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Article

An Ionic Liquid Solution of Chitosan as Organocatalyst

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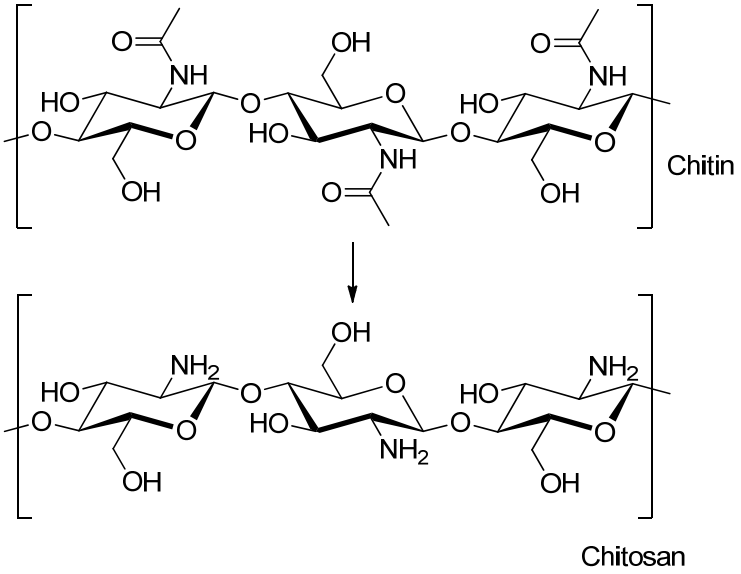
Abstract: Chitosan, which is derived from the biopolymer chitin, can be readily dissolved in different ionic liquids. The resulting homogeneous solutions were applied in an asymmetric Aldol reaction. Depending on the type of ionic liquid used, high asymmetric inductions were found. The influence of different additives was also studied. The best results were obtained in [BMIM][Br] without an additive.

Keywords: ionic liquids; chitosan; Aldol reaction

1. Introduction

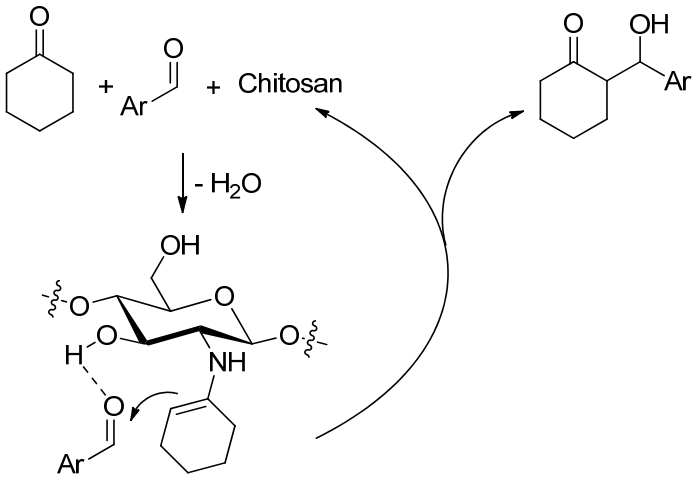
The research field of organocatalysis has in less than a decade become a well-established research field [1,2]. Organocatalysts can be categorized into Brønsted acids, Brønsted bases, Lewis acids and Lewis bases [3]. Among the different Lewis bases, secondary amines like MacMillan catalyst or (L)-proline have been used in enantioselective catalytic iminium [4] and enamine [5–9] cycles to perform an asymmetric Diels Alder or Aldol reaction. While the examples of secondary amines applied as catalysts in enamine cycles have been the major focus in many reactions, it is also known that primary amines can catalyze reactions involving an enamine cycle like the Aldol reaction or the Hajos-Parrish-Eder-Sauer-Wiechert reaction [5,6,10].

Scheme 1. Synthesis of Chitosan from Chitin.



In order to combine the recyclability of the catalyst and apply a cheap natural source of a catalytic material, the groups of Ricci and Quignard used chitosan as a sustainable source, derived from the deacetylation of the biopolymer chitin (Scheme 1), as heterogeneous catalyst in an asymmetric Aldol reaction [11,12]. Due to its free primary amino groups, chitosan could function as an organocatalyst. The reactions were performed in water with aerogel beads of chitosan and high enantioselectivities, with up to 93% *ee*, were achieved depending on the addition of different additives. The authors postulated the following reaction cycle shown in Scheme 2 and proposed the importance of hydrogen bonding between the hydroxy group of the chitosan and the aldehyde.

Scheme 2. Chitosan in an Aldol reaction.



Interestingly, in other studies, where hydrogel beads of chitosan were applied in an Aldol reaction in DMSO, the obtained Aldol product was racemic [13]. A further study with chitosan biohydrogel beads by the group of Diaz Diaz [14], explored several reactions including the Aldol reaction with the heterogeneous catalyst in different solvents such as DMSO and water. No enantiomeric excess was

reported. The authors concluded that in the presented case, the Aldol reaction was catalyzed by free hydroxide anions.

In addition, unmodified chitosan has also been applied as heterogeneous catalyst for the synthesis of α-amino nitriles and imines under neat conditions [15]. However, no enantiomeric excess of the product was reported. Furthermore, next to the application of chitosan itself as a catalyst, chitosan has been applied as support for several different catalysts [16].

Compared to cellulose or chitin, which are like most other biopolymers insoluble in standard solvents, chitosan can be dissolved in a dilute acidic aqueous solution, which is helpful to purify and handle chitosan. However, in other solvents under neutral conditions chitosan is insoluble. On the other hand ionic liquids are capable of dissolving many natural polymers like cellulose, chitin or chitosan, which has been used for processing strategies for those biopolymers [17]. For example, ionic liquids have been used to extract and process chitin from shrimp shells [18].

Ionic liquids, which are defined by a melting point below 100 °C, have attracted large interest as novel solvents for reactions and electrochemical processes [19]. An additional advantage is the efficient recovery of several of these salts and therefore some of these salts are expected to be "green solvents". The range of ionic liquids, based on various combinations of cations and anions, has dramatically increased as new salts and solvent mixtures are reported continuously. If these salts have a chiral center, they can be used in asymmetric catalysis [20] or applied as chiral solvating agents [21].

Due to our work on chiral ionic liquids [22–24] we were interested to use a solution of chitosan in an ionic liquid as a homogenous catalytic mixture to perform asymmetric reactions. Here, we present that chitosan, with different molar masses, is soluble in various ionic liquids and that these homogenic solutions can be successfully applied as an organocatalyst for the asymmetric Aldol reaction.

2. Results and Discussion

First, various ionic liquids were used to dissolve chitosan. Obviously, the type of ionic liquid as well as the natural source of the chitosan should have an influence on the catalytic process in terms of yield and enantiomeric excess, especially, if the chitosan is not further processed. It was possible to dissolve *ca.* 1 g of chitosan in 10 g of various ionic liquids by stirring the mixture for 24 h at 70 °C. Minor insolubilities remained and were removed via centrifuge and decantation. A clear viscous solution was obtained in all cases. For the study, chitosan from Acros Organics with a molecular weight of between 100,000 and 300,000 g/mol was used.

In order to have an increased solubility of the chitosan in the ionic liquids, solvents were chosen that can dissolve biopolymer chains by breaking up hydrogen bonds between them. [EMIM][Cl], [BMIM][Cl], [EMIM][OAc] and [BMIM][OAc] can perform this task due to their anions. In addition to these solvents also [EMIM][Br], [BMIM][Br], [EMIM][BF_4], [BMIM][BF_4], [EMIM][PF_6] and [BMIM][PF_6] were chosen. Although the anions are not strong hydrogen bond acceptors, the cations can still form hydrogen bonds with the chitosan as hydrogen bond donors. Hence these ionic liquids also dissolve chitosan. On the other hand very lipophilic ionic liquids such as [$N(Octyl)_3Me$][Cl] or [OMIM][Cl] do not dissolve chitosan.

With these different mixtures an Aldol reaction with cyclohexanone and 4-nitrobenzaldehyde was investigated (Scheme 3). The results are shown in Table 1. Although all ionic liquids shown in Table 1

dissolved chitosan, the different ionic liquids should have an influence on the structure of the chitosan polymer chains. Depending on the strength of the ionic liquids to form hydrogen bonds, a debundling of the polymer strings can be expected. Hence, an increase in accessible primary amine functions necessary to catalyze an enamine cycle should occur.

Scheme 3. Aldol reaction with cyclohexanone and 4-nitrobenzaldehyde.

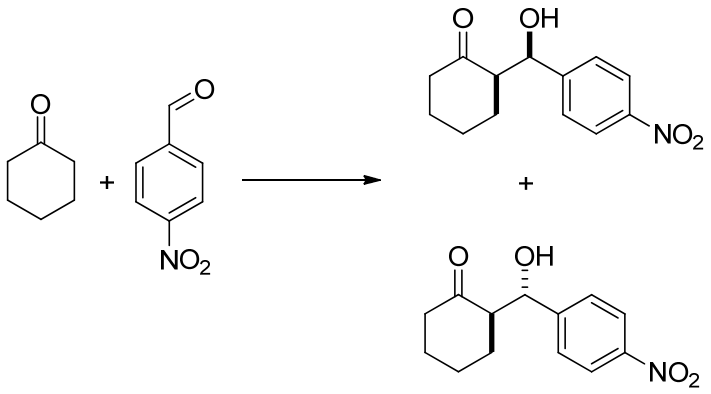


Table 1. Aldol reaction with cyclohexanone (20 equiv.), 4-nitrobenzaldehyde (1 equiv.) and chitosan (*ca.* 100 mg ≈ 2 equiv. primary amine functions) dissolved in different ionic liquids (1 g) and different additives (20 mol%) for 4 days at 37 °C.

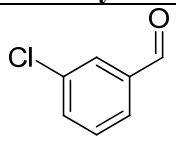
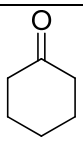
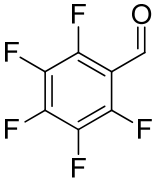
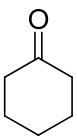
Entry	Ionic Liquid	Additive	Yield [%] [a]	dr [syn/anti] [b]	*ee* (syn) [%] [c]	*ee* (anti) [%] [c]
1	[BMIM][OAc]	TFA	71	66/34	34	51
2	[BMIM][OAc]	-	-	-	-	-
3	[EMIM][OAc]	TFA	46	56/44	8	2
4	[EMIM][OAc]	-	-	-	-	-
5	[BMIM][Cl]	-	27	49/51	0	14
6	[EMIM][Cl]	-	49	51/49	24	26
7	[BMIM][Br]	-	49	38/62	13	85
8	[BMIM][Br]	AcOH	61	47/53	4	13
9	[BMIM][Br]	TFA	-	-	-	-
10	[EMIM][Br]	-	44	52/48	43	17
11	[EMIM][Br]	AcOH	25	25/75	48	78
12	[EMIM][Br]	TFA	-	-	-	-
13	[BMIM][BF_4]	-	78	65/35	7	21
14	[EMIM][BF_4]	-	12	47/53	5	15
15	[BMIM][PF_6]	-	73	51/49	5	23
16	[EMIM][PF_6]	-	69	59/41	4	12
17	DMSO	-	-	-	-	-
18	H_2O	-	13	97/3	-	-

[a] yield after column chromatography; [b] determined by ^{1}H-NMR; [c] determined by HPLC.

A control reaction in the beginning with [BMIM][Cl] and [EMIM][Cl] without chitosan gave the diastereomers in less than 5% yield. The application of an [OAc] anion with a [BMIM] or [EMIM] cation with chitosan resulted in no desired product after 4 days (Table 1, Entries 2 and 4). This may be due to the fact that the [OAc] anions strongly interact with the chitosan and prohibit the formation of a

necessary transition state shown in Scheme 2. Nyulászi *et al.* [25–27] reported that in [EMIM][OAc] and [BMIM][OAc], the basic [OAc] anion can deprotonate [EMIM] and [BMIM] to their corresponding carbenes, and that these carbenes can catalyze the benzoin reaction and a subsequent oxidation and hydroacylation at 60 °C. Hence, it may be possible that the absence of product in Entries 2 and 4 in Table 1 could be due to a competing benzoin reaction. However, a repeat of the reaction in [EMIM][OAc] with chitosan showed nearly exclusively starting material, which means that in the presence of chitosan at 37 °C a competitive benzoin reaction cannot explain the absence of the desired product. When one equivalent of TFA related to the theoretical available primary amine functions in the mixture was added, the yield increased to 71% for [BMIM][OAc] (Table 1, Entry 1) giving a syn/anti ratio of 66/34 with an enantiomeric excess of the major diastereomer in 51%. [EMIM][OAc] gave as all salts with an [EMIM] counter cation lower yield and lower selectivities. An exception was [EMIM][Cl] which gave a yield of 49% compared to 25% with [BMIM][Cl]. However, in both cases selectivities were low (Table 1, Entries 5 and 6). The best results were obtained with [BMIM][Br] in the absence of an additive with an *ee* of 85% for the major diastereomer (Table 1, Entry 7). While TFA as an additive resulted in no product, the addition of AcOH could increase the yield to 61%, however, the selectivities declined (Table 1, Entry 8). In case of $[BF_4]$ or $[PF_6]$ as counter anions the obtained selectivities were very low (Table 1, Entries 13–16). In order to compare the homogenous chitosan ionic liquid solution with other solvents, the reaction was repeated with chitosan in DMSO and water. In both cases a heterogeneous mixture was observed. After 4 days at 37 °C in DMSO no yield was observed (Table 1, Entry 17), while in water a low yield of 13% of racemic compound was obtained (Table 1, Entry 18). A repeat of Entry 7 with a recycled [BMIM][Br] chitosan mixture resulted in a lower yield of 27% and low selectivities. This can be attributed to the contamination of the recycled solution with ethyl acetate. The contamination remained even after prolonged drying under high vacuum. Other aldehydes can also be applied under these conditions as shown in Table 2. Under the reaction conditions electron deficient aldehydes can be used. The best yield was obtained with *m*-chlorobenzaldehyde and cyclohexanone.

Table 2. Reaction with different aldehydes and ketones with chitosan in [BMIM][Br] at 37 °C.

Entry	Aldehydes	Ketones	Yield [%] [a]	dr [syn/anti] [b]	*ee* (syn) [%] [c]	*ee* (anti) [%] [c]
1			88	94/6	30	6
2			13	40/60	-	38

[a] yield after column chromatography; [b] determined by ^{1}H-NMR; [c] determined by HPLC.

3. Experimental Section

General methods and materials: Analytical grade solvents were from commercial sources. All reagents were commercially available and used as received. Chromatographic purifications were performed with mesh silica gel 60 (flash chromatography). ^{1}H- and ^{13}C-NMR spectroscopy were recorded with Bruker Avance 500 (125 MHz) spectrometer in $CDCl_3$. Enantiomeric excesses (*ee*) of products were determined by chiral stationary phase HPLC from Merck Hitachi (Daicel Chiralpak AD-H) with *n*-heptane and *i*-PrOH as solvents.

General procedure for the purification of chitosan: Chitosan (2.5 g) was added to acetic acid (100 mL, 0.055 mol). The mixture was gently stirred at 25 °C for 15 h. Afterwards the chitosan was dissolved in acetic acid. After removing the remaining crude chitosan on the bottom of the flask via centrifugation, the dissolved chitosan was precipitated by addition of ammonia (10 mL, 1 mol) and washed with deionized water until the removed water had a pH of 7. The chitosan was then dried under high vacuum for 5 days.

General procedure for dissolution of chitosan in ionic liquids: Chitosan (1.0 g) was added to the ionic liquid (10 g) and stirred for 24 h at 70 °C. Thereafter, the mixture between the dissolved chitosan in ionic liquid is prepared.

General procedure for the asymmetric Aldol reactions: The chitosan-ionic liquid mixture (1 g) was added to cyclohexanone (20 equiv.) and *p*-nitrobenzaldehyde (1 equiv.). An additive was added as indicated (~20 mol-% acetic acid or trifluoroacetic acid). The mixture was gently stirred at 37 °C for the stated time. EtOAc was then added, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The yellow solid was obtained in different yields (see Table 1) and as a mixture of diastereomers after chromatography on silica gel (petrolether/ethyl acetate: 60/40). The diasteroemeric ratio was determined by ^{1}H-NMR analysis. The enantiomeric excess of the product was determined by HPLC analysis (Daicel AD-H column, flow: 0.8 mL/min, *n*-heptane/*i*-PrOH: 90/10 and AD-H column, flow: 0.5 mL/min/*i*-PrOH: 98/2).

2-(Hydroxy-(4-nitrophenyl)-methyl)cyclohexanon: ^{1}H-NMR δ = 8.27–8.19 (m, $2H_{anti}$, $2H_{syn}$), 7.52 (t, *J* = 9.0 Hz, $2H_{anti}$, $2H_{syn}$), 5.51 (s, $1H_{syn}$), 4.92 (dd, *J* = 8.3, 2.6 Hz, $1H_{anti}$), 4.08 (d, *J* = 3.0 Hz, $1H_{anti}$), 3.19 (d, *J* = 3.1 Hz, $1H_{syn}$), 2.61–2.34 (m, $3H_{anti}$, $3H_{syn}$), 2.13 (m, $1H_{anti}$, $1H_{syn}$), 1.92–1.50 (m, $5H_{syn}$, $5H_{anti}$) ppm. Spectral data were consistent with literature values [28]. **HPLC:** anti-isomer: $t_{(2R,1S)}$ = 32.2 min, $t_{(2S,1R)}$ = 42.1 min; syn-isomer; $t_{(2R,1R)}$ = 23.4 min, $t_{(2S,1S)}$ = 29.4 min.

2-(m-Chlorphenyl-(hydroxy)-methyl)cyclohexanon: ^{1}H-NMR δ = 7.35–7.13 (m, $4H_{anti}$, $4H_{syn}$), 5.35 (d, *J* = 1.5 Hz, $1H_{syn}$), 4.75 (d, *J* = 9.0 Hz, $1H_{anti}$), 4.02 (s, H_{anti}), 3.08 (s, H_{syn}), 2.60–2.54 (m, $1H_{anti}$, $1H_{syn}$), 2.47–2.32 (m, $2H_{anti}$, $2H_{syn}$), 2.10–2.06 (m, $1H_{anti}$, $1H_{syn}$), 1.87–1.50 (m, $4H_{syn}$, $4H_{anti}$), 1.37–1.20 (m, $1H_{anti}$, $1H_{syn}$) ppm. Spectral data were consistent with literature values [28]. **HPLC:** anti-isomer: $t_{(2R,1S)}$ = 25.5.2 min, $t_{(2S,1R)}$ = 30.3 min; syn-isomer; $t_{(2R,1R)}$ = 42.3 min, $t_{(2S,1S)}$ = 46.6 min.

2-(Hydroxy-(perfluorphenyl)-methyl)cyclohexanon: ^{1}H-NMR δ = 5.43 (d, *J* = 6.5 Hz, $1H_{syn}$), 5.31 (d, *J* = 9.5 Hz, $1H_{anti}$), 3.86 (m, H_{anti}), 3.03–2.83 (m, H_{syn}), 2.54–2.01 (m, $3H_{anti}$, $3H_{syn}$), 2.10–1.78

(m, $1H_{anti}$, $1H_{syn}$), 1.73–1.55 (m, $3H_{syn}$, $3H_{anti}$), 1.40–1.23 (m, $2H_{anti}$, $2H_{syn}$) ppm. Spectral data were consistent with literature values [29]. **HPLC:** anti-isomer: $t_{(2R,1S)}$ = 25.6 min, $t_{(2S, 1R)}$ = 33.2 min.

4. Conclusions

Chitosan with a molecular weight of between 100,000 and 300,000 g/mol was dissolved in different ionic liquids. The resulting solutions were applied in an asymmetric Aldol reaction. The different ionic liquids had a strong influence on the yield and selectivity of the reaction. The best ionic liquid for the reaction was [BMIM][Br].

Conflicts of Interest

The authors declare no conflict of interest.

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