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PAPER

Simple and practical direct asymmetric aldol reaction of hydroxyacetone catalyzed by 9-amino *Cinchona* alkaloid tartrates†‡

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A novel organocatalytic procedure for the direct aldol reaction of unprotected acetol and activated aromatic aldehydes catalyzed by 9-amino-9-*epi*-*Cinchona* ditartrates is presented. The protocol presented avoids the use of problematic solvents and toxic reagents as well as chromatographic purification of the products – instead a simple extraction has been applied for the isolation of pure aldols from the reaction mixture. This catalytic system provides exclusively linear aldols with quantitative yields and good *syn*-diastereoselectivity and enantioselectvitiy up to 90% ee. Further upgrading of the enantiomeric excess of *syn*-aldols up to 99% ee is easily accomplished by a single and reliable crystallization. The use of cinchonine or quinine-derived catalysts gives access to both enantiomers of *syn*-aldols for which the absolute configuration has been determined by X-ray diffraction. The operationally convenient and scalable organocatalytic procedure using cheap and renewable chemicals – both acetol and the catalysts, offers a sustainable and green way for the synthesis of a number of α-keto-*syn*-diols.

Introduction

Catalytic enantioselective synthesis mediated by metal complexes, organocatalysts or enzymes contributed to a revolutionary progress in synthetic methodology, providing access to a broad range of enantiopure products from almost all types of reactions.[1]

The aldol addition leading to non-racemic *β*-hydroxyketones, *β*-hydroxyaldehydes, keto-1,2-diols and related products deserves special attention as one of the most important and straightforward methods of carbon–carbon bond formation in a stereoselective fashion.[2] The aldol addition occurring in water and at ambient temperature apparently has been selected by Nature for the extremely efficient synthesis of a wide array of sugars, ketoacids and other derivatives from very simple achiral building blocks like hydroxyacetone, dihydroxyacetone[3] and other simple carbonyl compounds.[4] Aldol additions in living organisms are catalyzed by aldolases which can be divided into two classes: aldolase I and II, depending on the mechanism of activation of the reactants and the reaction pathway. Class I aldolases work according to an imine-enamine mechanism, due to the presence of the primary amino group of Lys in the active cavity of the enzyme.[5] Class II aldolases are metaloenzymes in which the zinc-histidine complex activates the donor molecule by coordination.[6] For a long time the high efficiency of aldolases, regarding the selectivity and activity as well as the operating parameters (room temperature, water as a medium) has not been reached by their synthetic low-molecular weight mimics ("microaldolases") designed in the laboratory.[2] Another problem associated with early attempts to develop competitive aldol promoting systems was the necessity of preactivation of at least one of the reacting partners by formation of an enolate from the carbonyl donor, thus lowering the overall economy of such processes.[2e–d] The problems of selectivity and activity have partially been solved upon the recent introduction of catalytic systems mimicking aldolases I or II working by dual activation of substrates (bifunctional catalysis).[7] The most exciting examples of such catalytic systems were demonstrated by Shibasaki,[8] Trost,[2a,9] List,[10,24] Barbas[10,11] and others.[12,13]

Unfortunately, in the process of developing efficient and direct stereoselective aldol addition methodologies the practical and environmental aspects were largely overlooked. For this reason many catalytic aldol addition protocols were demonstrated only in mmol scale and appear impractical for large scale synthesis. For example, in order to obtain a high yield and a high level of asymmetric induction, a substantial amount of catalyst (often 20–30 mol%) is required. With the exception of natural proline and *Cinchona* alkaloids, most of the catalysts are non-commercial products of multi-step syntheses. In addition, many protocols use large amounts of co-catalysts or additives,

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‡ Dedicated to Professor Janusz Jurczak on the occasion of his 70th birthday.

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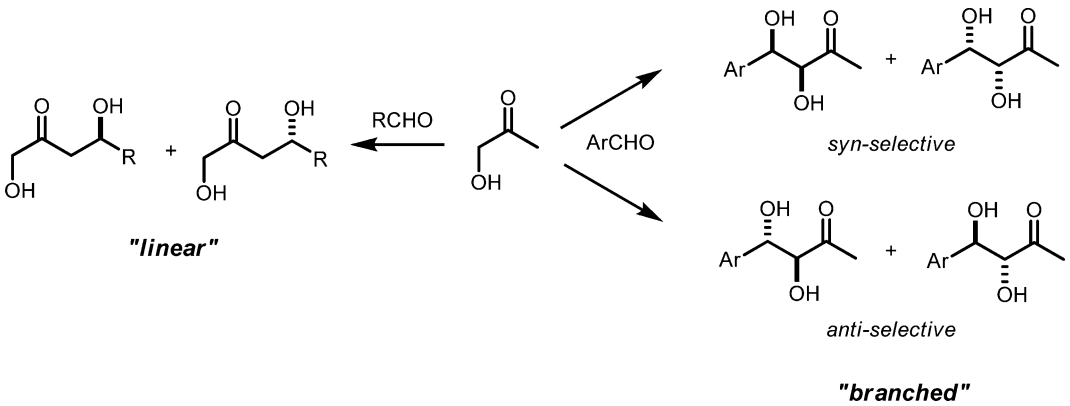

Scheme 1 Different activation pathways of hydroxyacetone (acetol) as a donor in the aldol addition.

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such as toxic and corrosive trifluoroacetic acid,[18,23] 1*H*-1,2,3-triazole or other rare heterocycles,[11a] 2,4-dinitrophenol[15] or metal salts.[2a,10,18] This increases the cost of the reaction and causes environmental problems associated with product separation and waste disposal on a large scale. Another drawback of many stereoselective aldol reactions is the use of anhydrous or environmentally problematic solvents, such as chlorinated hydrocarbons, DMSO, DMF or *N*-methylpyrolidone (NMP)[26] as well as column chromatography for products purification.

We took these limitations into consideration when we started the project on the green organocatalytic aldol reaction[27] of acetol (hydroxyacetone). Acetol is an important substrate for the aldol reaction which, depending on the catalytic system or the conditions, may generate two diastereomeric types of branched ketodiols or one type of a linear ketodiol. Thus potentially up to three pairs of distinct enantiomeric aldols can be obtained in one step (Scheme 1).

Moreover hydroxyacetone is a cheap product of partial hydrogenolysis of glycerol and is currently available in large quantities from the oleochemical/biofuel industry.[14] For this reason its conversion into high value chiral products offers a source of intermediates for asymmetric synthesis. Acetol also meets the green chemistry requirements – it is non-toxic, biodegradable and as a liquid it may serve simultaneously as a polar solvent in the reaction.

Unprotected hydroxyacetone has already been explored as a donor in the stereoselective aldol reaction although due to the need of simultaneous control of chemo-, enantio- and diastereoselectivity its use created problems and therefore it was less explored than other simple carbonyl donors.[2a] Most of the catalysts used for the aldol reaction of acetol have so far been based on the structures of aminoacids (proline) and their derivatives or on peptides. These catalysts often show insufficient control of reaction selectivity.[2] However List and Barbas reported examples of more efficient highly *anti*-selective reactions of hydroxyacetone with either aromatic or aliphatic aldehydes, catalyzed either by proline or by 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC).[10,11f] Another example of an *anti*-selective reaction has been published by Wu *et al.* and it involves the use of a tetrapeptide – (*S*)-BINOL complex as a catalytic system.[15] Efficient *syn*-selective aldol reactions of acetol and aliphatic aldehydes catalyzed by modified dipeptides has been reported by Wu.[16] Non-peptide catalysts, such as a monoprotected *trans*-(1*S*,2*S*)-diaminocyclohexane derivative designed by Singh,[17] primary-tertiary amine salts derived form aminoacids by Cheng[18] or pyrrolidinecarboxylic acid by Wu[19] showed high enantio- and *syn*-diastereoselectivity in the aldol or Mannich reaction of acetol and activated aromatic aldehydes. Linear products of the aldol reaction of acetol due to activation of the methyl group have been selectively obtained by using a tetrapeptide (Pro-Phe-Phe-Phe-OMe) or prolinamide catalysts, as reported by Gong *et al.*[20]

Interestingly, *Cinchona* alkaloids which belong to the group of "privileged catalysts" and promote a wide array of reactions, were not studied intensively in stereoselective aldol additions.[21] Only recently Młynarski *et al.* reported that quinine or quinidine catalyze the aldol reaction of acetol and aromatic aldehydes, albeit with modest yield and an asymmetric induction level.[22] Better results were obtained by Marhwald who used cinchonine as a catalyst for the stereoselective aldol reaction of protected (*R*)-glyceraldehyde with dihydroxyacetone leading to D-fructopyranose with >98% ee.[23]

Despite many successful applications in other stereoselective syntheses, 9-amino derivatives of *Cinchona* alkaloids which form a primary-tertiary amine catalytic system, have not been systematically tested in the area of aldol addition. Recently Liu *et al.* have shown that *in situ* generated 9-amino-9-epicinchoninium trifluoroacetate catalyzes *anti*-selective addition of aromatic aldehydes to cyclohexanone with high yield and enantiomeric excess (up to 99%).[24] Analogous primary amines derived from quinine and quinidine have been used by List in an intramolecular aldolization of substituted 1,5-diketone in the asymmetric synthesis of both enantiomers of the fragrant celery ketone.[25] Recently, Xiao has shown that the cinchonine-prolinamide hybrid is able to promote an aldol reaction of activated aldehydes with acetone with high enantioselectivity up to 98% ee.[26]

In the present work we describe the use of 9-amino-9-*epi*-*Cinchona* alkaloid ditartrates as new organocatalysts, designed for the direct aldol reaction of acetol and aromatic aldehydes without the use of solvent. The focus of this methodology is on providing an efficient, scalable, operationally simple and environmentally friendly aldol protocol, utilizing the renewable feedstock – acetol – and *Cinchona* alkaloid derivatives as organocatalysts.

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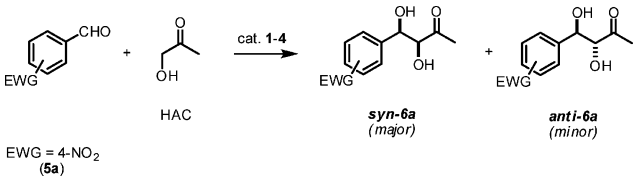
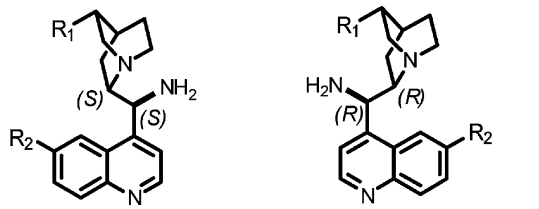
Results and discussion

For initial screening experiments a model system comprising of technical hydroxyacetone (1 mL) and *p*-nitrobenzaldehyde (0.5 mmol) leading to *syn*- and *anti*-aldols **6a** has been selected (Scheme 2). 9-Amino-9-*epi*-*Cinchona* derivatives which have been used as organocatalysts **1–4** (Fig. 1) were obtained in the form of trihydrochlorides in the Mitsunobu/Staudinger one-pot sequence of reactions from the corresponding *Cinchona* alkaloids.[28]



Scheme 2 Model aldol reaction of acetol and *p*-nitrobenzaldehyde.



1a (AeQN)
R_1 = *vinyl*, R_2 = OMe

1b (AeDDQN)
R_1 = *ethynyl*, R_2 = OMe

2 (AeCD)
R_1 = *vinyl*, R_2 = H

3 (AeQD)
R_1 = *vinyl*, R_2 = OMe

4a (AeCN)
R_1 = *vinyl*, R_2 = H

4b (AeDCH)
R_1 = *ethyl*, R_2 = H

Fig. 1 Structures of 9-amino-9-*epi*-*Cinchona* alkaloids used as catalysts **1–4**.

A simple salt such as 9-amino-9-epiquininium trihydrochloride **1a** × 3HCl (10% mol) used in a model reaction with acetol serving as the solvent produced only a low level of conversion (29%) of the aldehyde and gave a nearly racemic mixture of aldols **6a**, slightly favoring *syn*-**6a** (dr *syn*/*anti* 1.4 : 1). The use of the same catalyst in a 1 : 1 water–methanol mixture led to a slightly higher yield (33%) and a raise in enantioselectivity of *syn*-**6a**, up to 66% (dr *syn*/*anti* 1.8 : 1) (Table 1, runs 1, 2). These disappointing results shifted our interest to the organic salts of *Cinchona* amines. We tested a large number of combinations of 9-amino-9-epiquinine or 9-amino-9-epicinchonine and organic acids as additives. The respective salts having different ratios of amine and acid have been generated *in situ* by addition of an acid to the amine followed by addition of the substrates. The results are presented in Table 1. We have found that the most promising results were obtained for the combination of 10 mol% of *Cinchona* amines and trifluoroacetic acid in a ratio 1 : 2, giving quantitative conversion of *p*-nitrobenzaldehyde after 24 h at room temperature and providing the corresponding aldol *syn*-**6a** having 78% ee (dr *syn*/*anti* 2.5 : 1). Interestingly, nearly identical results were obtained when the same amine was combined with natural (*R*,*R*)-tartaric acid (TA) as an additive.[29] For example, the addition of 10 mol% of 9-amino-9-epicinchonine ditartrate as a catalyst gave quantitative yield of the aldols after 48 h at room temperature and *syn*-**6a** was formed with the same (78% ee) enantiomeric excess and only slightly lower dr 2.4 : 1 (*syn*/*anti*). It is worth noting that this catalyst also gave the highest induction level of diastereoisomeric *anti*-**6a** (51% ee). As expected, the use of pseudoenantiomeric 9-amino-9-epiquinine (*R*,*R*)-ditartrate salt gave predominantly the opposite enantiomer of *syn*-**6a** having 70% ee and dr 1.9 : 1 (*syn*/*anti*) with quantitative yield. In contrast to trifluoroacetic acid which is volatile, toxic, highly corrosive and expensive, natural tartaric acid is cheap, available from renewable sources and non-toxic. For this reason we have chosen natural tartaric acid as an acidic additive for further work. To make the protocol more practical, solid ditartrates of 9-amino *Cinchona* alkaloids have been obtained by dissolving the respective amines and two equivalents of tartaric acid in methanol and evaporation of the solvent. These solid salts are stable and easy to handle and they have been used in further experiments with exactly the same results as obtained with the salts generated *in situ*.[30] Other acidic additives, such as benzoic, succinic and (*S*)-malic acids have also been tested and although similarly high conversion of the aldehyde (about 100%) has been observed, the asymmetric

Table 1 Screening the acidic additives in the model reaction

				Product				
Run	Cat.[a]	Acid (eq.)[b]	Solvent	Time (h)	Yield **6a** (%)	ee (%) *anti*-**6a**	ee (%) *syn*-**6a**	dr (*anti*/*syn*)
1	**1a**	HCl (3)	HAC	48	29	5	6	1 : 1.4
2	**1a**	HCl (3)	MeOH/H_2O (1 : 1)	48	33	6	66	1 : 1.8
3	**4a**	**TFA** (2)	HCA	24	**100**	**43**	**78**	**1 : 2.5**
4	**4a**	(*R*,*R*)-TA (1)	HAC	48	100	51	72	1 : 2.1
5	**4a**	**(*R*,*R*)-TA** (2)	HAC	48	**100**	**51**	**78**	**1 : 2.4**
6	**4a**	(*R*,*R*)-TA (5)	HAC	48	93	44	76	1 : 2.0
7	**4a**	(*R*,*R*)-TA (10)	HAC	48	94	36	75	1 : 1.8
8	**1a**	(*R*,*R*)-TA (2)	HCA	48	100	36	70	1 : 1.9
9	**1a**	BA (2)	HCA	48	100	17	52	1 : 2.1
10	**1a**	(*S*)-MA (2)	HCA	48	100	34	71	1 : 2.3
11	**1a**	SA (2)	HCA	48	100	26	65	1 : 2.1
12	**1a**	DNP (2)	HCA	48	93	28	73	1 : 2.6

[a] 0.1 eq. of catalysts was used; cat **1a** and **4a** give products of opposite configuration. [b] Equivalents relative to catalyst used; abbreviations: HCA = hydroxyacetone, (*R*,*R*)-TA = (*R*,*R*)-tartaric acid, BA = benzoic acid, (*S*)-MA = (*S*)-malic acid, SA = succinic acid, DNP = 2,4-dinitrophenol.

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Table 2 Effect of water addition in the model reaction catalyzed by 10 mol% **4a** × 2 (*R*,*R*)-TA[a]

Run	Solvent	Product			
		Yield **6a** (%)	ee (%) *anti*-**6a**	ee (%) *syn*-**6a**	dr (*anti*/*syn*)
1[b]	HAC	100	51	78	1 : 2.4
2[c]	HAC + 2% H_2O	100	51	76	1 : 2.2
3[c]	HAC + 10% H_2O	100	51	78	1 : 2.3
4[c]	HAC + 50% H_2O	94	38	67	1 : 1.8
5[d]	HAC dried	100	52	83	1 : 3.1

[a] Reaction time 48 h at rt. [b] Technical acetol containing 1.8% water. [c] Technical acetol with water additive specified. [d] Technical acetol dried with anhydrous Na_2SO_4, water content *ca.* 0.5%.

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induction level was lower, compared to TFA or TA salts. The use of 2,4-dinitrophenol as an acid led to aldols with slightly better diastereoselectivity (dr 2.6 : 1 *syn*/*anti*) but with lower conversion (93%). We also checked the effect of the molar ratio of the amine and tartaric acid on the yield and the stereoselectivity of the model aldol reaction (Table 1, runs 4–7). Best results were observed with two equivalents of (*R*,*R*)-TA per one equivalent of the amine, although the monotartrate salt gave a very similar result with only a slightly lower asymmetric induction level (run 4). The use of a large excess of (*R*,*R*)-TA (5 or 10 eq.) did not result in a further increase of stereoselectivity.

Next step in the optimization of experimental procedure involved the investigation of the role of water as an additive or a co-solvent. The water content in technical acetol was found by the Karl-Fisher titration at the level 1.8%. In these set of experiments we added increasing amounts of water, up to 50% v/v. As can be seen in Table 2 water content in the range from 1.8% (technical acetol) up to 10% v/v had a moderate effect on the yield and the level of asymmetric induction in the model reaction. Continuous increase of the water content up to 50% v/v resulted in lowering both the conversion and the level of asymmetric induction. Thus, low water concentration seems to be optimal in order to obtain the highest level of asymmetric induction and the yield. To check this hypothesis we dried chemically acetol (by the use of anhydrous Na_2SO_4 for 12 h, <0.5% H_2O) and under similar reaction conditions we observed only a slight increase of enantioselectivity of the reaction, providing *syn*-**6a** with 83% ee and reaction diastereoselectivity of 3.1 : 1 (*syn*/*anti*).

Although acetol served both as a donor and as a solvent in the model reaction with good efficiency, we also tested other solvents to possibly identify a better reaction medium. The results of these experiments are shown in Table 3. As it can be seen from the data, none of the solvents screened offered a better reaction selectivity as compared to acetol itself. The only comparable results regarding asymmetric induction level were obtained for methanol but this solvent significantly compromised the overall yield. Less polar solvents, such as dichloromethane or THF, showed very low reagent conversion and lower selectivity.

The subsequent optimization of our protocol has been carried out by screening the catalytic performance of all four major members of *Cinchona* amines (**1**–**4**) as well as by subtle tuning of their structures involving the replacement of the pendant vinyl group by the ethynyl (catalyst **1b**) or the ethyl group (catalyst **4b**). The results of these experiments are presented in Table 4. As expected, two pseudoenantiomeric pairs of amines (**1**, **2** *vs.* **3**, **4**) gave the corresponding main diastereoisomers of the aldols having opposite absolute configuration. We have also found that the best catalysts are those lacking the methoxy group in the quinoline ring (derived from cinchonine or cinchonidine). For example, quinidine derived amine **3** and its demetoxylated analogue **4a** (cinchonine) led to *syn*-**6a** with

Table 4 Catalysts screening in model reaction[a]

Run	Cat.[b]	Product			
		Yield **6a** (%)	ee (%) *anti*-**6a**	ee (%) *syn*-**6a**	dr (*anti*/*syn*)
1	**1a**	100	36	70	1 : 1.9
2	**1b**	100	30	72	1 : 2.4
3	**2**	100	40	76	1 : 2.0
4	**3**	92	23	66	1 : 2.2
5	**4a**	100	51	78	1.2.4
6	**4b**	100	53	75	1 : 2.2

[a] Reaction in HAC, 48 h at rt. [b] 0.1 eq. of catalysts was used in the form of (*R*,*R*)-ditartrate salt.

Table 3 Solvent effect on model reaction catalyzed by 10 mol% **4a** × 2 (*R*,*R*)-TA[a]

Run	Solvent	Product			
		Yield **6a** (%)	ee (%) *anti*-**6a**	ee (%) *syn*-**6a**	dr (*anti*/*syn*)
1	HAC	100	51	78	1 : 2.4
2	MeOH	75	22	75	1 : 2.8
3	MeOH–H_2O (1 : 1)	57	32	68	1 : 1.9
4	H_2O–MeOH (95 : 5)	43	16	61	1 : 1.6
5	THF	31	3	57	1 : 2.1
6	DCM	21	19	56	1 : 2.0

[a] Reaction time 48 h at rt.

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Table 5 Temperature effect on the model reaction catalyzed by 10 mol% **4a** × 2 (*R*,*R*)-TA

Run	Temp. (°C)	Solvent	Time (d)	Product			
				Yield **6a** (%)	ee (%) *anti*-**6a**	ee (%) *syn*-**6a**	dr (*anti*/*syn*)
1	25	HAC	2	100	51	78	1 : 2.4
2	0	HAC	5	100	61	82	1 : 2.1
3	–20	HAC/MeOH (2 : 1)	7	74	61	90	1 : 2.5

66 and 78% ee, respectively. Interestingly, the use of a more basic 10,11-dehydroquinine amine **1b** masks the unfavorable effect of the methoxy substituent leading eventually to a higher asymmetric induction level in the formation of *syn*-**6a** (run 1 *vs.* 2, Table 4). The ethyl analogue **4b** of cinchonine derived amine showed comparable catalytic efficiency in the model reaction. Attempts to reduce the catalyst load from 10 to 5 and to 2 mol% showed that at lower catalyst concentration the raction rate was considerably lower giving **6a** with only 50 and 30% yield, respectively. However the enantioselectivity remained at a comparable level 66–71% ee.[31]

Having at hand the optimized protocol giving quantitative yield of the aldol products **6a** we attempted to upgrade the asymmetric induction level by lowering the reaction temperature. Two reactions catalyzed by 10 mol% of **4a** ditartrate salt have been conducted at 0 and –20 °C. In the latter case 30% (v/v) of methanol was added as antifreezing co-solvent. In both cases, enhancement of the enantioselectivity was observed with respect to either *syn*-**6a** or *anti*-**6a** aldols, which was more substantial in the reaction carried out at –20 °C (Table 5). In this case *syn*-**6a** and *anti*-**6a** have been obtained with 90% and 61% ee, respectively. Unfortunately, the rate of the reaction at –20 °C was significantly lower, resulting in a 74% yield of the isolated product after seven days of continuous process.

Finally, we investigated the scope of the aldol reaction catalyzed by *Cinchona* amine ditartrate with respect to the aldehyde acceptors. As it is evidenced in Table 6 the reaction proceeded well with activated aromatic aldehydes bearing an electron-withdrawing substituent such as the nitro group or the halogen atom (**5b–e**). The halogen substituted aldehydes are less active and require significantly longer reaction times. The aldol addition is not affected by any substitution pattern as either *ortho*-, *meta*- or *para*-nitroaldehydes underwent the reaction with comparable efficiency. However, a notable exception was observed for 2-nitrobenzaldehyde which gave the corresponding aldol **6b** with substantially higher diastereoselectivity 8.7 : 1 (*syn*/*anti*). This behavior can be explained on the basis of an additional stabilization of the transition state by hydrogen bond formation between the 2-nitro group of the aldehyde and the hydroxy groups of acetol, leading to the *syn*-product (*vide infra*). Unfortunately, benzaldehyde reacted sluggishly giving only traces of the corresponding aldols **6f**.

Having at hand the catalysts providing aldol product with nearly quantitative yield, reasonable enantioselectivity and rather poor diastereselectivity we tried to develop a protocol allowing easy isolation and to upgrade the enantiomeric excess of the desired *syn*-aldols in a simple (preferably non-chromatographic) way. The first goal has been easily achieved by simple extraction of the reaction mixture with ethyl acetate–water which separates the aldols from the excess of acetol and the catalyst. We found that triple extraction of the reaction mixture led to the quantitative separation of aldol products **6a–e**, which were obtained as a crystalline mass after evaporation of the solvent. They showed usually >95% purity (TLC, NMR). The enantiomeric excess upgrade of the predominant *syn*-**6a** aldol as well as its separation from the *anti*-diastereomer has been successfully completed by crystallization. We were pleased to find that single crystallization of crude *syn*/*anti*-aldols **6a** from the mixture of ethyl acetate–hexane gave practically enantiopure *syn*-**6a** with 99% ee, which contained only a very minor amount of one of *anti*-**6a** enantiomer (dr ~50 : 1 *syn*/*anti*, Fig. 2). Similarly, opposite enantiomer *ent*,*syn*-**6a** could also be obtained by crystallization of the crude products of the reaction catalyzed by quinine derived catalyst (*ent*,*syn*-**6a** 99% ee, 40 : 1 dr). This methodology has also been tested on a larger scale with the use of 1–5 g of *p*-nitrobenzaldehyde giving a similar level of the ee and dr upgrade and with a typical isolated yield of 35–55%. Similar favorable results have been obtained for *syn*-aldols **6b** and **6c** which had 99.5% and 97% ee, respectively, after single crystallization of the products from a mixture EtOAc–hexane with the yield 40–50%.

Table 6 Other activated aldehydes as substrates[a]

Run	Aldehyde	Time (d)	Yield (%)	ee (%) *anti*	ee (%) *syn*	dr (*anti*/*syn*)
1	2-$NO_2C_6H_4CHO$ (**5b**)	2	100	11	87	1 : 8.7
2	3-$NO_2C_6H_4CHO$ (**5c**)	2	97	54	73	1 : 2.3
3	4-FC_6H_4CHO (**5d**)	2	89	39	72	1 : 1.9
4	4-BrC_6H_4CHO (**5e**)	7	87	33	82	1 : 1
5	PhCHO (**5f**)	7	Trace	nd	nd	nd

[a] Reaction catalyzed by 10 mol% **4a** × 2 (*R*,*R*)-TA, at rt; nd = not determined.

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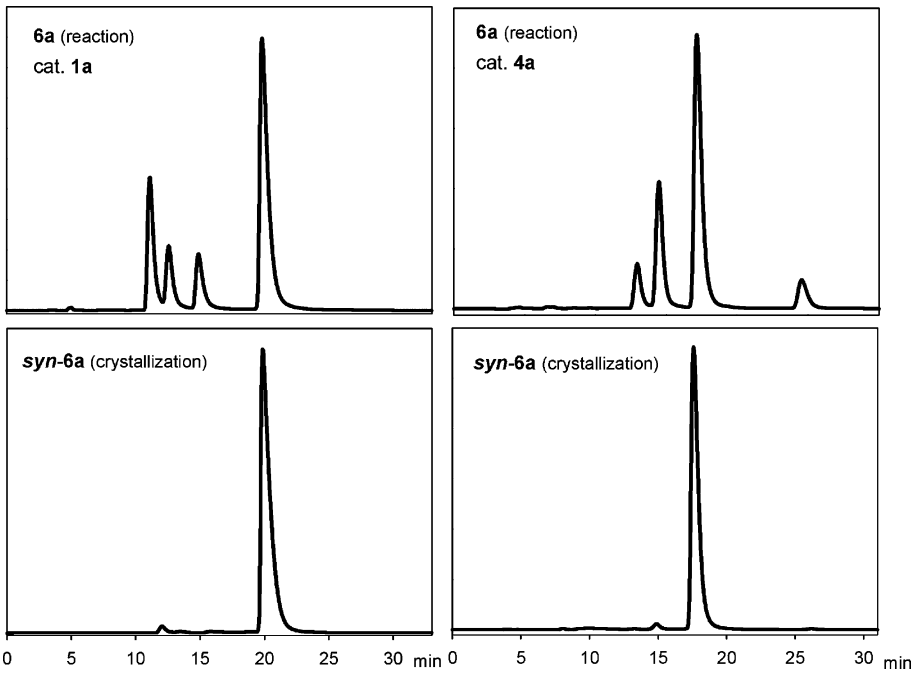

Fig. 2 HPLC data for crude aldols-**6a** obtained by extraction of the reaction mixture (upper panel, left - catalyst **4a**, right - catalyst **1a**) and *syn*-**6a** product obtained after single crystallization from ethyl acetate–hexane.

Proposed model for the stereoselectivity of the reaction

In a number of published papers it is suggested that primary amine organocatalysts work by an iminium-enamine activation of the donor with subsequent attack of an electrophile. In the reaction of acetol (dihydroxyacetone) *syn*- selectivity is usually attributed to the additional stabilization of *Z*-enamine in the transition state by an intramolecular *N–H* ··· *O* hydrogen bond.[11a] The proposed mechanism and the tentative transition state model based on the molecular modeling data are shown in Fig. 3. It is assumed that the primary amino group of the *Cinchona* amine activates the acetol by the formation of *Z*-enamine which has one face hindered by a bulky quinoline ring. On the other hand, the aldehyde group is activated by a hydrogen bond formation with the protonated nitrogen atom of the quinuclidine. The mutual orientation of these two partners force the *syn*-addition direction. Nevertheless, flexibility of the system is responsible for the observed non-perfect enantio- and diastereoselectivity of the reaction.

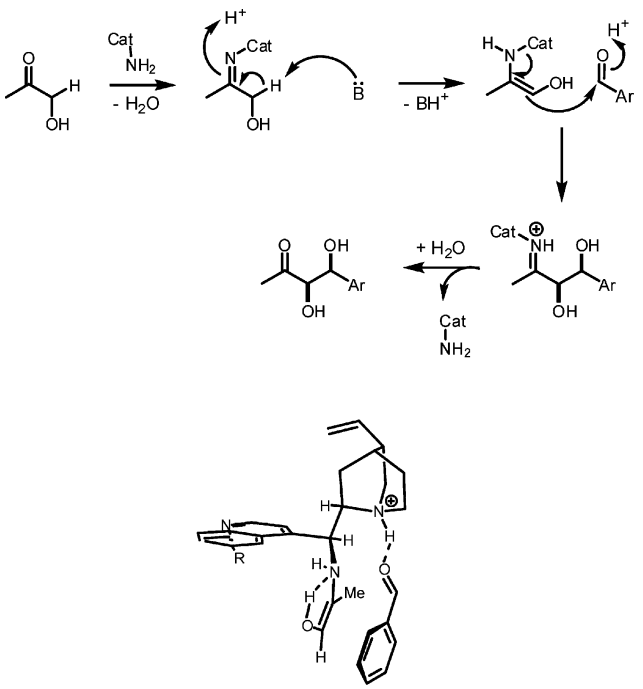

Fig. 3 Proposed stereoselectivity in the aldol reaction.

Absolute configuration of the aldols

In order to confirm the relative[32] and to determine the absolute configuration of the crystalline *syn*-**6a** product, X-ray diffraction method has been applied. Thus, the absolute structure of the crystal of *syn*-**6a** was investigated on the basis of the anomalous signal originating mostly from the O atoms at the Cu-Kα wavelength. For the examined enantiomerically pure crystal, the refined value of Flack *x* was sufficiently small (0.09) to indicate that the assumed absolute structure was correct. However, a slightly greater standard uncertainty (0.16) than the upper limit (0.10) for the enantiopure compounds needed to be confronted by an independent method.[33] Therefore, apart from the conventional Flack parameter, the absolute structure of the crystal was further investigated by the Hooft method[34] implemented within PLATON.[35] From the analysis of 5964 Bijvoet pairs, the Hooft *y* parameter 0.059(23) was found with the probability $p2 = 1.000$, showing that the correct enantiomer has been chosen. Hence, based on the Hooft parameter the absolute configuration of *syn*-**6a** obtained with the use of cinchonine derived catalysts **4a** could be unambiguously determined as 3*S*,4*R* (Fig. 4).

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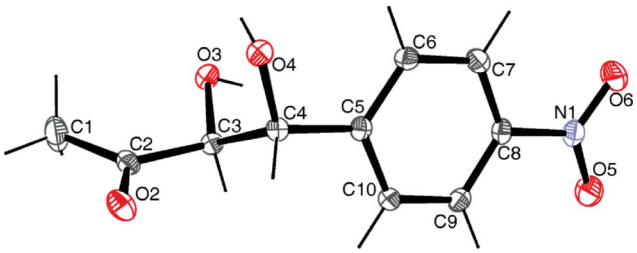

Fig. 4 ORTEP diagram of the molecular structure of *syn*-(3*S*,4*R*)-3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one (*syn*-**6a**) showing the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 40% probability level.

Conclusion

The transformation of inexpensive hydroxyacetone derived from glycerin (available currently in large quantities from the biodiesel industry) into more complex chiral chemicals constitutes a timely and attractive area of current research. Such methodologies, when properly focused on economical and environmental issues, may result in the development of new sustainable organic technologies. Presented here is our attempt to make a more green, practical and scalable direct aldol reaction of acetol and activated aromatic aldehydes catalyzed by 9-amino-9-*epi*-*Cinchona* ditartrates as novel organocatalysts. This organocatalytic system combined with a single crystallization step provides exclusively branched enantiopure (>98% ee) aldols **6a–c** with good yield. Additional benefits of the presented protocol include no need for the use of chromatographic purification of the product, instead simple extraction has been applied for the isolation of pure aldols from the reaction mixture. We believe that this organocatalytic procedure which uses inexpensive and renewable chemicals, both the acetol and the catalysts, and meets the modern criteria of sustainable chemical processes and provides a competitive way to *syn*-aldols.

Experimental section

Typical procedure for the direct asymmetric aldol reaction

Screening (small scale) procedure (catalyst generation *in situ*). In a small vial equipped with a stirring bar 9-amino-9-(deoxy)epicinchonine (**4a**, 14,5 mg, 0.05 mmol, 10 mol%) and (*R*,*R*)-tartaric acid monohydrate (15 mg, 0,1 mmol, 20% mol, or other additives, see Table 1) were added, followed by the addition of methanol (1 mL). After dissolution, the mixture was magnetically stirred for 5 min followed by solvent evaporation. To the resulting salt 75 mg (0.5 mmol, 1 eq.) of 4-nitrobenzaldehyde **5a** (or equivalent amount of other aldehydes **5b–f**) and acetol (1 mL) were added. The resulting solution was stirred typically for 48 h at room temperature after which time quantitative consumption of the activated aldehydes was observed. The reaction mixture was transferred to the separating funnel followed by the addition of EtOAc (5 mL) and water (10 mL). After extraction, the organic phase was separated and the aqueous phase was extracted twice with EtOAc (2 × 5 mL). The organic phases were collected, dried over anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure the crude product was obtained as yellowish crystals. Alternatively, in the case of incomplete aldehyde conversion, the products were separated by flash chromatography using a mixture hexane–EtOAc (10 : 1, aldehyde removal) and then hexane–EtOAc (1 : 1, products). Yields **6a–f** see Table 5.

Large scale procedure (*syn*-6a)

In a 150 mL round-bottom flask equipped with a stirring bar 9-amino-9-(deoxy)epiquinine ditartrate **1a** (2.0 g, 10 mol%) was placed followed by 4-nitrobenzaldehyde (**5a**, 5 g, 1 eq.). The solids were then mixed with acetol (35 mL) resulting in the formation of a homogenous solution within approximately 30 min. The reaction mixture was stirred for 48 h at room temperature after which time quantitative consumption of the aldehyde was observed (TLC). The reaction mixture was transferred to a large separatory funnel, diluted with water (500 mL) and extracted with EtOAc (3 × 50 mL). Combined organic phases were separated and the aqueous phase was additionally extracted twice with EtOAc (2 × 50 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, the crude product was obtained as yellowish crystals. Yield 7.47 g, 100%. Crystallization of the crude product from EtOAc–hexane (see supporting material†) afforded 2.51 g (3*R*,4*S*)-*syn*-**6a** (35%), ee 99%, dr 1 : 50.

Similarly, the use catalyst **4a** afforded the aldols in 100% yield; after crystallization from EtOAc–hexane *ent*,*syn*-**6a** was obtained with the yield 40–55%, ee 99%, dr 1 : 42.

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31 Note that almost half of the catalysts weight is cheap tartaric acid.

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