased diastereoselectivity. In addition, in all cases, *syn* ratios of diastereoisomers were similar as opposed to *anti* ratios for which diastereoselectivity depends on the sugar additive and follows the same trend as for the *syn*/*anti* ratio (two last columns in Table 3). Finally, it should be pointed that higher yields and improved *anti*/*syn* ratio were obtained with respect to the decrease in reaction time.

The rationalization of the observed selectivity in correlation with the type of glycosidic chains is tenuous but might be the consequence of hydrophobic interactions in the transition state. ^{1}H NMR experiments were performed in order to demonstrate the presence of these latter (see ESI†). The addition of increased amounts of cyclohexanone to the allyl sugar derivative **2d** caused a significant perturbation of the signals corresponding to the allyl group that was more pronounced in the presence of the catalyst. Thus, the facial amphiphilic carbohydrate seems to interact more with the transient enamine-incoming aldehyde intermediate (Fig. 2) and favour the *anti* aldol product.

Conclusion

In summary, the direct aldol reaction of *m*-nitrobenzaldehyde with various cyclohexanones has been accomplished by organocatalysis, using only 2 mol% of (*R*)-3-pyrrolidinol in aqueous solutions of alkyl β-D-fructopyranosides with excellent yields, short reaction times and improved diastereoselectivities up to 13 : 1. It represents a "green" alternative to previously described diastereoselective procedures implied in natural product synthesis.[11] Therefore, such sugar additives turn out to be a promising approach to control the selectivity, probably by

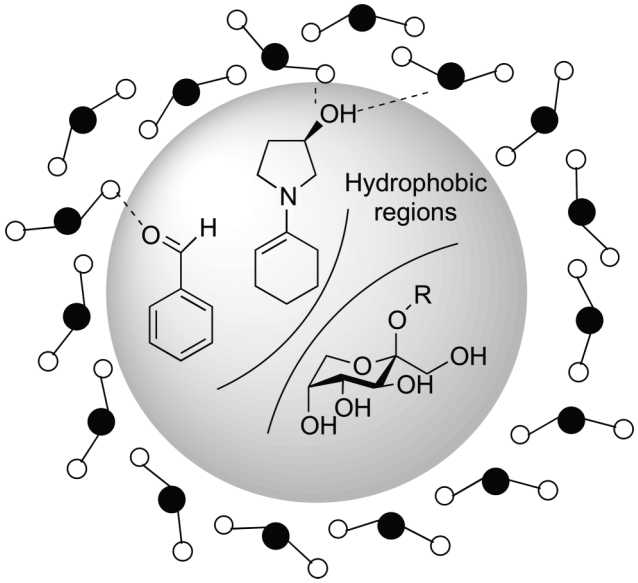


Fig. 2 Proposed intermediate for the direct aldol reaction in the presence of an aqueous solution of amphiphilic carbohydrate **2**.

mimicking an enzyme's sequestration of intermediates away from bulk water. Such sustainable media pave the way to the further development of organic reactions by non-covalent induction in water and will benefit from a better understanding of the hydrophobic interactions.[12] Works towards the generation of amphiphilic sugar additives able to induce enantioselectivity are actually under progress.

General procedure

A mixture of 3-nitrobenzaldehyde (75.8 mg, 0.50 mmol), ketone (2.50 mmol), the catalyst (2 mol%) with or without the sugar derivative (1.0 M) was stirred vigorously at RT in water (1.0 mL). Then, the reaction mixture was quenched by adding saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2 several times. The combined organic layers were dried with $MgSO_4$, concentrated, and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 3/1) to give the aldol products (**3–7**) as yellow oils.

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